

**Impact of synovial biopsy procedures and disease specific aspects on synovial tissue outcome: a systematic literature review informing the EULAR points to consider for the minimal reporting requirements in synovial tissue research in rheumatology.**

## **Online Supplementary Material**

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### Online Supplementary Text S1: PICO framework for the 5 research questions.

<b>Question</b>	<b>1.A Does the guiding procedure of the synovial biopsy affect tissue quality and/or acceptance tolerability and safety of the procedure?</b>	
<b>Type</b>	<input checked="" type="checkbox"/> Efficacy <input type="checkbox"/> Prognostic <input type="checkbox"/> Diagnostic <input checked="" type="checkbox"/> Safety <input type="checkbox"/> Etiological <input type="checkbox"/> Descriptive	
<b>Population</b>	Patients undergoing Synovial biopsies	Key words related to <b>Synovial membrane</b> <b>AND</b> Key words related to <b>Joints, Tendons and Bursa</b> <b>AND</b> Key words related to <b>RMDs</b>
<b>Intervention (Factor)</b>	Ultrasound guided biopsy	Key words related to <b>Ultrasound guided and Biopsy</b>
<b>Comparator</b>	Arthroscopic biopsy Anatomical guided needle biopsy MRI guided CT guided	Key words related to <b>Arthroscopic guided and Biopsy</b> <b>OR</b> Key words related to <b>Blind needle biopsy</b> <b>OR</b> Key words related to <b>MRI guided biopsy</b> <b>OR</b> Key words related to <b>CT guided biopsy</b>
<b>Outcome</b>	Procedure outcome	Key words related to <b>Biopsy yield</b> <b>OR</b> Key words related to <b>Tissue quality</b> <b>OR</b> Key words related to <b>Acceptance, Tolerability</b> <b>OR</b> Key words related to <b>Adverse events and Safety</b> <b>OR</b> Key words related to <b>Patient perspective</b> <b>OR</b> Key words related to <b>Patient reported outcomes</b>
<b>Type of study</b>	Comparison studies	

### Research Question 1.

<b>Question</b>	<b>1.B Does the instrument used during synovial biopsy affect tissue quality and/or acceptance, tolerability and safety of the procedure?</b>	
<b>Type</b>	<input checked="" type="checkbox"/> Efficacy <input type="checkbox"/> Prognostic <input type="checkbox"/> Diagnostic <input checked="" type="checkbox"/> Safety <input type="checkbox"/> Etiological <input type="checkbox"/> Descriptive	
<b>Population</b>	Patients undergoing Synovial biopsies	Key words related to <b>Synovial membrane</b> <b>and</b> Key words related to <b>Joints, Tendons and Bursae</b> <b>AND</b> Key words related to <b>RMDs</b>
<b>Intervention (Factor)</b>	Needle biopsy	Key words related to <b>Needle and Needle size</b> <b>AND</b> Key words related to <b>Biopsy</b>
<b>Comparator</b>	Forceps, port	Key words related to <b>Port and forceps</b> <b>AND</b> Key words related to <b>Biopsy</b>

<b>Outcome</b>	Procedure outcome	Key words related to <b>Biopsy yield</b> <b>OR</b> Key words related to <b>Tissue quality</b> <b>OR</b> Key words related to <b>Acceptance, Tolerability</b> <b>OR</b> Key words related to <b>Adverse events and Safety</b> <b>OR</b> Key words related to <b>Patient perspective</b>
<b>Type of study</b>	Comparison studies	

### Research Question 2.

<b>Question</b>	<b>2. Is the pathology in one joint a surrogate of all disease joints?</b>	
<b>Type</b>	<input type="checkbox"/> Efficacy <input type="checkbox"/> Prognostic <input type="checkbox"/> Diagnostic <input type="checkbox"/> Safety <input checked="" type="checkbox"/> Etiological <input type="checkbox"/> Descriptive	
<b>Population</b>	Patients undergoing Synovial biopsies	Key words related to <b>Synovial membrane</b> <b>and</b> Key terms related to <b>RMDs</b>
<b>Intervention (Factor)</b>	Joint	Key words related to <b>Knee</b>
<b>Comparator</b>	Other joint	Key words related to <b>Every other joint</b>
<b>Outcome</b>	Procedure outcome	Key words related to <b>Tissue outcome (Histology, RNA, cell isolation)</b>
<b>Type of study</b>	Comparison studies	

## Research Question 3.

<b>Question</b>	<b>3. Does the tissue handling following synovial biopsy affect the tissue quality?</b> <b>a) Handling</b>	
<b>Type</b>	<input checked="" type="checkbox"/> Efficacy <input type="checkbox"/> Prognostic <input type="checkbox"/> Diagnostic <input type="checkbox"/> Safety <input type="checkbox"/> Etiological <input type="checkbox"/> Descriptive	
<b>Population</b>	Patients undergoing Synovial biopsies	Key words related to <b>Synovial Biopsy</b> <b>and</b> Key terms related to <b>RMDs</b>
<b>Intervention (Factor)</b>	Fresh tissue handling	Key words related to <b>Tissue Handling, Fresh tissue</b>
<b>Comparator</b>	Other tissue Handling	Key words related to <b>Tissue Handling Formalin, Frozen</b>
<b>Outcome</b>	Procedure outcome	Key words related to <b>Tissue outcome (Histology, RNA, cell isolation)</b>
<b>Type of study</b>	Comparison studies	

<b>Question</b>	<b>3. Does the tissue handling following synovial biopsy affect the tissue quality?</b> <b>b) Sample randomization</b>	
<b>Type</b>	<input checked="" type="checkbox"/> Efficacy <input type="checkbox"/> Prognostic <input type="checkbox"/> Diagnostic <input type="checkbox"/> Safety <input type="checkbox"/> Etiological <input type="checkbox"/> Descriptive	
<b>Population</b>	Patients undergoing Synovial biopsies	Key words related to <b>Synovial Biopsy</b> <b>and</b> Key terms related to <b>RMDs</b>
<b>Intervention (Factor)</b>	Sample randomization	Key words related to <b>Sample randomisation</b>
<b>Comparator</b>	(No sample randomization)	
<b>Outcome</b>	Procedure outcome	Key words related to <b>Tissue outcome (Histology, RNA, cell isolation)</b>
<b>Type of study</b>	Comparison studies	

**Research Question 4.**

<b>Question</b>	<b>4. How does the tissue quality affect the study results?</b>	
<b>Type</b>	<input checked="" type="checkbox"/> Efficacy <input type="checkbox"/> Prognostic <input type="checkbox"/> Diagnostic <input type="checkbox"/> Safety <input type="checkbox"/> Etiological <input type="checkbox"/> Descriptive	
<b>Population</b>	Patients undergoing Synovial biopsies	Key words related to <b>Synovial Biopsy</b> <b>and</b> Key terms related to <b>RMDs</b>
<b>Intervention (Factor)</b>	Quality	Key words related to <b>Tissue Quality</b> , (including Histology, lining layer, sample size, RNA RIN and quantity, Viable cells)
<b>Comparator</b>	(No quality assessment)	
<b>Outcome</b>	Procedure outcome	Key words related to <b>Tissue outcome (Histology, RNA, cell isolation)</b>
<b>Type of study</b>	Comparison studies	

**Research Question 5.**

<b>Question</b>	<b>5. Does the disease stage affect synovial biopsy results?</b>	
<b>Type</b>	<input type="checkbox"/> Efficacy <input type="checkbox"/> Prognostic <input type="checkbox"/> Diagnostic <input type="checkbox"/> Safety <input type="checkbox"/> Etiological <input type="checkbox"/> Descriptive <input checked="" type="checkbox"/> Other types: <b>Validation</b>	
<b>Population</b>	Patients undergoing Synovial biopsies	Key words related to <b>Synovial Biopsy</b> <b>and</b> Key terms related to <b>RMDs</b>
<b>Intervention (Factor)</b>	Early disease	Key words related to <b>Early RMDs</b> (early RA, naïve RA...)
<b>Comparator</b>	Established disease	Key words related to <b>Established RMDs</b>
<b>Outcome</b>	Procedure outcome	Key words related to <b>Tissue outcome (Histology, RNA, cell isolation)</b>
<b>Type of study</b>	Comparison studies	

**Online Supplementary Text S2: Search strategies of the 5 research questions.****Research Question 1**

**Pubmed:** (((((((patient reported outcomes) OR ("Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("immune tolerance"[MeSH Terms] OR ("immune"[All Fields] AND "tolerance"[All Fields]) OR "immune tolerance"[All Fields] OR "tolerance"[All Fields] OR "drug tolerance"[MeSH Terms] OR ("drug"[All Fields] AND "tolerance"[All Fields]) OR "drug tolerance"[All Fields] OR "tolerabilities"[All Fields] OR "tolerability"[All Fields] OR "tolerable"[All Fields] OR "tolerableness"[All Fields] OR "tolerably"[All Fields] OR "tolerances"[All Fields] OR "tolerant"[All Fields] OR "tolerants"[All Fields] OR "tolerate"[All Fields] OR "tolerated"[All Fields] OR "tolerates"[All Fields] OR "tolerating"[All Fields] OR "toleration"[All Fields] OR "tolerator"[All Fields] OR "tolerators"[All Fields] OR "tolerence"[All Fields])) OR ("accept"[All Fields] OR "acceptabilities"[All Fields] OR "acceptability"[All Fields] OR "acceptable"[All Fields] OR "acceptably"[All Fields] OR "acceptance"[All Fields] OR "acceptances"[All Fields] OR "acceptation"[All Fields] OR "accepted"[All Fields] OR "accepter"[All Fields] OR "accepters"[All Fields] OR "accepting"[All Fields] OR "accepts"[All Fields])) OR (("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields]) AND ("yield"[All Fields] OR "yielded"[All Fields] OR "yielding"[All Fields] OR "yields"[All Fields])) OR (("tissue s"[All Fields] OR "tissues"[MeSH Terms] OR "tissues"[All Fields] OR "tissue"[All Fields]) AND ("qualities"[All Fields] OR "quality"[All Fields] OR "quality s"[All Fields])) AND (((biopsy forceps) OR (portal)) OR ((ultrasound guided biopsy) AND (((joint s"[All Fields] OR "joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) AND ("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields])) OR (synovial biopsy))) OR (((("arthroscoped"[All Fields] OR "arthroscopes"[MeSH Terms] OR "arthroscopes"[All Fields] OR "arthroscope"[All Fields] OR "arthroscopic"[All Fields] OR "arthroscopical"[All Fields] OR "arthroscopically"[All Fields] OR "arthroscopy"[All Fields]) AND ("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields])) OR ("computed tomography"[All Fields] OR "ct"[All Fields]) AND ("guide"[All Fields] OR "guided"[All Fields] OR "guides"[All Fields] OR "guiding"[All Fields]) AND ("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields])) OR (mri guided)) OR (needle biopsy))) AND (((joint s"[All Fields] OR "joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) AND ("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields])) OR (synovial biopsy))

**Embase**

('joint biopsy'/exp OR 'synovial biopsy' OR 'synovial biopsies') AND ('biopsy technique'/exp OR 'tissue quality' OR 'biopsy yield' OR 'tolerability'/exp OR tolerability OR 'acceptance'/exp OR acceptance OR 'procedure outcome' OR 'procedure outcomes' OR 'adverse event'/exp) OR (('joint biopsy'/exp OR 'synovial biopsy' OR 'synovial biopsies') AND 'synovial tissue

analysis')) AND ('arthrosomy'/exp OR 'needle biopsy'/exp OR 'ct guided biopsy'/exp OR mri OR ultrasound OR 'biopsy forceps'/exp OR portal OR 'ct'/exp OR port)

**Cinhal**

synovial biopsy OR synovial biopsies

**CENTRAL (Cochrane)**

synovial biopsy OR synovial biopsies

**Research Questions 2, 3, 4****Pubmed:**

(human tissue) AND ((((((osteoarthritis) OR (arthritis)) OR (rheumatoid)) OR (rheumatic)) OR (musculoskeletal system inflammation)) AND (((("joint s"[All Fields] OR "joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) AND ("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields])) OR (synovial biopsy))) AND ((cell isolation) OR (rna) OR (procedure outcomes) OR (tissue histology) OR (tissue reaction) OR (tissue outcome))

**Embase**

'human tissue'/exp AND ('rheumatic disease'/exp OR 'musculoskeletal system inflammation'/exp) AND ('joint biopsy'/exp OR 'synovial biopsy' OR 'synovial biopsies')

**Cinhal**

synovial biopsy OR synovial biopsies

**CENTRAL (Cochrane)**

synovial biopsy OR synovial biopsies

**Research Question 5****Pubmed**

(human tissue) AND (late OR early OR stage OR duration OR established) AND ((( (arthritis) OR (rheumatoid)) OR (rheumatic)) OR (musculoskeletal system inflammation)) AND (((("joint s"[All Fields] OR "joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) AND ("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields])) OR (synovial biopsy)))

**Embase**

'human tissue'/exp AND ('joint biopsy'/exp OR 'synovial biopsy' OR 'synovial biopsies') AND (early OR late OR established OR duration OR stage)

**Cinhal**

synovial biopsy OR synovial biopsies

**CENTRAL (Cochrane)**

synovial biopsy OR synovial biopsies.

**Online Supplementary text S3**

## Risk of Bias Tool

## JBI Checklist for Analytical Cross Sectional Studies

## 8 QUESTIONS

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way? (technique)
4. Were objective, standard criteria used for measurement of the condition? (scoring)
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Number of YES	RoB
8	LOW
6-7	UNCLEAR
< or = 5	HIGH