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PROTOCOL Version 3

Inceptions Cohort for Juvenile Systemic Sclerosis (jSSc)

Amendment 01. August 2017

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1. Aim of the Study

Aim 1:
To assess patients with juvenile systemic sclerosis jSSc prospectively using a standardized assessment method.

Aim 2:
To assess the sensitivity and specificity of the current provisional paediatric classification criteria and comparing them to the current validated suggested adult criteria.

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2. Inclusion and Exclusion Criteria

Inclusion Criteria:

Patients are at the time point of inclusion less than 18 years old.

1. Patient diagnosed with juvenile systemic scleroderma under the age of 16 years according:
   A, the paediatric classification criteria for juvenile systemic sclerosis [1], see table 1.
   B, the adult criteria for systemic sclerosis [2], see table 2.
2. Patients, who have possible evolving juvenile systemic scleroderma, will be recruited as a control group. Patient can be included, if they have any of these items
   a) pulmonary hypertension*
   b) interstitial lung disease*
   c) Raynauds phenomenon with capillary changes and ANA positivity*
   d) scleroderma antibody positive patients with or without other features*

* but not fulfilling the adult or paediatric systemic scleroderma criteria.

By collecting this control patients, we plan to assess the sensitivity and specificity of the current paediatric criteria and compare them to the currently published recent adult criteria.

Table 1: The Paediatric Rheumatology European Society, American College of Rheumatology and the European League Against Rheumatism criteria for the classification of juvenile systemic sclerosis [1]

Major criteria:	Proximal sclerosis or induration of the skin (specific for SSc)	
Minor criteria:	Cutaneous	Sclerodactyly
	Vascular	Raynaud's phenomenon Nailfold capillary abnormalities Digital tip ulcers
	Gastrointestinal	Dysphagia Gastro-oesophageal reflux
	Renal	Renal crisis New onset arterial hypertension
	Cardiac	Arrhythmias Heart failure
	Respiratory	Pulmonary fibrosis (HRCT/X-ray) Decreased DLCO Pulmonary Hypertension
	Musculo Skeletal	Tendon friction rubs Arthritis Myositis
	Neurological	Neuropathy Carpal tunnel syndrome
	Serology	Antinuclear antibodies SSc selective autoantibodies (anti-centromere, anti-topoisomerase I (Scl70), anti-fibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III)

Diagnosis of jSSc requirement: one major criteria and two minor criteria exists [1].

Table 2: The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis [2]

Item	Sub-item(s)	Weight/ score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions (only count the higher score)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti–Scl-70], anti–RNA polymerase III) (maximum score is 3)	Anticentromere 3 Anti–topoisomerase I Anti–RNA polymerase III	3

Diagnosis of SSc requirement: patients with a score of ≥ 9. [2]

Exclusion Criteria:

1) Patient does not fulfil any clinical criteria mentioned in the inclusion criteria.
2) Age at onset greater than 17 years.
3) Patient or parent unwilling to consent to the study.

3. Follow Up

Planned follow up is for at least 120 months after the inclusion of the patient into the cohort. Depending on the flow of the project, eventually an extension of the observation period is planned.

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4. Ethical Approval

Interested centres gain local IRB approval according the local regulations, before a patient from a centre can be included in the cohort.

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5. Patient Recruitment

If a patient fulfils the inclusion criteria, then the parent (guardian) will sign study consent and if applicable the patient too will be asked to sign the agreement to participate in the cohort. The signed study consent will remain with the centre, where the patient is recruited. The centre will report to the coordinating study nurse in Hamburg, that the patient/parent have agreed to participate, then the patient data can be de-identified from the reporting centre for the data transfer.

The patients will be de-identified/pseudomized according the international regulations coding

- 6 digits country/ centre/ patient number
- abbreviation of the country (two first letter of the country in English)
- two-digit code of the centre (given by the coordinating study nurse)
- number of the patient at the centre

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6. Data Entry

Data will be submitted either over the internet or per secure fax or postal mail, (whichever is allowed according the local guidelines) to the juvenile SSc cohort study coordinator
email: juvenile-scleroderma@gmx.de ; fax: +494020923693 ;

- Data assessment sheets are attached for each visit.

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7. Visits

Visits are planned at time point "0" (inclusion into the cohort) and then every 6 months for at least 120 months. The time range for the visit is ± 14 days from the exact calculated date.

The coordinating study nurse from Hamburg will send out data collection sheets or in the future these can be download on the secure site of the homepage, where the date and the time range for the visits will be printed. The coordinating study nurse will remind the participating centres regarding upcoming follow up visits and will request missing data.

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8. Assessment of the Organ Systems

At the time of the inclusion of the patients, the epidemiologic data will be collected with a baseline assessment sheet. Assessment forms will be used for the follow ups at 6, 12, 18, 24, 30, 36, … at least 120 months. The proposal for the current assessment is based on and modified from the adult and paediatric literature.

The suggested data collection reflects the good clinical standard for examination and testing for jSSc patients. The use of the term “optional” in this protocol and patient information sheets refer to situations where the assessment method can be considered according accessibility of the examination or depending on the patient condition. All assessments are at the discretion of the clinician. This form is meant to be completed completely, beside the optional items, if possible. The data sheets contain assessment of following items:

1. **Skin** – *every 6 months*
    1. Modified Rodnan Skin Score with scores from 0-3 for each of the 17 regions and filling out the scores in the “Rodnan-Man”, to record the distribution of the skin involvement
    2. Sclerodactyly – yes or no
    3. Calcinosis – yes or no, if yes mark the distribution of the skin involvement
    4. Digital photo documentation of the skin involvement
    5. Oral aperture
        a. Mouth opening > 3 vertical fingers of the patients wide or more - yes or no
        b. Measurement of the distance in cm between the lower edge of the upper and the upper edge of the lower middle incisor teeth
    6. Other skin changes:
        a. Gottron papules – yes or no
        b. SSc specific rashes – yes or no
            1. if possible please take a digital photograph as documentation
2. **Quality of Life** (under the age of 8 years parents will complete QoL, over the age of 8 years the patients will complete) – *every 6 months*

1. PedSQL (Paediatric Quality of Life Inventory) Generic module
2. PedSQL (Paediatric Quality of Life Inventory) Rheumatology module
3. CHAQ with Pain Visual Analogue Scale
    a. Optional – Hand function questionnaire

3. Sexual Maturation – *every 6 months*

1. Tanner stage (self-assessment sheet for Tanner 1-5 is attached)

4. Weight and Length – *every 6 months*

1. Weight in kg and height in cm

5. Laboratory Parameters

Every 6 months:

1. CRP / ESR
2. Full blood count with haemoglobin, white blood count with differential and platelet count
3. nt-pro-BNP
4. Creatinine
5. CK
6. GGT / GPT / GOT

Every 12 months:

7. ANA – by IFA suggested to give a titre defined as low < 1:80/middle < 1:640 / > 1:640 high positive
8. ENA (anti-Ro, -La, -Sm, -RNP) – by ELISA suggested
    a. Scl 70
    b. anticentromere antibodies
    c. anti-RNA polymerase III
    d. anti-PMScl
    e. other subtypes of ENA
9. Serum IgG and IGM
10. Optional
    a. Anticardiolipin antibody, anti-ß-2-Glycoprotein I -antibody and Lupus anticoagulant

6. Vascular Involvement (under the age of 8 years parents will complete a visual analogue scale (VAS), over the age of 8 years the patients will complete it) – *every 6 months*

1. Raynaud´s phenomenon
    a. Patient assessment VAS-Score 0-10 - Raynaud´s Activity-duration and frequency of the attacks for the last 7 days
    b. Assessment of the nail fold capillary changes – with otoscope / ophthalmoscope or dermatoscope – abnormality present yes or no
        - If possible using a capillaroscope (300 magnifiction), provide a description of number of capillaries, number of the dilated capillaries, avascular regions and tortuous capillaries [3]

   c. Pain Visual Analogue Scale measured on the CHAQ questionnaire (under the age of 8 years parents will complete a visual analogue scale (VAS), over the age of 12 years the patients will complete it)
   d. Disability Score for the hands/fingers – recorded as a component of the CHAQ
2. Ulceration – *every 6 months*
   a. Loss of tissue – yes or no
   b. Scars – yes or no
   c. Number of open lesions
   d. Patient assessment VAS-Score 0-10 - Ulceration Activity
   e. Physician assessment VAS-Score 0-10 - Ulceration Activity
   f. Pain – Visual Analogue Scale measured on the CHAQ questionnaire
   g. Disability Score for hands and fingers – recorded as a component of the CHAQ
   h. The DUCAS: a new composite tool for the evaluation and follow-up of DU in systemic sclerosis

7. Cardio-Pulmonary Involvement

1. 6-minute walking test – *every 6 months*

8. Pulmonary Involvement

1. Pulmonary function tests – standard spirometry with FVC, and DLCO – *every 6 months*
2. High resolution CT of the lung according to the physician's discretion
   a. at baseline
   b. if deterioration of the measurements of the pulmonary function test fall by 20% compared to the previous values occurs or clinical deterioration occurs judged by treating physician.
   c. HRCT should be collected on disc, and a paediatric radiologist should read all HRCTs centrally
3. Optional - Bronchoalveolar lavage – if HRCT changes occur, where progression of disease and possible infection cannot be differentiated. If performed, results will be collected and reported to the coordinating centre.
4. Optional – MRI of the lung

9. Cardiac Involvement

1. Cardiac ultrasound with transthoracic Doppler – *every 6 months*
   Assessed parameters – effusion score, RA area, RVET (Tei index), RV EF (surrogate), mitral valve early filling, LV diastolic dimensions, estimated pulmonary artery pressure
   a. Optional – Right heart catheterisation -
      1. if resting estimated pulmonary pressure with cardiac ultrasound is over 35 mm/Hg
      2. if any increased clinical suspicion for pulmonary hypertension exists

3. before any specific treatment against pulmonary hypertension is started
   b. Optional – MRI of the heart
2. ECG – *every 12 months*
   a. Optional – 24 h ECG, if there is increased suspicion of arrhythmia

10. Renal Involvement – *every 6 months*

1. Blood pressure
   a. Optional – Blood pressure for 24 h, if suspected hypertension
2. Creatinine-Serum
   a. Optional – 24 h Urine creatinine
3. Urine
   a. Urine dip-stick
   b. Protein / Creatinine – spot urine
   c. Optional – 24 h urine for protein excretion and creatinine clearance
   d. Optional – Kidney biopsy, if significant proteinuria
4. Report of occurrence of Renal crisis

11. Gastrointestinal Involvment – *every 6 months*

1. Diarrhoea - yes or no (defined by more than 3 fluid stools/day)
2. Constipation – yes or no (defined by stool frequency less than once every 3 days)
3. Reflux symptoms - yes or no
4. Laboratory marker for malabsorption - serum Folate and B 12, stool trypsin *optional*
   a. Optional – if clinical suspicion
      1. Barium swallow with small bowel follow-through (if unable to tolerate, use gastrograffin)
      2. Oesophageal scintigraphy
      3. 24h pH manometry
      4. Endoscopy
      5. Colon scintigraphy
      6. Breath test - bacterial overgrowth
      7. Abdominal MRI
      8. Stool Calprotectin

12. Musculoskeletal Involvement – *every 6 months*

1. Joint count – limited - swollen - painful
2. Tendon friction rub – yes or no
3. Muscle strength - CMAS
   a. MMT8 score
4. Contractures – yes or no

13. Neurologic Involvement – *every 6 months*

1. Carpal Tunnel syndrome - yes or no

a. Optional – Nerve conduction studies, if suspicion for peripheral neuropathy
b. Optional – MRA or MRI with angiography and/or lumbar puncture results, if suspicion for CNS involvement
c. Other neurologic involvements

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9. Statistical Evaluation

The collected data will be entered via a spreadsheet to a database. Statistical analyses will be conducted by SAS. Categorical variables will be reported by absolute and relative frequencies, continuously distributed variables by mean and standard deviations or median and interquartile range depending on the distribution of the variable. Comparison of patients with diffuse and limited subtype of jSSc were done by a Chi2-Test for categorical variables and a students t-test for continuously distributed variables.

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10. Data Evaluation

Data will be evaluated every 12 months and summarized, participating centres will receive a summary of the data every 12 months and the newsletter.
The international Steering Committee (Dr. Jordi Anton (Barcelona), Eilleen Baildam (UK), Dr. Ivan Foeldvari (Germany) , Jens Klotsche (Germany), Clarissa Pilkington (UK), Ann Stevens (USA) Teresa Terreri (Brazil)) will meet every 12 months, mostly during the annual meeting of the PRES and/or ACR to evaluate the results.

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11. Publication of the Data

All contributing authors will be co-authors on the publications. Several publications are planned, summarizing different stages and aspects of the data evaluation.

References:

1. Zulian F, Woo P, Athreya BH, Laxer RM, Medsger TA, Jr., Lehman TJ, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum. 2007;57(2):203-12.

2. Frank van den Hoogen, Dinesh Khanna, Jaap Fransen, et al. 2013 Classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative *Ann Rheum Dis* 2013 72: 1747-1755

3. Smith V, et al. An EULAR study group pilot study on reliability of simple capillaroscopic definitions to describe capillary morphology in rheumatic diseases *Rheumatology 2016;55:883_890*