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European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA): rationale, design and methods of a multinational, multicenter, multilingual, longitudinal qualitative study

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ABSTRACT

Introduction: Including the patient perspective is important to achieve optimal outcomes in the treatment of rheumatoid arthritis (RA). Ample qualitative studies exist on patient outcomes in RA. A Belgian study recently unraveled what matters most to patients throughout the overwhelming and rapidly evolving early stage of RA. The present study, European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA) was created to contribute to a more universal understanding of patient-preferred health and treatment outcomes by integrating the perspectives of patients with early RA from three European countries.

Methods and analysis: In EQPERA, a qualitative, explorative, longitudinal study will be implemented in The Netherlands and Sweden, parallel to the methods applied in the previously conducted Belgian study. In each country, a purposive sample of patients with early RA will be individually interviewed 3-6 months after start of the initial RA treatment and subsequently, the same participants will be invited to take part in a focus group 12-18 months after RA treatment initiation. Data collection and analysis will be independently conducted by the local research teams in their native language. A meta-analysis of the local findings will be performed to explore and describe similarities, differences and patterns across countries.

Ethics and dissemination: Ethics approval was granted by the responsible local ethics committees. EQPERA follows the recommendations of the Declaration of Helsinki. Two main papers are foreseen (apart from the data reporting on the local findings) for peer-reviewed publication.

Key words: Rheumatoid Arthritis, Qualitative research, Longitudinal study, Patient Preference

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The specific nature of the study, in which qualitative studies are carried out in different countries and languages using a uniform methodology, is novel, and we report in a transparent way about our approach and challenges.
- As no formal meta-analysis method was present in literature applicable to our study, we developed a method based on established techniques for the synthesis of qualitative research, which can guide other researchers interested in conducting this type of research.
- Several quality enhancing strategies are applied to yield sound results in this multinational, multilingual, longitudinal qualitative study.
- The participating countries might have rather similar cultural views and healthcare systems, which would strengthen the Belgian findings, however, the study protocol offers a methodological framework for research in different parts of the world.

INTRODUCTION

In rheumatoid arthritis (RA), the outcome landscape dramatically changed over the past decades. RA is the most prevalent chronic, auto-immune inflammatory joint disease. It was typically described as an inevitably progressive disease with a destructive and disabling natural course. The continuous growth in effective pharmacological treatments contributed to this change, but the introduction of early therapy was one of the main drivers of transformed health outcomes of patients with RA.[1] Nowadays, remission or at least low disease activity have become realistic treatment targets for a notable proportion of the population.[2]

Nevertheless, the burden of disease and unmet needs remain considerable.[3 4] For example, most of the patients are at working age upon diagnosis, but work disability rates remain high.[5] Furthermore, patients with RA indicated the need for greater emotional support, and greater psychological support to manage the impact of disease on domains such as pain, fatigue, work and leisure.[6 7] Hence, it seems that patient preferences are not sufficiently understood and met by health professionals. In a recent report, patient-centered care was identified as a recurrent unmet need across rheumatic diseases, including RA.[8] Patient-centered care can be translated as care that is guided by the values and preferences of the patients,[9] with patient preferences referring to the perspective, beliefs and expectations of patients regarding their health and life.[10] As patient-centeredness is acknowledged as one of the key dimensions of high-quality care,[11] integrating the patient perspective in outcome assessment is increasingly advocated to achieve optimal outcomes in the treatment of RA.[12 13]

Qualitative studies shed light on the different views that patients with RA have on outcome compared to health professionals. These studies revealed the importance of fatigue and independence, among others, [14-16] to consider in daily practice on top of the traditional measures of disease activity, i.e., the swelling of joints and laboratory parameters of inflammation. Remarkably, limited attention has been given to the perspective of recently

diagnosed patients. The early disease stage is probably the most daunting period for patients, indicating specific needs and preferences.[17 18] The Belgian qualitative study of Van der Elst et al. provided new insights into patient-preferred outcomes in early RA, concluding that returning to 'normality' as soon as possible was the core preferred outcome, which related to aspects of disease control and participation, physical and mental aspects.[19] However, understanding is lacking about the transferability of these local findings to other settings and cultures.

Despite recommendations for RA management, literature shows that there are differences in how rheumatology services are viewed and practiced across countries.[20 21] These differences may be attributable to characteristics of the national healthcare systems, local customs, practices, and values. Such cultural differences may consequently influence how patients evaluate their disease. For example, the survey study of Van Tuyl et al. demonstrated that the country in which patients were sampled resulted in slightly different key domains on how they perceived remission of disease.[22] Hifinger et al. showed that country of residence had an important influence on how patients with RA experienced fatigue.[23] It can thus be questioned whether patients in other countries would bring out other preferred outcomes.

To examine the transferability of the Belgian findings and to contribute to a more universal understanding of patient-preferred outcomes, we initiated the EQPERA consortium. EQPERA is the acronym for European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis. It is a multicenter, multilingual, longitudinal qualitative study across Belgium, The Netherlands and Sweden. The present paper reports about the international study protocol, based on the Belgian study procedures.

Objectives

The overall research objective in EQPERA is to explore how local context influences patient-preferred health and treatment outcomes throughout the early disease course by integrating the perspectives of patients with early RA from three European countries.

The objective is twofold:

(i) to describe patient-preferred outcomes in early RA and how they change throughout the early disease course (national objective);

(ii) to identify differences, similarities and patterns in patient-preferred outcomes across the three European countries (international objective).

METHODS AND ANALYSIS

The Belgian study was conducted during 2012-2013 .[19] Based on the lessons learned and after multiple discussion rounds with the EQPERA steering group, an improved research protocol was written with the aim to implement a protocol as similar as possible in the other countries. Start of patient inclusion was 2016 in The Netherlands and 2017 in Sweden.

Study design

A qualitative, explorative, longitudinal research design will be applied within a European context. As we study a research domain still lacking evidence, the use of qualitative methods is justified because we will learn from the rich descriptions of participants being shaped in their local contexts.[24 25] Longitudinal designs are relevant for studying complex phenomena and are specifically applicable in the context of a recent diagnosis since patients' perceptions and expectations may change during the overwhelming and rapidly evolving early disease stage. Previous research also suggests that the way patients experience and evaluate their disease can differ depending on disease duration.[15 26 27]

Patients with early RA will be invited to participate at two time points (Figure 1). At t_1, participants will be individually interviewed 3-6 months after they have started their initial

treatment for RA. At t_2, participants will be invited to take part in a focus group 12-18 months after RA treatment initiation. To address a potential dropout of participants at t_2, those who decline to participate in a focus group will be invited for a repeated individual interview instead. However, the preferred interview method at t_2 remains the focus group method to align with the original design of the Belgian study.

The reason for selecting different interview methods at t_1 and t_2 is based on the input of patient research partners and aims to match with patient preference in the context of a recent diagnosis. At t_1, the individual interview method is chosen because adjusting to a recent diagnosis can be seen as a primarily individual matter. Consequently, sharing personal experiences and opinions in a group setting can be too confronting at that stage of disease. A timeframe of 3-6 months after initiation of the initial RA treatment is chosen to not interfere with the diagnostic and therapeutic procedures, however, still including patients' earliest views on preferred outcomes. Furthermore, it is assumed that a few months of experience with the disease and treatment would help patients to communicate more easily about their outcome preferences.

At t_2, focus groups are chosen above the individual interview method for two reasons. Firstly, compared to the first interview moment, participants may probably feel more comfortable in a group setting, because of a grown disease perspective and the potential interaction with other patients (e.g., in the waiting room) by then. Secondly, group interactions potentially help participants to remember significant events and bring out personal thoughts, which in turn may result in more and diverse data.[25 28] It is reasoned that after 12-18 months of treatment experience, participants have had sufficient time to develop their view on the disease, with perhaps an observable change in their preferences accordingly.

Research context

EQPERA involves three countries in Northwest Europe: Belgium, The Netherlands and Sweden. These countries have a comparable organized healthcare system including a comprehensive social security system, however, differences exist in for example their reimbursement and referral system.

Participants will receive usual care according to local standards. Across countries, a comparable early RA management is implemented in respect of current international guidelines:[29 30] patients should be treated (i) early: as soon as the diagnosis is made; (ii) intensively, with methotrexate in the first treatment if possible; (iii) to target: treatment adjustments according to a predefined target of sustained remission or low disease activity. In addition, there is a common culture across the countries regarding interdisciplinary team care as key in disease management, but diversity can be expected concerning implementation aspects. For example, it has been shown that there is a wide variation in the role of nurses in the management of patients with chronic inflammatory arthritis[20], and in the composition of rheumatology multidisciplinary teams [31].

In each country, an early RA cohort is available, the local teams include experienced qualitative researchers with a good command of the English language, and funding possibilities are available to work out their national project. The EQPERA steering group consists of team members with different disciplinary backgrounds: nurses (KE, IL, EM, YH), physiotherapists (AB, AG), a psychologist (JV), a patient representative (AG) and a rheumatologist (RW).

Level of collaboration between countries

Individual projects will be conducted in each country. The studies in Sweden and The Netherlands will be led by the local principal investigator (IL and EM, respectively) and supervised by the EQPERA project leader (KE), who designed and completed the Belgian qualitative study.[19]

Considering qualitative studies, potential language issues can be approached in two ways: either translate the transcripts and do the analysis in one place, or have the analysis done at each location and combine the data afterwards. We decided that (i) data will be collected in the local settings by the local teams in their native language; (ii) interviews will be transcribed in the original language and the transcripts will be analyzed by the local teams; (iii) only the results of the local analysis (i.e., interpreted data) will be combined for EQPERA purposes, and this after ending the analysis procedures and writing up the findings and conclusions in every country.

Original data will thus not be reviewed by the other teams (Figure 1). Centralizing data would mean translation of local transcripts to the common language in EQPERA (English). Translation holds the risk of losing the real meaning of words,[32] and would be expensive and time consuming because of the mountains of words that will be produced in every country. Above and beyond translation issues, we assumed that local data should ideally be analyzed by the people who are familiar with the local culture and context in order to get the most appropriate interpretations.

Collaboration with patient research partners

As EQPERA aims to capture the patient perspective, the project would benefit from active collaboration with patient representatives, or those who have the lived experience of RA. Following the recommendations of the European League Against Rheumatism for the inclusion of patient representatives in scientific projects,[33] each local team will preferably collaborate with two patient research partners.

The local principal investigators will be responsibility for coordinating this research partnership, being guided by the FIRST (i.e., Facilitate, Identify, Respect, Support and Train) framework of Hewlett and colleagues.[34] The exact level of the patient researchers'

contribution will depend on local agreements (feasibility). In general, they will help by reflecting on the methods, formulating clear and understandable interview questions, interpreting and explaining data, and providing feedback on the readability of the patient information leaflet and informed consent form.

Participants

Eligible patients will have to meet the following inclusion criteria: (i) confirmed diagnosis of RA, in accordance with the American College of Rheumatology/European League Against Rheumatism 2010 criteria;[35] (ii) time between diagnosis and start of RA treatment of less or equal than 1 year; (iii) minimum age of 18 years; (iv) speak, read and write the local language; (v) started the initial RA treatment 3-6 months ago.

Sampling

Every country will strive to include a broad range of perspectives in their sample. To ensure this variation, participants will be purposively sampled based on their (i) age/life phase; (ii) gender; and (iii) treatment progress/treatment experience. Moreover, every country will apply a multicenter recruitment to account for possible variation in region.

Sampling in qualitative research corresponds to the assumption that collected data is of sufficient depth, i.e., representing the various views and opinions of the population with no added value of including more participants for answering the research question.[36 37] As there is no standardized definition of data saturation, we decided that data collection can be stopped if three consecutive interviews do not result in new themes or additional understanding (local team decision).

At t_1, we estimate that around 20 participants in every country will be needed to reach data saturation. At t_2, the sample sizes will foremost depend on the interest and willingness of

participants to participate again. We aim for 4-8 participants in each focus group, which seems an appropriate number to keep the discussions manageable and stimulate contribution of every group member.[36 38] If possible, patient characteristics will be taken into account to create a mix of perspectives in the groups.

Recruitment

In each country, patients are recruited from multiple centers across different geographic locations, including academic and non-academic rheumatology centers. In Belgium, patients were sampled from nine centers across Flanders. The participating centers in The Netherlands are located in Nijmegen and Woerden, and in Sweden these are located in Lund, Malmö and Halmstad. A recruitment template will help the local teams to consider the main variables for creating heterogeneity in their samples.

Data collection

The interview guides

The semi-structured interview guides include pre-defined topics, with open-ended questions, and probing questions to reach a higher level of detail. All questions relate to the central interview question: 'Which outcomes of your illness and antirheumatic treatment are important to you at this moment?'. In every country, the interview guides will have the same content at start, and main questions will be fixed across countries. Data collection and analysis will be performed simultaneously, making it possible to adapt the interview guides if necessary to increase participants' understanding or to reach data saturation (local team decision). If adaptations are needed, these will be documented in the local research journal.

The content of the interview guides is inspired by previous qualitative studies on outcomes from the patient perspective.[14 16 39] In EQPERA, Dutch and Swedish versions of the Belgian interview guides (Flemish language) will be prepared by the local teams. Given similarities

between the Flemish and Dutch language, minor adaptations will be applied after discussion and consensus with the Belgian team. Forward and backward translation will be used to prepare translations to English and Swedish (Figure 2).[40 41] The main interview questions and the interview procedures are elucidated in Supplementary file 1.

Individual interviews (t_1)

At t_1, individual, face-to-face interviews will be conducted by maximum 2 interviewers per country, who are not involved in participants' clinical care. As the patient research partners noted that patients are in general not used to talk about outcome preferences, they will be asked to prepare written key words regarding the central interview question. The interviewer will start by elaborating on these key words. It is anticipated that interviews will last no longer than 60 minutes.

Focus groups (t_2)

Focus groups will be facilitated by one of the interviewers of t_1 in assistance of at least one participating observer. The focus groups will consist of three rounds: Round 1: preparatory phase; Round 2: (i) round-robin listing, (ii) developing a group list of patient-preferred outcomes, (iii) eliciting personal preferred outcomes, (iv) eliciting preferred outcomes in the actual stage of RA; Round 3: exploring the view of participants on the evolution of their patient preferred outcomes over the past year. The second round of the focus groups was inspired by the Nominal Group Technique methodology (NGT).[42] NGT is a consensus method that creates two types of data: (i) written ideas and prioritization, and (ii) the wider discussion, generating and clarifying ideas.[43] Our interest for using a prioritizing methodology is firstly, to create discussion between participants about a potential inconvenient topic; and secondly, to capture participants' underlying reasoning regarding preferences in outcomes. It is anticipated that focus groups will last about 60 minutes.

Individual interviews *(t_2)*

If necessary, the interviewer of t_1 will conduct individual interviews at t_2. The interview guide for these interviews is slightly adapted compared to t_1 in order to question participants about their view on changes in their preferred outcomes over time.

Procedures at both time points

Both individual interviews and focus groups will be held at a neutral and convenient location, and will be audio-recorded and transcribed verbatim according to transcription guidelines.[44]

Prior to the (focus group) interview, participants will document socio-demographic information. After the interviews, they will report about their general health, level of pain and fatigue during the past week on a visual analog scale. Clinical information will be extracted from the medical records by the local health professionals and shared with the local principal investigator.

Data analysis

Data analysis will be conducted at two levels: (i) the local analyses of t_1 and t_2 data, followed by the longitudinal analysis; (ii) the meta-analysis with locally interpreted local data. The process of data analysis was based on several frameworks, which is summarized in Figure 3.

The local analyses

In every country, the analysis process will be a team activity involving patient representatives. Preferably two researchers, including at least the local lead investigator, will independently code the interview transcripts. Data analysis will start after the first interview or focus group.

The local researchers will follow the steps that are presented in Qualitative Analysis Guide of Leuven (QUAGOL) to analyze the interview data of t_1 and t_2.[45] The central activity in QUAGOL is the constant comparison process: between researchers' interpretations and the actual participant story, as well as to check new ideas for their presence in previous interviews. QUAGOL divides data analysis into two phases.

The first phase suggests five steps of preparation, implying only paper and pencil work: 1) rereading of the transcript to get knowledge of what the interview is about, and highlighting the relevant fragments; 2) preparing a narrative summary by describing the key story lines close to participants' words; 3) schematically describing the key ideas of the interview in a conceptual scheme; 4) fitting test and adaptation of the conceptual scheme by going back to the transcript; 5) looking for common ideas/concepts across conceptual schemes as a first comparison with the other interviews.

The second phase comprises another five steps, representing the actual coding process: 6) creating a common code list, without hierarchical structure and based on the insights from the refined conceptual schemes; 7) coding of each significant passage in a qualitative software program, while critically reviewing and refining the introduced code list; 8) defining the concepts by looking across-cases and reviewing all citations connected to a concept; 9) integration of all concepts in one story line that answers the research question, followed by verification of this overarching framework against all interviews and interview schemes; 10) describing the results.

QUAGOL is not specifically developed for focus group analysis. Therefore, the group process will also be analyzed (i.e., how the conversation in the group is organized, developing and changing), as well as the differences within and between the groups will be taken into account.[25]

For the longitudinal analysis, the local teams will merge their data of t_1 and t_2, in which meaningful individual statements will be extracted and compared between time points. There

are no universal frameworks for analyzing longitudinal qualitative data. The local teams will be guided by the method described by Saldaña,[46 47] who developed a 16-question template including (i) framing questions to help focusing on the context and conditions that influence changes over time; (ii) descriptive questions to describe what kinds of changes occur; and (iii) analytic and interpretive questions to reach richer levels of analysis.

The meta-analysis

The findings of the three independently performed qualitative studies will be combined in a meta-analysis. Several methods for synthesizing qualitative studies have been developed,[49] with some studies also using a combination of methods.[50] The methodology developed for EQPERA is inspired by the principles of meta-ethnography as practiced by Britten et al.,[48] and by the coding process of QUAGOL (preparatory phase) that is based on grounded theory principles.[45] We combined key methodological elements of both approaches and summarized these into four steps: 1) describing each case; 2) recognizing differences, similarities and patterns across cases; 3) disentangling differences and similarities across cases; 4) fitting-test of the meta-interpretations.

The findings of the participating countries will be integrated by face to face interaction between the different local teams about their data in a consensus meeting. Local findings will be translated into English. The local teams of Belgium, The Netherlands and Sweden will at least consist of the principal investigator, a patient research partner and a rheumatologist to achieve an interdisciplinary view and prevent bias due to solo interpretations. A senior researcher of the EQPERA team (YH), who is not linked to the local teams and data, will moderate the meeting. Below, we describe our stepwise approach.

Step 1: Describing each case

In step 1, the aim is to understand the course and results of each study on its own. Each country will be viewed as a case, with each case reflecting the overarching story of all local participants.

The lead investigators (KE, IL, EM) will present their findings (including quotes) and conclusions, covering: (i) the name and description of the patient-preferred outcomes; (ii) when, where, why, and in which circumstances they were put forward by the participants; (iii) the change through time of the description participants attached to the different outcomes. Furthermore, they will report about study details, using three short reports:[45] 1) a descriptive report, including what is specific to the participants, the treatment strategy, the research group and the healthcare system; 2) a methodological report, including deviations from the protocol, such as modifications to the interview guide, recruitment problems and level of data saturation; 3) a content report, including the main message derived from the data. A standard form will be used to enhance uniformity across presentations. The three cases will be presented one by one without immediate cross-comparison. After the case description, local teams will have familiarized with the other team's data and the particular context in each country.

In preparation of step 2, each team will individually reflect upon the following questions to stimulate the across-case analysis: 'What do I hear in every case?', 'What do I only hear in our case?', 'What do I not hear in our case?'. Furthermore, they will write down the patient-preferred outcomes they identified (codes and concepts) on color-coded sticky notes, each country representing another color, to support visually the comparison of the local findings in step 2.

Step 2: Recognizing differences, similarities and patterns across cases

In step 2, the aim is to translate concepts from one study to another,[48] to determine how studies are related (i.e., what emerges across cases) and to recognize what is typical for each case.

An affinity diagram will be created to organize the multinational data.[51] The patient-preferred outcomes of the three studies will be displayed side by side (using the color-coded sticky notes). Their meaning will constantly be compared from one country to another in order to identify common and recurring, as well as conceptually different outcomes. We will start with a small set of concepts including the higher level concepts of each study, after which we will refine our first interpretations by discussing the lower-level codes.[45] During this process similar outcomes will be grouped if possible (by replacing the sticky notes), and we will look specifically for subtle differences between grouped outcomes.

After reaching consensus on similarities and differences, a 'saturation grid' will be completed in preparation of step 3. This is a technique used in qualitative studies to identify covered (sub)themes in each interview and decide on data saturation.[52] However, we will use a prespecified grid to identify the coverage of outcomes across the three studies.[48] Firstly, the grouped outcomes will be renamed. Secondly, all outcomes will be listed, meaning that each outcome of each local study is encompassed by one of the renamed outcomes in the grid. The main explanation of each outcome will be added. Thirdly, each country will represent a column and their sticky notes will be pasted next to the outcome in the grid that fits best the description on the sticky note. Hence, the empty cells will represent the outcomes that do not emerge across countries. By completing the grid, an overview will be developed of differences and similarities across cases.

Step 3: Disentangling differences and similarities across cases

In step 3, the aim is to explain the recognized differences and similarities by discussing why (or why not) certain outcomes emerge in a particular country or across countries.

Starting from the saturation grid (step 2), we will first go back to the methodological considerations and contextual features (step 1), before looking for possible cultural explanations. The group discussion will be an essential element in this step. For this reason we will view this discussion as a focus group, producing data that will be audio recorded and

transcribed verbatim. After step 3, we will have obtained consensus on cross-cultural variation in patient-preferred outcomes in early RA.

In preparation of step 4, the local teams will separately draft a written summary of the discussion immediately after the focus group and with special attention to how their case was similar or different to the other cases.

Step 4: Fitting-test of the meta-interpretations

In step 4, the aim is to verify the appropriateness of the interpretations made during the focus group (step 3) regarding similarities and differences across countries.

Each local team will perform a fitting-test of common and own meta-interpretations with their local data. The local researchers will go back to their data, after rereading the focus group transcript and with their written summary in mind. Two questions will need to be answered: (1) Do the contextual interpretations actually reflect what is seen in our data? Is certain context information overlooked in the focus group? (2) Can we support the meta-interpretations with quotes that typically describe the perspective of our participants? During conference call meetings, the meta-interpretations will be adapted, completed or refined based on the fitting-test in each country.[45]

Enhancing data quality and methodological rigor

Quality assurance

EQPERA is a large, multicountry, multicenter, multilingual, longitudinal qualitative research project. To yield sound results, several strategies are applied to ensure trustworthiness. These are: (i) recruitment of a qualified and motivated team; (ii) use of forward-backward translation procedures; (iii) uniformity in recruitment, conducting the interviews and focus groups, transcription of audio files, data coding, data storing, and reporting; (iv) interdisciplinary team analysis (v) training of local staff to the protocol and hands-on

guidance by the project leader. In Table 1, a detailed description is provided of the used strategies according to four quality criteria (i.e., credibility, dependability, confirmability, and transferability).[53 54]

Quality appraisal

As the findings of independently performed primary studies will be combined, quality is an important aspect to consider requiring a formal system for appraisal. The local teams will use a quality reporting tool to support a consistent use of methods and documentation across studies. Johnson et al. provided a useful template,[51] based on the consolidated criteria for reporting qualitative research,[55] and the quality criteria suggested by Mays and colleagues.[56] In EQPERA, several items were added regarding data management and quality appraisal in qualitative research.[32 44 57-59] Our tool comprises 50 items regarding four domains: 1) research team and reflexivity; 2) study design; 3) analysis and findings; 4) data management strategies (Supplementary file 2).

Table 1 Applied quality assurance strategies in EQPERA, described for each research stage, according to Lincoln and Guba's framework for evaluating trustworthiness.[53]

Research stage	Employed strategies for supporting trustworthiness	Assessing quality: (1) How congruent are the findings with reality? (2) Would the research findings be the same if the study would be replicated in essentially the same way? (3) Do the research findings emerge from the context and the respondents and not solely from the minds of the researchers? (4) Can the research be applied in other contexts?			
		(1) **Credibility** (internal validity)	(2) **Dependability** (reliability)	(3) **Confirmability** (objectivity)	(4) **Transferability** (generalizability)
Study design	- developed around the patient perspective and in collaboration with patient representatives	●			
	- triangulation of interview methods	●			
	- addressing potential drop-out at t_2	●			
Establishment of the EQPERA team	- recruitment of a qualified team, with a passion for the topic: ○ skilled in conducting qualitative research ○ familiar with the patient population ○ including patient research partners	●	●	●	●
Protocol development and implementation	- a clear understanding of the overall project objective by all co-workers		●		●
	- use of detailed study protocol, including a methods and analysis plan, an interview protocol, a data management plan, and templates	●	●		
	- training of local staff to the protocol (project leader) prior to patient recruitment of t_1 and data collection of t_2	●	●		
	- monitoring of local progress and hands-on guidance (project leader)		●		●
	- documentation of local decisions (use of a research journal): ○ when, why, what changes, and who was involved in making this decision (e.g., modifications to the interview guide) ○ personal and/or practical comments	●	●	●	●
Sampling and recruitment	- purposive sampling informed by simultaneous data collection and analysis	●			●
	- multicountry and multicenter recruitment	●			●

	-	applying a definition for data saturation	•				•
	-	use of an enrollment template to support heterogeneity in the local samples and systematically keep records		•			
Data collection	-	semi-structured interview guides:	•	•	•		
		○ the same main interview questions in every country					
		○ collaboration with patient research partners to support clarity and understandability of interview questions					
		○ forward-backward translation					
		○ the same key points in the introduction					
	-	use of a data collection template and at least 2 audio recorders/interview to prevent missing data		•			
	-	verbatim transcription of the audio-recorded data		•			
	-	use of transcription guidelines		•			
	-	neutral and convenient interview location	•				
t_1	-	maximum 2 interviewers/country		•			
	-	maximum 2 interviews/day per interviewer to avoid interview burden and take time to reflect upon each interview					
t_2	-	the interviewer of t_1 is moderator of the focus groups		•			
	-	1 moderator/country and the same observer(s) for each focus group					
Data analysis	-	independent coding by at least 2 researchers	•		•		
Local level	-	data collection and analysis in parallel	•				
	-	constant comparison method	•				
	-	use of field notes	•		•		
	-	reflection after each interview/focus group: descriptive, content and methodological report	•		•		
	-	use of a qualitative software program		•			
	-	peer debriefings: more frequently early in de coding process	•		•		
	-	looking at data from multiple perspectives, including collaboration with patient researchers to help understand and describe the data	•		•		
	-	uniform procedure across countries based on established frameworks		•			•
International level	-	translation of the local findings and conclusions using a structured forward-backward procedure, supported by professional translators		•			
Reporting	-	use of guidelines for reporting the synthesis of qualitative research[60]					•

t_1: time point 1= three to six months after start of the initial treatment for early rheumatoid arthritis; t_2: time point 2= at least one year after start of the initial treatment for early rheumatoid arthritis.

ETHICS AND DISSEMINATION

Ethical considerations

EQPERA will apply the principles established in the Declaration of Helsinki.[61] Participants will provide written informed consent before data collection of t_1 and t_2. Only coded and interpreted data will be shared between the local teams for the meta-analysis. Ethics approval for the original studies were granted by the responsible institutional review boards.

Dissemination of results

Every country will prepare a publication on their national findings. Two EQPERA main papers are foreseen: 1) the present paper describes the rationale, design and methods of EQPERA; 2) a publication on the results of the meta-analysis. Next to peer-reviewed publications, we will also disseminate our findings in (inter)national research presentations, and also patient organizations will be updated about the study findings.

CONCLUSION

In EQPERA, the aim is to confirm the Belgian findings on patient-preferred outcomes in early RA in a European context, and provide a study protocol that has the potential to offer a methodological framework for further exploration of transferability in other contexts. Ultimately, study findings will be used to inform and optimize current care initiatives in early RA in order to address the unmet need of patient-centered care in RA.

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Author contributions

KE and RW had the main idea of the study. KE, AB, AG, IL, EM, JV, RW and YH contributed to the design of the study. KE, YH and RW drafted the manuscript. KE, AB, AG, IL, EM, JV, RW and YH were involved in the editing of the manuscript. All authors read and approved the final version of the manuscript. Apart from the first and last author, the other authors are listed in alphabetical order.

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Competing interest statement

None declared.

Patient consent

Will be obtained.

Ethics approval

The Netherlands: the Medical Research Ethical Committee of Arnhem-Nijmegen waived ethical approval since the medical research involving human subjects act did not apply to this study; Sweden: ethical approval was obtained from the Regional Ethical Review Board at Lund University, Sweden; Belgium: ethical approval was obtained from the Human Research Ethics Committee of the University Hospitals Leuven.

Data sharing statement

Not applicable.

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Figure 1 Overview of the European, longitudinal, multimethod qualitative research design. *t*: time point.

Figure 2 Forward-backward translation framework applied to translate the interview questions and procedures.

Figure 3: Simplified outline of the used frameworks,[25 45-48] and the included steps in the local analyses and the meta-analysis.

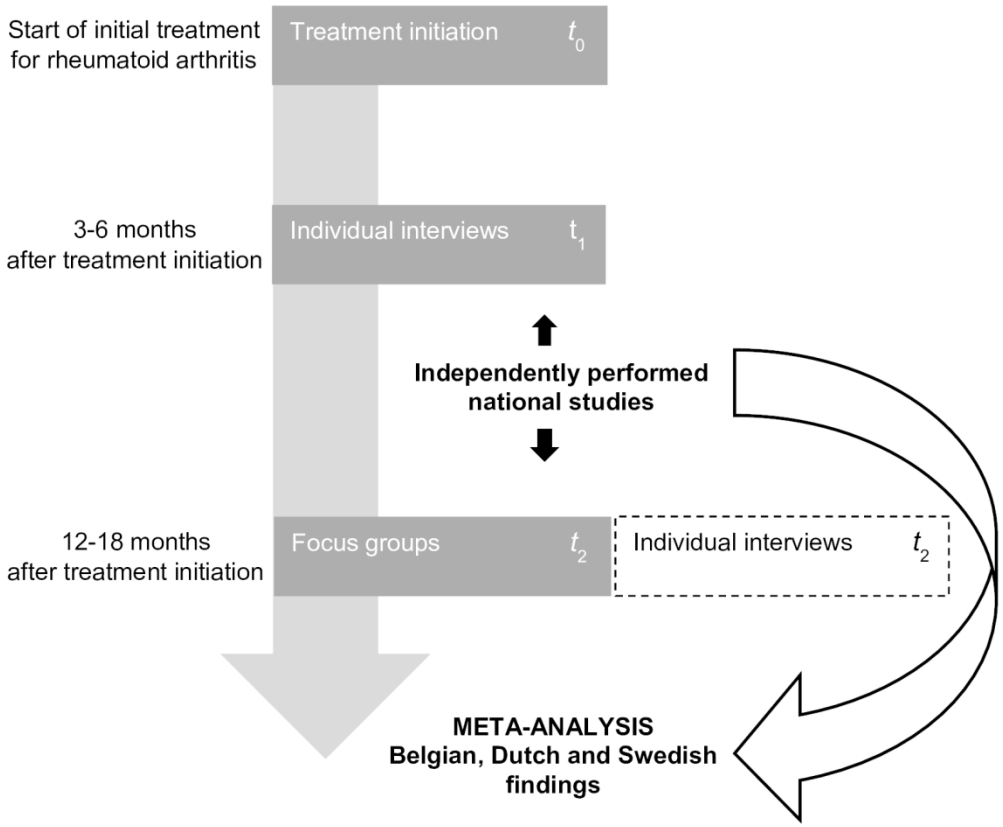

Figure 1 Overview of the European, longitudinal, multimethod qualitative research design. *t*: time point.

143x118mm (300 x 300 DPI)

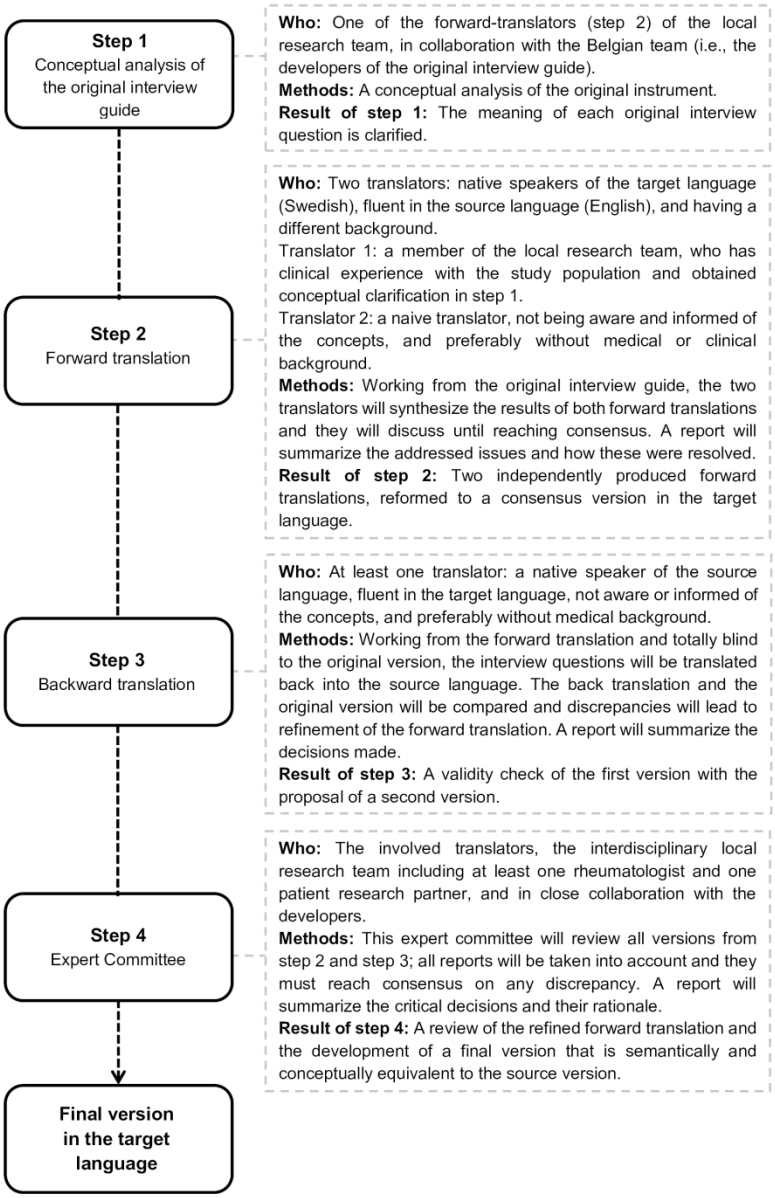

Figure 2 Forward-backward translation framework applied to translate the interview questions and procedures.

163x249mm (300 x 300 DPI)

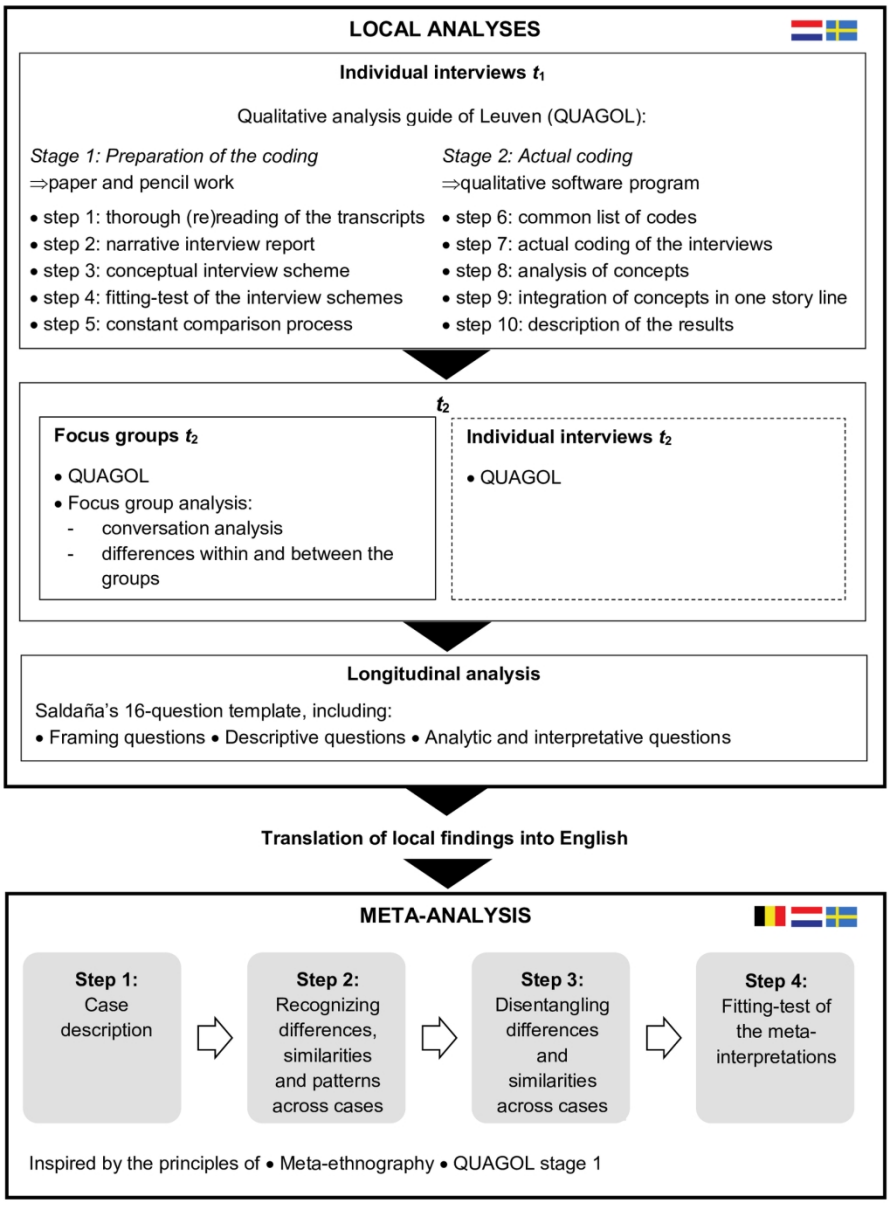

Figure 3: Simplified outline of the used frameworks,[25 45-48] and the included steps in the local analyses and the meta-analysis.

146x197mm (300 x 300 DPI)

Supplementary file 1 Main interview questions and procedures for the individual interviews (t_1 and t_2) and focus groups (t_2). Most aspects of the methods of t_1 and t_2 have been used in the study of Van der Elst et al.

Individual interviews (t_1 and t_2) and focus groups (t_2)	**Context questions**
	- What type of treatment are you currently receiving? - Have there been any changes in your treatment plan? If so, why and what type of changes?
Individual interviews at t_1	**Interview questions and procedures**
	Preparatory phase (5 to 10 minutes) To set the scene for the interview, participants were asked to write down as many keywords as possible describing: - the impact of RA on their life - which outcomes of their illness and treatment they considered most important.
	Start of the interview The interviews began by discussing participants' written answers to those two questions. Participants were asked to elaborate on their keywords. - Can you tell me how RA affects your daily life? - Which outcomes of your illness and antirheumatic treatment are important to you at this moment?
	Proceeding of the interview The order of the other interview questions was determined by the participants' answers during the interview: - How has the treatment been working for you so far? - How do you decide whether or not your treatment is working? - What made you decide to start treatment? - What were your expectations of your antirheumatic treatment at the start of treatment? - To what extent do the expectations you had at the start of your treatment match your current expectations?
	Three questions were added after the first interviews: Other patients talked about taking less medication, returning to a normal life*, feeling better*. Is this something you recognize? What do you feel about that?

	Probing questions: Could you tell me more about that? Could you give an example?
	End of the individual interview: Is there anything else you would like to add?
Focus groups at t_2	
	Round 1: Preparatory phase (5 to 10 minutes) The moderator introduced the phenomenon of interest, after which each group member was asked to independently prepare answers to the question below by writing down as many keywords as possible. Each answer was written on a separate Post-it®. - Which outcomes of your illness and antirheumatic treatment are important to you at this moment? Next, participants were asked to try to order their Post-its® on a vertical scale, from most important (top) to least important (bottom). Participants were simultaneously asked to think about the following questions: - What important treatment results have already been achieved? - At present, is there anything you would like to change or improve regarding your disease or treatment?
	Round 2-step 1: Round-robin listing All group members were asked to reveal and clarify, one by one, their personally preferred outcomes in order of importance. Meanwhile, the observer wrote these outcomes on a flipchart in front of the group. - Who would like to share your personally valued outcomes with the group, in order of importance? - Could you please clarify why these outcomes of your disease and antirheumatic treatment are important to you? - Why did you designate that specific outcome to be the most important? - Is there anything else you would like to add?
	Round 2-step 2: Developing a group list of patient-preferred outcomes The group was asked to generate a consensus list by reviewing and merging all recorded outcomes and agreeing on the name and properties of each outcome on the list. - Could any of the individual expectations be grouped? - Who would like to suggest a name and meaning for this outcome?

- Do you think all the important outcomes are mentioned on the group list? Is there anything else you would like to add?

Round 2-step 3: Eliciting personal preferred outcomes

Starting from the consensus list of patient-preferred outcomes that resulted in step 2, each group member was asked to independently try to select his or her five top outcomes from this list, using the Post-it® ordering scheme.

Round 2-step 4: Eliciting preferred outcomes in the actual stage of RA

The group was then asked to discuss a collective top 5 outcomes and to consider influencing factors.

- Looking at the group list, what outcome would you order as most important?
- What outcome would you order second…fifth?
- Can you tell us why this outcome is either important to you or not?

End of round 2: That is it for the second round. Is there anything else to add?

Round 3: Exploring the view of participants on the evolution of their patient-preferred outcomes over the past year

The focus groups ended by exploring the participants' views on potential changes in personally preferred outcomes over time: During the individual interview of last year, you were asked for your preferred illness and treatment outcomes. In the meantime, you have gained more experience with your disease and treatment and the critical disease stage has passed.

- Do you feel that other results are now more important to you than the ones you identified at the start or during your interview last year?
- Could you explain why this has or has not changed?
- Are there outcomes that are now more, less or no longer important to you?
- Why do you think that these are now more or less, or no longer important than a year ago, or are no longer important? What may have caused this change in importance?
- Do you have an example of an outcome that has changed in importance compared to that outcome in the early disease stage? Why do you think this has changed? Could you clarify this in more detail?

	- In general you mention (more or less) similar/different outcomes of importance compared to last year (in the early disease stage). What is your opinion on this observation?
	End of round 3: This is the end of the third round. Is there anything else to add?
	Probing sub-questions: Is this outcome also important or not important to other group members? Are there any suggestions from other group members? Is there anyone who has a different opinion on the matter? Is it difficult for you to share your opinion on this? Who agrees or disagrees and why? Does everyone agree? Who would like to add something?
	End of the focus group - What is your general conclusion about today's focus group on preferred and important outcomes of disease and treatment in the actual disease stage? - To summarize, you talked about […]. - Do you agree with this summary of today's focus group?
Individual interviews at t_2	
	Preparatory phase (5 to 10 minutes) Please, consider the next 5 to 10 minutes the question below by writing down as many keywords as possible. The interviews will begin by discussing your written answers to this question: - Which outcomes of your illness and antirheumatic treatment are important to you at this moment?
	Start of the interview - Can you tell me what you have written down? So, which outcomes of your illness and antirheumatic treatment are important to you at this moment?
	Proceeding of the interview **Exploring patient-preferred outcomes** - How has the treatment been working for you so far? - To what extent do the expectations you had at the start of your treatment match your current expectations?
	Exploring the view of participants on the evolution of their preferred outcomes over the past year Last year, during the interview, you mentioned that the following outcomes of your treatment were important: ..... (t_1 keywords of the t_2 participant).

	- Do you feel that other results are now more important to you than the ones you identified at the start or during your interview last year? Could you explain why this has or has not changed? - Are there outcomes that are now more, less or no longer important to you? - Why do you think that these are now more or less, or no longer important than a year ago, or are no longer important? What may have caused this change in importance? - Do you have an example of an outcome that has changed in importance compared to that outcome in the early disease stage? Why do you think this has changed? Could you clarify this in more detail?
	Patient-preferred outcomes compared to the focus groups at t_2 During the focus groups the following 5 treatment outcomes were found to be most important: 1) preferred outcome; 2) preferred outcome; 3) preferred outcome; 4) preferred outcome; 5) preferred outcomes. - I wonder if you recognize yourself in this? Could you explain why this is or is not the case?
	End of the individual interview: Is there anything else you would like to add?

t_1: time point 1= three to six months after start of the initial treatment for early rheumatoid arthritis.

t_2: time point 2= at least one year after start of the initial treatment for early rheumatoid arthritis.

Van der Elst K, Meyfroidt S, De Cock D, et al. Unraveling Patient-Preferred Health and Treatment Outcomes in Early Rheumatoid Arthritis: A Longitudinal Qualitative Study. Arthritis Care Res (Hoboken) 2016;68(9):1278-87.

Supplementary file 2 EQPERA data quality assurance reporting tool

Domain 1: Research team and reflexivity	
Item	**Guide questions/description**
Researcher characteristics	
1. Interviewer/moderator/observer	Who conducted the interviews/ focus groups? (who observed the focus groups?) *Maximum 2 interviewers at t_1 and t_2 /country and maximum 1 moderator at t_2/country; preferably the same observer(s) for each focus group*
2. Credentials / background	What were the researcher's credentials? (e.g., PhD, RN)
3. Occupation	What were the researcher's occupation at the time of the study?
4. Gender	Was the researcher male or female?
5. Experience and training	What experience or training did the researcher have?
Relationship with participants	
6. Relationship established	Was a relationship established prior to study commencements? *(e.g., health professional)*
7. Participant knowledge of the interviewer	What did the participant know about the researcher? *(e.g., personal goals, reasons for doing the research)*
8. Interviewer characteristics	What characteristics were reported about the interviewer/moderator/observer? *(e.g., bias, assumptions, reasons and interest in the research topic)*
Domain 2: Study design (a longitudinal, qualitative, explorative study)	
Participant selection	
9. Sampling	- How were participants selected (purposive) - Mono or multicenter sampling? - Type of recruitment center(s)? (*i.e., academic hospital, general hospital or private practice?)*
10. Method of approach	- Who invited the participants? - How were participants approached? *(e.g., face to face, telephone, mail, email)*
11. Sample size	How many participants were in the study? - at t_1: number of individual interviews - at t_2: number of participants per focus group / number of individual interviews

12. Non-participation	- How many eligible patients could potentially be recruited?
	- How many people were approached and how many of them refused to participate or dropped out?
	- Reasons? (if shared)
	  ○ Not interested in participation (refusal)
	  ○ Drop out (type 1): in case t_1 interview was scheduled and cancelled
	  ○ Not interested in participation at t_2 (drop out, type 2)
	  ○ Not interested in participation in a focus group, but willing to participate in an individual interview instead at t_2
	  ○ Drop out (type 3): in case t_2 interview was scheduled and cancelled

Setting	
13. Setting of data collection	Where was the data collected?
14. Presence of non-participants	Was anyone else present besides the participant and researchers?
15. Description of sample	What are the important characteristics of the sample? *(e.g., demographic data)*
Data collection	
16. Interview guide	- Were questions, prompts, guides provided by the authors? - Was the interview guide pilot tested? - Is it being made available?
17. Focus group guide	- Were questions, prompts, guides provided by the authors? - Was the interview guide pilot tested? - Is it being made available?
18. Audio / visual recording	Did the research use audio or visual recording to collect the data?
19. Data collection method	- How were the data collected? (t_2: focus group or individual interview?) - Were repeat interviews carried out at t_2?
20. Field notes	- Were field notes made during and/ or after the interview or focus group? ⇒ if yes, please record them in the descriptive or methodological interview report.

	- Were short reports prepared after each interview?
21. Duration	What was the duration of the interviews or focus groups?
22. Data saturation	- Was data saturation discussed? - After how many interviews was data saturation reached? *(Definition in EQPERA: "if the last 3 interviews do not provide new information, insights or additional understanding to accomplish the study aims")*
Domain 3: Analysis and findings	
Data analysis	
23. Number of data coders	- How many data coders coded the data? - Who coded the data?
24. Independent coding	Was the analysis repeated by more than one researcher to ensure reliability?
25. Data analysis method	How were themes and concepts identified from the data? *(e.g., Were themes identified in advance (framework-based) or derived from the data (data-driven)?)*
26. Patient research partners	Did patient research partners provide feedback on the findings, and in which part(s) of the data analysis were they involved?
27. Software	What software was used to manage the data?
Reporting	
28. Quotations presented	- Were participant quotations presented to illustrate the themes/findings? - Was each quote identified? *(e.g., participant number, gender, age)*
29. Data and findings consistent	Was there consistency between the data presented and the findings?
30. Clarity of themes	Were themes clearly presented in the findings?
Domain 4: Data management strategies	
Data recording	
31. Recording changes and decisions	Were changes to the interview guide, the evolution in themes, deviations from the research protocol, and major local project decisions carefully documented along with the rationale for change? ⇒ *to recall decisions* ⇒ *the use of a research log book is recommended*

32. Recording interview data	Did you record the data with at least 2 audio recorders? ⇒ *to prevent missing data*
Data storing	
33. Routinely storing of data	Was the data *(e.g., audio files, transcripts, interview reports and field notes, patient-reported and clinical data, informed consents)* or the project database routinely submitted to a central data repository or a secured cloud storage system? ⇒ *to avoid missing data and to easily manage large amounts of data like in qualitative research* ⇒ *a uniform transcript header and file name could facilitate data storing (e.g., T1.number of interview.ddmmyyyy.initials of interviewer)*
Data check	
34. Internal audit	Could the evidence (field notes, interview transcripts, recordings, reasons for interview guide adaptations,…) be inspected by others?
35. Preventing missing data	Did the principal investigator routinely check for missing data?
Data collection	
36. Recruitment flow	Was the recruitment flow carefully documented? ⇒ *the use a research log book (enrollment spread sheet) is suggested*
37. Templates	Did you check the data collection templates and the Excel spread sheet?
38. Local interview guide	Translation/cultural adaptation interview guide: ○ Did you use the proposed framework to translate the interview guide into the source language? ○ Were cultural adaptations needed? ⇒ *please record these in your research log book, together with the timing and the reason for adjustment*
39. Avoiding and handling the presence of a third person	⇒ *focus of attention during interview scheduling: Was the purpose of a one to one interview mentioned to the participant?* ⇒ *if someone else was present, did this affect the interview/data collection? Please reflect on this in the descriptive interview report.*

40. Introducing the interview	Did you prepare and practice the interview introduction? ⇒ *to maximize the interview return* ⇒ *key words: welcoming the participant; introducing yourself; clarifying the purpose and importance of research, the importance of participant contribution, expectations regarding the participant (e.g., no good or wrong answers), role of the interviewer/moderator/observer, (t_2: "rules" regarding group discussion), ethical aspects; "Any questions?"; mobile phone on silent mode)*
41. Interview burden	It is recommended to conduct 1 individual interview/day, with a maximum of 2 interviews/day ⇒ *to avoid interview burden and to have sufficient time to reflect on each interview*
42. Interview reports	Did you write for each interview/focus group 3 short reports? *(i.e., content report, descriptive report, methodological report)*
43. Iterative process	Did you use an iterative process of data collection and analysis? ⇒ *to support data saturation*
Data analysis	
44. Analysis guide	Did you use Qualitative Analysis Guide of Leuven (QUAGOL) to guide your data analysis? Did you use Saldaña's guiding questions for analyzing the longitudinal data)
45. Peer debriefings	Were regular peer debriefings held? ⇒ *time for reflection (in team): to discuss the interview return, the development of new themes and to question and confirm saturation of themes* ⇒ *early in de coding and interviewing process, more frequent meetings are suggested* ⇒ *please make a short report of each debriefing to recall discussions*
46. Team analysis	Was looked at the data in team (from different perspectives looking at the data)
Transcription	
47. Transcription guidelines	Who transcribed the data? ⇒ *>1 person: did you apply a uniform transcription method? (e.g., agreements about the level of details, to obtain confidentially, to reproduce the exact words spoken)*

	⇒ *external transcriber: was the interview transcript reviewed by the interviewer on data quality and accuracy of transcribing? How did you approach this quality check?*
Team approach	
48. Patient research partners	What was the exact role of the patient research partners in the study
49. Interdisciplinary team	Who joined the interdisciplinary team, and what was their contribution?
Initiation session	
50. Project initiation	Did the local research team (at least the principal investigator) followed the initiation session lead by the project leader at t_1 and at t_2?

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European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA): rationale, design and methods of a multinational, multicenter, multilingual, longitudinal qualitative study

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European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA): rationale, design and methods of a multinational, multicenter, multilingual, longitudinal qualitative study

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ABSTRACT

Introduction: Including the patient perspective is important to achieve optimal outcomes in the treatment of rheumatoid arthritis (RA). Ample qualitative studies exist on patient outcomes in RA. A Belgian study recently unraveled what matters most to patients throughout the overwhelming and rapidly evolving early stage of RA. The present study, European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA) was created to contribute to a more universal understanding of patient-preferred health and treatment outcomes by integrating the perspectives of patients with early RA from three European countries.

Methods and analysis: In EQPERA, a qualitative, explorative, longitudinal study will be implemented in The Netherlands and Sweden, parallel to the methods applied in the previously conducted Belgian study. In each country, a purposive sample of patients with early RA will be individually interviewed 3-6 months after start of the initial RA treatment and subsequently, the same participants will be invited to take part in a focus group 12-18 months after RA treatment initiation. Data collection and analysis will be independently conducted by the local research teams in their native language. A meta-analysis of the local findings will be performed to explore and describe similarities, differences and patterns across countries.

Ethics and dissemination: Ethics approval was granted by the responsible local ethics committees. EQPERA follows the recommendations of the Declaration of Helsinki. Two main papers are foreseen (apart from the data reporting on the local findings) for peer-reviewed publication.

Key words: Rheumatoid Arthritis, Qualitative research, Longitudinal study, Patient Preference

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The specific nature of the study, in which qualitative studies are carried out in different countries and languages using a uniform methodology, is novel, and we report in a transparent way about our approach and challenges.
- As no formal meta-analysis method was present in literature applicable to our study, we developed a method based on established techniques for the synthesis of qualitative research, which can guide other researchers interested in conducting this type of research.
- Several quality enhancing strategies are applied to yield sound results in this multinational, multilingual, longitudinal qualitative study.
- The participating countries might have rather similar cultural views and healthcare systems, which would strengthen the Belgian findings, however, the study protocol offers a methodological framework for research in different parts of the world.

INTRODUCTION

In rheumatoid arthritis (RA), the outcome landscape dramatically changed over the past decades. RA is the most prevalent chronic, auto-immune inflammatory joint disease. It was typically described as an inevitably progressive disease with a destructive and disabling natural course. The continuous growth in effective pharmacological treatments contributed to this change, but the introduction of early therapy was one of the main drivers of transformed health outcomes of patients with RA.[1] Nowadays, remission or at least low disease activity have become realistic treatment targets for a notable proportion of the population.[2]

Nevertheless, the burden of disease and unmet needs remain considerable.[3 4] For example, most of the patients are at working age upon diagnosis, but work disability rates remain high.[5] Furthermore, patients with RA indicated the need for greater emotional support, and greater psychological support to manage the impact of disease on domains such as pain, fatigue, work and leisure.[6 7] Hence, it seems that patient preferences are not sufficiently understood and met by health professionals. In a recent report, patient-centered care was identified as a recurrent unmet need across rheumatic diseases, including RA.[8] Patient-centered care can be translated as care that is guided by the values and preferences of the patients,[9] with patient preferences referring to the perspective, beliefs and expectations of patients regarding their health and life.[10] As patient-centeredness is acknowledged as one of the key dimensions of high-quality care,[11] integrating the patient perspective in outcome assessment is increasingly advocated to achieve optimal outcomes in the treatment of RA.[12 13]

Qualitative studies shed light on the different views that patients with RA have on outcome compared to health professionals. These studies revealed the importance of fatigue and independence, among others,[14-16] to consider in daily practice on top of the traditional measures of disease activity, i.e., the swelling of joints and laboratory parameters of inflammation. Remarkably, limited attention has been given to the perspective of recently

diagnosed patients. The early disease stage is probably the most daunting period for patients, indicating specific needs and preferences.[17 18] The Belgian qualitative study of Van der Elst et al. provided new insights into patient-preferred outcomes in early RA, concluding that returning to 'normality' as soon as possible was the core preferred outcome, which related to aspects of disease control and participation, physical and mental aspects.[19] However, understanding is lacking about the transferability of these local findings to other settings and cultures.

Despite recommendations for RA management, literature shows that there are differences in how rheumatology services are viewed and practiced across countries.[20 21] These differences may be attributable to characteristics of the national healthcare systems, local customs, practices and values. Such cultural differences may consequently influence how patients evaluate their disease. For example, the survey study of Van Tuyl et al. demonstrated that the country in which patients were sampled resulted in slightly different key domains on how they perceived remission of disease.[22] Hifinger et al. showed that country of residence had an important influence on how patients with RA experienced fatigue.[23] It can thus be questioned whether patients in other countries would bring out other preferred outcomes.

To examine the transferability of the Belgian findings and to contribute to a more universal understanding of patient-preferred outcomes, we initiated the EQPERA consortium. EQPERA is the acronym for European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis. It is a multicenter, multilingual, longitudinal qualitative study across Belgium, The Netherlands and Sweden. The present paper reports about the international study protocol, based on the Belgian study procedures.

Objectives

The overall research objective in EQPERA is to explore how local context influences patient-preferred health and treatment outcomes throughout the early disease course by integrating the perspectives of patients with early RA from three European countries.

The objective is twofold:

(i) to describe patient-preferred outcomes in early RA and how they change throughout the early disease course (national objective);

(ii) to identify differences, similarities and patterns in patient-preferred outcomes across the three European countries (international objective).

METHODS AND ANALYSIS

The Belgian study was conducted during 2012-2013.[19] Based on the lessons learned and after multiple discussion rounds with the EQPERA steering group, an improved research protocol was written with the aim to implement a protocol as similar as possible in the other countries. Start of patient inclusion was 2016 in The Netherlands and 2017 in Sweden. We intend to publish the final results by the end of 2019.

Study design

A qualitative, explorative, longitudinal research design will be applied within a European context. As we study a research domain still lacking evidence, the use of qualitative methods is justified because we will learn from the rich descriptions of participants being shaped in their local contexts.[24 25] Longitudinal designs are relevant for studying complex phenomena and are specifically applicable in the context of a recent diagnosis since patients' perceptions and expectations may change during the overwhelming and rapidly evolving early disease stage. Previous research also suggests that the way patients experience and evaluate their disease can differ depending on disease duration.[15 26 27]

Patients with early RA will be invited to participate at two time points (Figure 1). At t_1, participants will be individually interviewed 3-6 months after they have started their initial treatment for RA. At t_2, participants will be invited to take part in a focus group 12-18 months after RA treatment initiation. To address a potential dropout of participants at t_2, those who decline to participate in a focus group will be invited for a repeated individual interview instead. However, the preferred interview method at t_2 remains the focus group method to align with the original design of the Belgian study.

The reason for selecting different interview methods at t_1 and t_2 is based on the input of patient research partners and aims to match with patient preference in the context of a recent diagnosis. At t_1, the individual interview method is chosen because adjusting to a recent diagnosis can be seen as a primarily individual matter. Consequently, sharing personal experiences and opinions in a group setting can be too confronting at that stage of disease. A timeframe of 3-6 months after initiation of the initial RA treatment is chosen to not interfere with the diagnostic and therapeutic procedures, however, still including patients' earliest views on preferred outcomes. Furthermore, it is assumed that a few months of experience with the disease and treatment would help patients to communicate more easily about their outcome preferences.

At t_2, focus groups are chosen above the individual interview method for two reasons. Firstly, compared to the first interview moment, participants may probably feel more comfortable in a group setting, because of a grown disease perspective and the potential interaction with other patients (e.g., in the waiting room) by then. Secondly, group interactions potentially help participants to remember significant events and bring out personal thoughts, which in turn may result in more and diverse data.[25 28] It is reasoned that after 12-18 months of treatment experience, participants have had sufficient time to develop their view on the disease, with perhaps an observable change in their preferences accordingly.

Research context

EQPERA involves three countries in Northwest Europe: Belgium, The Netherlands and Sweden. These countries have a comparable organized healthcare system including a comprehensive social security system, however, differences exist in for example their reimbursement and referral system.

Participants will receive usual care according to local standards. Across countries, a comparable early RA management is implemented in respect of current international guidelines:[29 30] patients should be treated (i) early: as soon as the diagnosis is made; (ii) intensively, with methotrexate in the first treatment if possible; (iii) to target: treatment adjustments according to a predefined target of sustained remission or low disease activity. In addition, there is a common culture across the countries regarding interdisciplinary team care as key in disease management, but diversity can be expected concerning implementation aspects. For example, it has been shown that there is a wide variation in the role of nurses in the management of patients with chronic inflammatory arthritis[20], and in the composition of rheumatology multidisciplinary teams.[31]

In each country, an early RA cohort is available, the local teams include experienced qualitative researchers with a good command of the English language, and funding possibilities are available to work out their national project. The EQPERA steering group consists of team members with different disciplinary backgrounds: nurses (KE, IL, EM, YH), physiotherapists (AB, AG), a psychologist (JV), a patient representative (AG) and a rheumatologist (RW).

Level of collaboration between countries

Individual projects will be conducted in each country. The studies in Sweden and The Netherlands will be led by the local principal investigator (IL and EM, respectively) and

supervised by the EQPERA project leader (KE), who designed and completed the Belgian qualitative study.[19]

Considering qualitative studies, potential language issues can be approached in two ways: either translate the transcripts and do the analysis in one place, or have the analysis done at each location and combine the data afterwards. After consideration, the project team decided that (i) data will be collected in the local settings by the local teams in their native language; (ii) interviews will be transcribed in the original language and the transcripts will be analyzed by the local teams; (iii) only the results of the local analysis (i.e., interpreted data) will be combined for EQPERA purposes, and this after ending the analysis procedures and writing up the findings and conclusions in every country.

Original data will thus not be reviewed by the other teams (Figure 1). Centralizing data would mean translation of local transcripts to the common language in EQPERA (English). Translation holds the risk of losing the real meaning of words,[32] and would be expensive and time consuming because of the mountains of words that will be produced in every country. Above and beyond translation issues, we assumed that local data should ideally be analyzed by the people who are familiar with the local culture and context in order to get the most appropriate interpretations.

Collaboration with patient research partners

As EQPERA aims to capture the patient perspective, the project would benefit from active collaboration with patient representatives, or those who have the lived experience of RA. Following the recommendations of the European League Against Rheumatism for the inclusion of patient representatives in scientific projects,[33] each local team will preferably collaborate with two patient research partners.

The local principal investigators will be responsibility for coordinating this research partnership, being guided by the FIRST (i.e., Facilitate, Identify, Respect, Support and Train) framework of Hewlett and colleagues.[34] The exact level of the patient researchers' contribution will depend on local agreements (feasibility). In general, they will help by reflecting on the methods, formulating clear and understandable interview questions, interpreting and explaining data, and providing feedback on the readability of the patient information leaflet and informed consent form.

Participants

Eligible patients will have to meet the following inclusion criteria: (i) confirmed diagnosis of RA, in accordance with the American College of Rheumatology/European League Against Rheumatism 2010 criteria;[35] (ii) time between diagnosis and start of RA treatment of less or equal than 1 year; (iii) minimum age of 18 years; (iv) speak, read and write the local language; (v) started the initial RA treatment 3-6 months ago.

Sampling

Every country will strive to include a broad range of perspectives in their sample. To ensure this variation, participants will be purposively sampled based on their (i) age/life phase; (ii) gender; and (iii) treatment progress/treatment experience. Moreover, every country will apply a multicenter recruitment to account for possible variation in region.

Sampling in qualitative research corresponds to the assumption that collected data is of sufficient depth, i.e., representing the various views and opinions of the population with no added value of including more participants for answering the research question.[36 37] As there is no standardized definition of data saturation, we decided that data collection can be stopped if three consecutive interviews do not result in new themes or additional understanding (local team decision).

At t_1, we estimate that around 20 participants in every country will be needed to reach data saturation. At t_2, the sample sizes will foremost depend on the interest and willingness of participants to participate again. We aim for 4-8 participants in each focus group, which seems an appropriate number to keep the discussions manageable and stimulate contribution of every group member.[36 38] If possible, patient characteristics will be taken into account to create a mix of perspectives in the groups.

Recruitment

In each country, patients are recruited from multiple centers across different geographic locations, including academic and non-academic rheumatology centers. In Belgium, patients were sampled from nine centers across Flanders. The participating centers in The Netherlands are located in Nijmegen and Woerden, and in Sweden these are located in Lund, Malmö and Halmstad. A recruitment template will help the local teams to consider the main variables for creating heterogeneity in their samples.

Data collection

The interview guides

The semi-structured interview guides include pre-defined topics, with open-ended questions, and probing questions to reach a higher level of detail. All questions relate to the central interview question: 'Which outcomes of your illness and antirheumatic treatment are important to you at this moment?'. In every country, the interview guides will have the same content at start, and main questions will be fixed across countries. Data collection and analysis will be performed simultaneously, making it possible to adapt the interview guides if necessary to increase participants' understanding or to reach data saturation (local team decision). If adaptations are needed, these will be documented in the local research journal.

The content of the interview guides is inspired by previous qualitative studies on outcomes from the patient perspective.[14 16 39] In EQPERA, Dutch and Swedish versions of the Belgian interview guides (Flemish language) will be prepared by the local teams. Given similarities between the Flemish and Dutch language, minor adaptations will be applied after discussion and consensus with the Belgian team. Forward and backward translation will be used to prepare translations to English and Swedish (Figure 2).[40 41] The main interview questions and the interview procedures are elucidated in Supplementary file 1.

Individual interviews (t_1)

At t_1, individual, face-to-face interviews will be conducted by maximum 2 interviewers per country, who are not involved in participants' clinical care. As the patient research partners noted that patients are in general not used to talk about outcome preferences, they will be asked to prepare written key words regarding the central interview question. The interviewer will start by elaborating on these key words. It is anticipated that interviews will last no longer than 60 minutes.

Focus groups (t_2)

Focus groups will be facilitated by one of the interviewers of t_1 in assistance of at least one participating observer. The focus groups will consist of three rounds: Round 1: preparatory phase; Round 2: (i) round-robin listing, (ii) developing a group list of patient-preferred outcomes, (iii) eliciting personal preferred outcomes, (iv) eliciting preferred outcomes in the actual stage of RA; Round 3: exploring the view of participants on the evolution of their patient preferred outcomes over the past year. The second round of the focus groups was inspired by the Nominal Group Technique methodology (NGT).[42] NGT is a consensus method that creates two types of data: (i) written ideas and prioritization, and (ii) the wider discussion, generating and clarifying ideas.[43] Our interest for using a prioritizing methodology is firstly, to create discussion between participants about a potential inconvenient topic; and

secondly, to capture participants' underlying reasoning regarding preferences in outcomes. It is anticipated that focus groups will last about 60 minutes.

Individual interviews *(t_2)*

If necessary, the interviewer of t_1 will conduct individual interviews at t_2. The interview guide for these interviews is slightly adapted compared to t_1 in order to question participants about their view on changes in their preferred outcomes over time.

Procedures at both time points

Both individual interviews and focus groups will be held at a neutral and convenient location, and will be audio-recorded and transcribed verbatim according to transcription guidelines.[44]

At both time points, the following information will be obtained. Prior to the (focus group) interview, participants will document socio-demographic information. They will report about their general health, level of pain and fatigue during the past week on a visual analog scale after the interviews to avoid influencing patient opinion in advance. Clinical information will be extracted from the medical records by the local health professionals and shared with the local principal investigator. A detailed overview of all collected variables can be found in Supplementary file 2.

Data analysis

Data analysis will be conducted at two levels: (i) the local analyses of t_1 and t_2 data, followed by the longitudinal analysis; (ii) the meta-analysis with locally interpreted local data. The process of data analysis was based on several frameworks, which is summarized in Figure 3.

The local analyses

In every country, the analysis process will be a team activity involving patient representatives. Preferably two researchers, including at least the local lead investigator, will independently code the interview transcripts. Data analysis will start after the first interview or focus group.

The local researchers will follow the steps that are presented in Qualitative Analysis Guide of Leuven (QUAGOL) to analyze the interview data of t_1 and t_2.[45] The central activity in QUAGOL is the constant comparison process: between researchers' interpretations and the actual participant story, as well as to check new ideas for their presence in previous interviews. QUAGOL divides data analysis into two phases.

The first phase suggests five steps of preparation, implying only paper and pencil work: 1) rereading of the transcript to get knowledge of what the interview is about, and highlighting the relevant fragments; 2) preparing a narrative summary by describing the key story lines close to participants' words; 3) schematically describing the key ideas of the interview in a conceptual scheme; 4) fitting test and adaptation of the conceptual scheme by going back to the transcript; 5) looking for common ideas/concepts across conceptual schemes as a first comparison with the other interviews.

The second phase comprises another five steps, representing the actual coding process: 6) creating a common code list, without hierarchical structure and based on the insights from the refined conceptual schemes; 7) coding of each significant passage in a qualitative software program, while critically reviewing and refining the introduced code list; 8) defining the concepts by looking across-cases and reviewing all citations connected to a concept; 9) integration of all concepts in one story line that answers the research question, followed by verification of this overarching framework against all interviews and interview schemes; 10) describing the results.

QUAGOL is not specifically developed for focus group analysis. Therefore, the group process will also be analyzed (i.e., how the conversation in the group is organized,

developing and changing), as well as the differences within and between the groups will be taken into account.[25]

For the longitudinal analysis, the local teams will merge their data of t_1 and t_2, in which meaningful individual statements will be extracted and compared between time points. There are no universal frameworks for analyzing longitudinal qualitative data. The local teams will be guided by the method described by Saldaña,[46 47] who developed a 16-question template including (i) framing questions to help focusing on the context and conditions that influence changes over time; (ii) descriptive questions to describe what kinds of changes occur; and (iii) analytic and interpretive questions to reach richer levels of analysis.

The meta-analysis

The findings of the three independently performed qualitative studies will be combined in a meta-analysis. Several methods for synthesizing qualitative studies have been developed,[48] with some studies also using a combination of methods.[49] The methodology developed for EQPERA is inspired by the principles of meta-ethnography as practiced by Britten et al.,[50] and by the coding process of QUAGOL (preparatory phase) that is based on grounded theory principles.[45] We combined key methodological elements of both approaches and summarized these into four steps: 1) describing each case; 2) recognizing differences, similarities and patterns across cases; 3) disentangling differences and similarities across cases; 4) fitting-test of the meta-interpretations.

The findings of the participating countries will be integrated by face to face interaction between the different local teams about their data in a consensus meeting. Local findings will be translated into English. The local teams of Belgium, The Netherlands and Sweden will at least consist of the principal investigator, a patient research partner and a rheumatologist to achieve an interdisciplinary view and prevent bias due to solo interpretations. A senior

researcher of the EQPERA team (YH), who is not linked to the local teams and data, will moderate the meeting. Below, we describe our stepwise approach.

Step 1: Describing each case

In step 1, the aim is to understand the course and results of each study on its own. Each country will be viewed as a case, with each case reflecting the overarching story of all local participants.

The lead investigators (KE, IL, EM) will present their findings (including quotes) and conclusions, covering: (i) the name and description of the patient-preferred outcomes; (ii) when, where, why, and in which circumstances they were put forward by the participants; (iii) the change through time of the description participants attached to the different outcomes. Furthermore, they will report about study details, using three short reports:[45] 1) a descriptive report, including what is specific to the participants, the treatment strategy, the research group and the healthcare system; 2) a methodological report, including deviations from the protocol, such as modifications to the interview guide, recruitment problems and level of data saturation; 3) a content report, including the main message derived from the data. A standard form will be used to enhance uniformity across presentations. The three cases will be presented one by one without immediate cross-comparison. After the case description, local teams will have familiarized with the other team's data and the particular context in each country.

In preparation of step 2, each team will individually reflect upon the following questions to stimulate the across-case analysis: 'What do I hear in every case?', 'What do I only hear in our case?', 'What do I not hear in our case?'. Furthermore, they will write down the patient-preferred outcomes they identified (codes and concepts) on color-coded sticky notes, each country representing another color, to support visually the comparison of the local findings in step 2.

Step 2: Recognizing differences, similarities and patterns across cases

In step 2, the aim is to translate concepts from one study to another,[50] to determine how studies are related (i.e., what emerges across cases) and to recognize what is typical for each case.

An affinity diagram will be created to organize the multinational data.[51] The patient-preferred outcomes of the three studies will be displayed side by side (using the color-coded sticky notes). Their meaning will constantly be compared from one country to another in order to identify common and recurring, as well as conceptually different outcomes. We will start with a small set of concepts including the higher level concepts of each study, after which we will refine our first interpretations by discussing the lower-level codes.[45] During this process similar outcomes will be grouped if possible (by replacing the sticky notes), and we will look specifically for subtle differences between grouped outcomes.

After reaching consensus on similarities and differences, a 'saturation grid' will be completed in preparation of step 3. This is a technique used in qualitative studies to identify covered (sub)themes in each interview and decide on data saturation.[52] However, we will use a prespecified grid to identify the coverage of outcomes across the three studies.[50] Firstly, the grouped outcomes will be renamed. Secondly, all outcomes will be listed, meaning that each outcome of each local study is encompassed by one of the renamed outcomes in the grid. The main explanation of each outcome will be added. Thirdly, each country will represent a column and their sticky notes will be pasted next to the outcome in the grid that fits best the description on the sticky note. Hence, the empty cells will represent the outcomes that do not emerge across countries. By completing the grid, an overview will be developed of differences and similarities across cases.

Step 3: Disentangling differences and similarities across cases

In step 3, the aim is to explain the recognized differences and similarities by discussing why (or why not) certain outcomes emerge in a particular country or across countries.

Starting from the saturation grid (step 2), we will first go back to the methodological considerations and contextual features (step 1), before looking for possible cultural

explanations. The group discussion will be an essential element in this step. For this reason we will view this discussion as a focus group, producing data that will be audio recorded and transcribed verbatim. After step 3, we will have obtained consensus on cross-cultural variation in patient-preferred outcomes in early RA.

In preparation of step 4, the local teams will separately draft a written summary of the discussion immediately after the focus group and with special attention to how their case was similar or different to the other cases.

Step 4: Fitting-test of the meta-interpretations

In step 4, the aim is to verify the appropriateness of the interpretations made during the focus group (step 3) regarding similarities and differences across countries.

Each local team will perform a fitting-test of common and own meta-interpretations with their local data. The local researchers will go back to their data, after rereading the focus group transcript and with their written summary in mind. Two questions will need to be answered: (1) Do the contextual interpretations actually reflect what is seen in our data? Is certain context information overlooked in the focus group? (2) Can we support the meta-interpretations with quotes that typically describe the perspective of our participants? During conference call meetings, the meta-interpretations will be adapted, completed or refined based on the fitting-test in each country.[45]

Patient and Public Involvement

Patients were involved in every step of the research project, as described throughout the paper. Research findings will be disseminated at Patient and Public Engagement events where appropriate.

Enhancing data quality and methodological rigor

Quality assurance

EQPERA is a large, multicountry, multicenter, multilingual, longitudinal qualitative research project. To yield sound results, several strategies are applied to ensure trustworthiness. These are: (i) recruitment of a qualified and motivated team; (ii) use of forward-backward translation procedures; (iii) uniformity in recruitment, conducting the interviews and focus groups, transcription of audio files, data coding, data storing, and reporting; (iv) interdisciplinary team analysis (v) training of local staff to the protocol and hands-on guidance by the project leader. In Table 1, a detailed description is provided of the used strategies according to four quality criteria (i.e., credibility, dependability, confirmability, and transferability).[53 54]

Quality appraisal

As the findings of independently performed primary studies will be combined, quality is an important aspect to consider requiring a formal system for appraisal. The local teams will use a quality reporting tool to support a consistent use of methods and documentation across studies. Johnson et al. provided a useful template,[51] based on the consolidated criteria for reporting qualitative research,[55] and the quality criteria suggested by Mays and colleagues.[56] In EQPERA, several items were added regarding data management and quality appraisal in qualitative research.[32 44 57-59] Our tool comprises 50 items regarding four domains: 1) research team and reflexivity; 2) study design; 3) analysis and findings; 4) data management strategies (Supplementary file 3).

Table 1 Applied quality assurance strategies in EQPERA, described for each research stage, according to Lincoln and Guba's framework for evaluating trustworthiness.[53]

Research stage	Employed strategies for supporting trustworthiness	Assessing quality: (1) How congruent are the findings with reality? (2) Would the research findings be the same if the study would be replicated in essentially the same way? (3) Do the research findings emerge from the context and the respondents and not solely from the minds of the researchers? (4) Can the research be applied in other contexts?			
		(1) **Credibility** (internal validity)	(2) **Dependability** (reliability)	(3) **Confirmability** (objectivity)	(4) **Transferability** (generalizability)
Study design	- developed around the patient perspective and in collaboration with patient representatives	●			
	- triangulation of interview methods	●			
	- addressing potential drop-out at t_2	●			
Establishment of the EQPERA team	- recruitment of a qualified team, with a passion for the topic: ○ skilled in conducting qualitative research ○ familiar with the patient population ○ including patient research partners	●	●	●	●
Protocol development and implementation	- a clear understanding of the overall project objective by all co-workers		●		●
	- use of detailed study protocol, including a methods and analysis plan, an interview protocol, a data management plan, and templates	●	●		
	- training of local staff to the protocol (project leader) prior to patient recruitment of t_1 and data collection of t_2	●	●		
	- monitoring of local progress and hands-on guidance (project leader)		●		●
	- documentation of local decisions (use of a research journal): ○ when, why, what changes, and who was involved in making this decision (e.g., modifications to the interview guide) ○ personal and/or practical comments	●	●	●	●
Sampling and recruitment	- purposive sampling informed by simultaneous data collection and analysis	●			●
	- multicountry and multicenter recruitment	●			●

	-	applying a definition for data saturation	•				•
	-	use of an enrollment template to support heterogeneity in the local samples and systematically keep records		•			
Data collection	-	semi-structured interview guides:	•	•	•		
		○ the same main interview questions in every country					
		○ collaboration with patient research partners to support clarity and understandability of interview questions					
		○ forward-backward translation					
		○ the same key points in the introduction					
	-	use of a data collection template and at least 2 audio recorders/interview to prevent missing data		•			
	-	verbatim transcription of the audio-recorded data		•			
	-	use of transcription guidelines		•			
	-	neutral and convenient interview location	•				
t_1	-	maximum 2 interviewers/country		•			
	-	maximum 2 interviews/day per interviewer to avoid interview burden and take time to reflect upon each interview					
t_2	-	the interviewer of t_1 is moderator of the focus groups		•			
	-	1 moderator/country and the same observer(s) for each focus group					
Data analysis	-	independent coding by at least 2 researchers	•		•		
Local level	-	data collection and analysis in parallel	•				
	-	constant comparison method	•				
	-	use of field notes	•		•		
	-	reflection after each interview/focus group: descriptive, content and methodological report	•		•		
	-	use of a qualitative software program		•			
	-	peer debriefings: more frequently early in de coding process	•		•		
	-	looking at data from multiple perspectives, including collaboration with patient researchers to help understand and describe the data	•		•		
	-	uniform procedure across countries based on established frameworks		•			•
International level	-	translation of the local findings and conclusions using a structured forward-backward procedure, supported by professional translators		•			
Reporting	-	use of guidelines for reporting the synthesis of qualitative research[60]					•

t_1: time point 1= three to six months after start of the initial treatment for early rheumatoid arthritis; t_2: time point 2= at least one year after start of the initial treatment for early rheumatoid arthritis.

ETHICS AND DISSEMINATION

Ethical considerations

EQPERA will apply the principles established in the Declaration of Helsinki.[61] Participants will provide written informed consent before data collection of t_1 and t_2. Only coded and interpreted data will be shared between the local teams for the meta-analysis. Ethics approval for the original studies were granted by the responsible institutional review boards.

Dissemination of results

Every country will prepare a publication on their national findings. Two EQPERA main papers are foreseen: 1) the present paper describes the rationale, design and methods of EQPERA; 2) a publication on the results of the meta-analysis. Next to peer-reviewed publications, we will also disseminate our findings in (inter)national research presentations, and also patient organizations will be updated about the study findings.

CONCLUSION

In EQPERA, the aim is to confirm the Belgian findings on patient-preferred outcomes in early RA in a European context, and provide a study protocol that has the potential to offer a methodological framework for further exploration of transferability in other contexts. Ultimately, study findings will be used to inform and optimize current care initiatives in early RA in order to address the unmet need of patient-centered care in RA.

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Author contributions

The following authors were involved in this study: Kristien Van der Elst (KE), Ann Bremander (AB), An De Groef (AG), Ingrid Larsson (IL), Elke Mathijssen (EM), Johanna Vriezekolk (JV), René Westhovens (RW), Yvonne van Eijk-Hustings (YH). KE and RW had the main idea of the study. KE, AB, AG, IL, EM, JV, RW and YH contributed to the design of the study. KE, YH and RW drafted the manuscript. KE, AB, AG, IL, EM, JV, RW and YH were involved in the editing of the manuscript. All authors read and approved the final version of the manuscript. Apart from the first and last author, the other authors are listed in alphabetical order.

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Competing interest statement

None declared.

Patient consent

Will be obtained.

Ethics approval

The Netherlands: the Medical Research Ethical Committee of Arnhem-Nijmegen waived ethical approval since the medical research involving human subjects act did not apply to this study; Sweden: ethical approval was obtained from the Regional Ethical Review Board at Lund University, Sweden; Belgium: ethical approval was obtained from the Human Research Ethics Committee of the University Hospitals Leuven.

Data sharing statement

Not applicable.

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Figure 1 Overview of the European, longitudinal, multimethod qualitative research design. *t*: time point

Figure 2 Forward-backward translation framework applied to translate the interview questions and procedures

Figure 3 Simplified outline of the used frameworks,[25 45-47 50] and the included steps in the local analyses and the meta-analysis

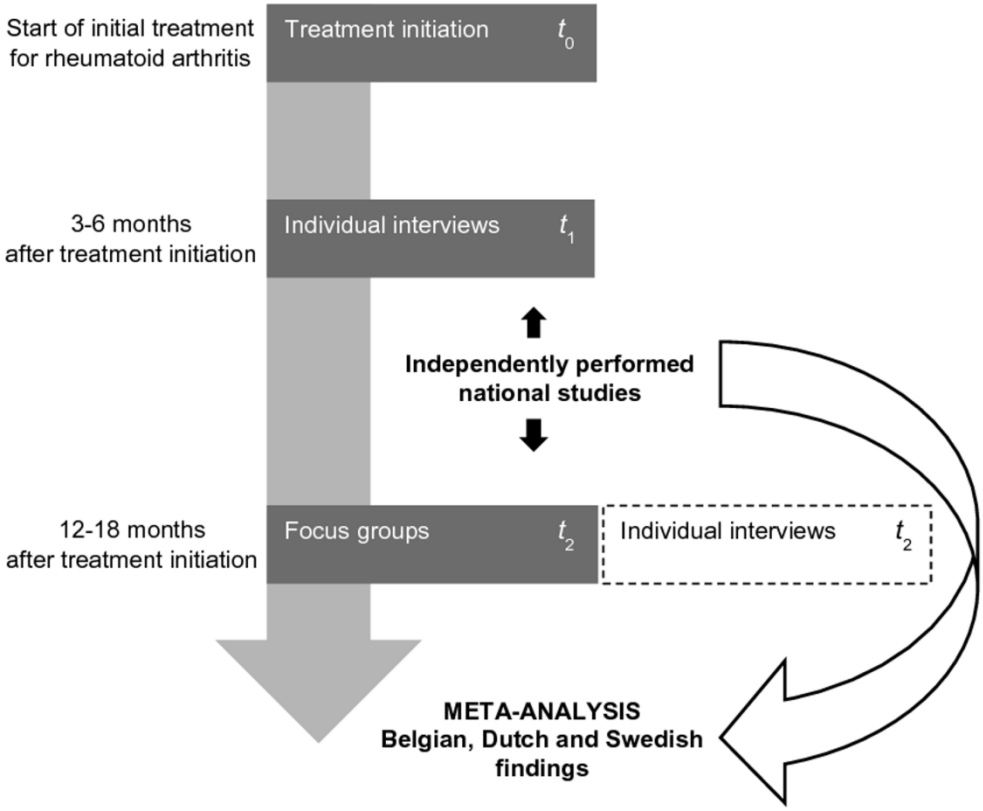

Figure 1 Overview of the European, longitudinal, multimethod qualitative research design. *t*: time point.

166x138mm (300 x 300 DPI)

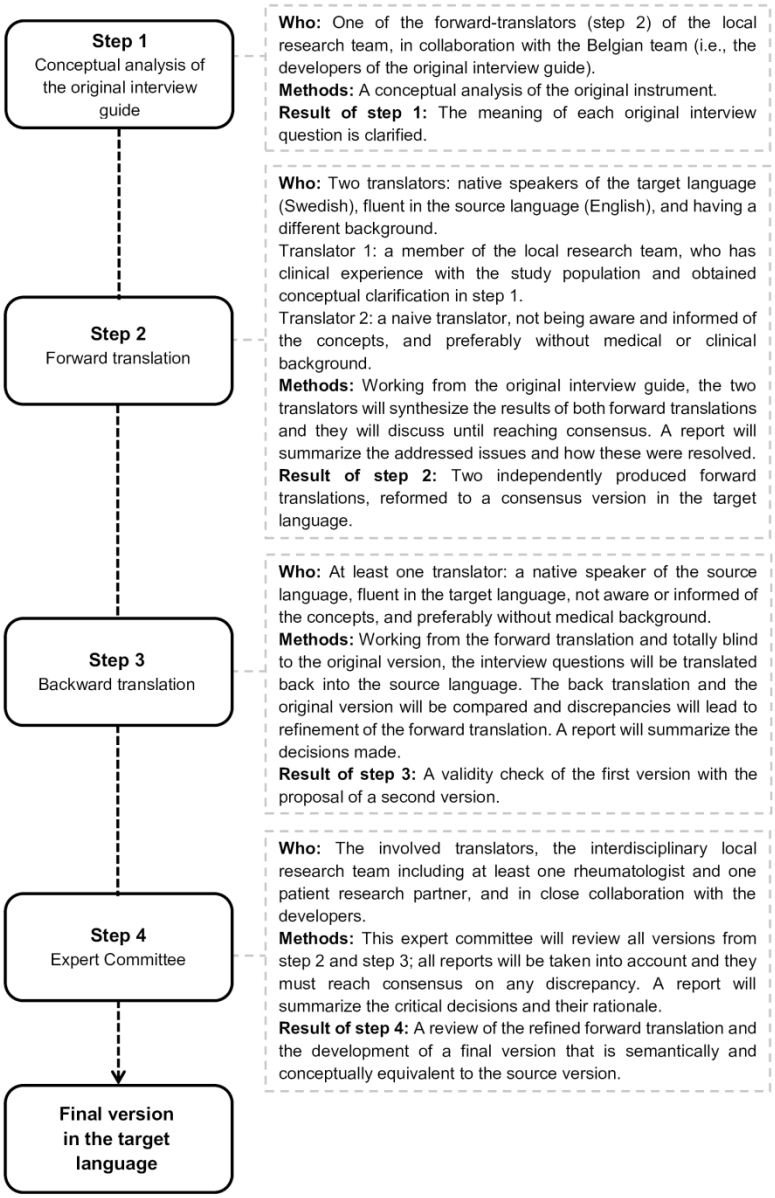

Figure 2 Forward-backward translation framework applied to translate the interview questions and procedures.

163x249mm (300 x 300 DPI)

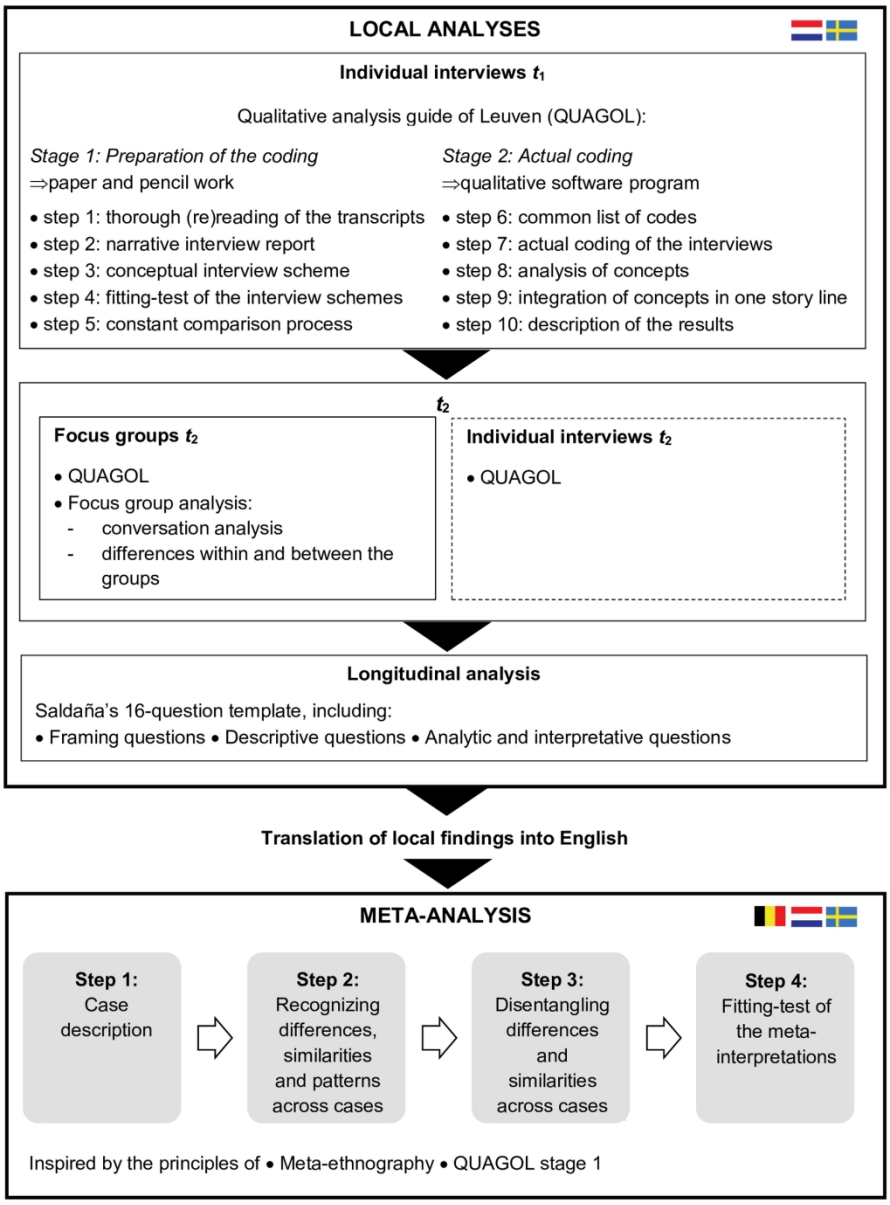

Figure 3: Simplified outline of the used frameworks,[25 45-48] and the included steps in the local analyses and the meta-analysis.

146x197mm (300 x 300 DPI)

Supplementary file 1 Main interview questions and procedures for the individual interviews (t_1 and t_2) and focus groups (t_2). Most aspects of the methods of t_1 and t_2 are adopted from the original Belgian study*

Context questions
- What type of treatment are you currently receiving? - Have there been any changes in your treatment plan? If so, why and what type of changes?
Individual interviews at t_1
Preparatory phase (5 to 10 minutes) To set the scene for the interview, participants were asked to write down as many keywords describing: - the impact of rheumatoid arthritis (RA) on their life - which outcomes of their illness and treatment they considered most important. *Start of the interview* The interviews began by discussing participants' written answers to those 2 questions. Participants were asked to elaborate on their keywords: - Can you tell me how RA affects your daily life? - Which outcomes of your illness and antirheumatic treatment are important to you at this moment? *Proceeding of the interview* The order of the other interview questions was determined by the participants' answers during the interview. - How has the treatment been working for you so far? - How do you decide whether or not your treatment is working? - What made you decide to start treatment? - What were your expectations of your antirheumatic treatment at the start of treatment? - To what extent do the expectations you had at the start of your treatment match your current expectations? Three questions were added after the first interviews: Other patients talked about 1) taking less medication, 2) returning to a normal life, 3) feeling better. Is this something you recognize? What do you feel about that? Probing questions: Could you tell me more about that? Could you give an example? *End of the individual interview* Is there anything else you would like to add?
Focus groups at t_2
Round 1: preparatory phase (5 to 10 minutes) The moderator introduced the phenomenon of interest, after which each group member was asked to independently prepare answers to the question below by writing down as many keywords as possible. Each answer was written on a separate sticky note. - Which outcomes of your illness and antirheumatic treatment are important to you at this moment? Next, participants were asked to try to order their sticky notes on a vertical scale, from most important (top) to least important (bottom). Participants were simultaneously asked to think about the following questions: - What important treatment results have already been achieved? - At present, is there anything you would like to change or improve regarding your disease or treatment?

Round 2, step 1: round-robin listing

All group members were asked to reveal and clarify, one by one, their personally preferred outcomes in order of importance. Meanwhile, the observer wrote these outcomes on a flipchart in front of the group.

- Who would like to share your personally valued outcomes with the group, in order of importance?
- Could you please clarify why these outcomes of your disease and antirheumatic treatment are important to you?
- Why did you designate that specific outcome to be the most important?
- Is there anything else you would like to add?

Round 2, step 2: developing a group list of patient-preferred outcomes

The group was asked to generate a consensus list by reviewing and merging all recorded outcomes and agreeing on the name and properties of each outcome on the list.

- Could any of the individual expectations be grouped?
- Who would like to suggest a name and meaning for this outcome?
- Do you think all the important outcomes are mentioned on the group list?
- Is there anything else you would like to add?

Round 2, step 3: eliciting personal preferred outcomes

Starting from the consensus list of patient-preferred outcomes that resulted in step 2, each group member was asked to independently try to select his or her 5 top outcomes from this list, using the sticky note ordering scheme.

Round 2, step 4: eliciting preferred outcomes in the actual stage of RA

The group was then asked to discuss a collective top 5 outcomes and to consider influencing factors.

- Looking at the group list, what outcome would you order as most important?
- What outcome would you order second…fifth?
- Can you tell us why this outcome is either important to you or not?

End of round 2

That is it for the second round. Is there anything else to add?

Round 3: exploring the view of participants on the evolution of their patient-preferred outcomes over the past year

The focus groups ended by exploring the participants' views on potential changes in personally preferred outcomes over time. During the individual interview of last year, you were asked for your preferred illness and treatment outcomes. In the meantime, you have gained more experience with your disease and treatment and the critical disease stage has passed.

- Do you feel that other results are now more important to you than the ones you identified at the start or during your interview last year?
- Could you explain why this has or has not changed?
- Are there outcomes that are now more, less, or no longer important to you?
- Why do you think that these are now more or less important than a year ago, or are no longer important? What may have caused this change in importance?
- Do you have an example of an outcome that has changed in importance compared to that outcome in the early disease stage? Why do you think this has changed? Could you clarify this in more detail?
- In general you mention (more or less) similar/different outcomes of importance compared to last year (in the early disease stage). What is your opinion on this observation?

End of round 3

This is the end of the third round. Is there anything else to add?

Probing questions: Is this outcome also important or not important to other group members? Are there any suggestions from other group members? Is there anyone who has a different opinion on the matter? Is it difficult for you to share your opinion on this? Does everyone agree? Who agrees or disagrees and why? Who would like to add something?

End of the focus group

- What is your general conclusion about today's focus group on preferred and important outcomes of disease and treatment in the actual disease stage?
- To summarize, you talked about […]. Do you agree with this summary of today's focus group?

Individual interviews at t_2

Preparatory phase (5 to 10 minutes)

Please, consider the next 5 to 10 minutes the question below by writing down as many keywords as possible. The interviews will begin by discussing your written answers to this question:

- Which outcomes of your illness and antirheumatic treatment are important to you at this moment?

Start of the interview

- Can you tell me what you have written down? So, which outcomes of your illness and antirheumatic treatment are important to you at this moment?

Proceeding of the interview

Exploring patient-preferred outcomes

- How has the treatment been working for you so far?
- To what extent do the expectations you had at the start of your treatment match your current expectations?

Exploring the view of participants on the evolution of their preferred outcomes over the past year

Last year, during the interview, you mentioned that the following outcomes of your treatment were important: ..... (t_1 keywords of the t_2 participant).

- Do you feel that other results are now more important to you than the ones you identified at the start or during your interview last year? Could you explain why this has or has not changed?
- Are there outcomes that are now more, less, or no longer important to you?
- Why do you think that these are now more or less important than a year ago, or are no longer important? What may have caused this change in importance?
- Do you have an example of an outcome that has changed in importance compared to that outcome in the early disease stage? Why do you think this has changed? Could you clarify this in more detail?

Patient-preferred outcomes compared to the focus groups at t_2

During the focus groups the following 5 treatment outcomes were found to be most important: 1) preferred outcome; 2) preferred outcome; 3) preferred outcome; 4) preferred outcome; 5) preferred outcome.

- I wonder if you recognize yourself in this? Could you explain why this is or is not the case?

End of the individual interview

Is there anything else you would like to add?

t_1: time point 1= 3-6 months after start of the initial treatment for early rheumatoid arthritis;

t_2: time point 2= 12-18 months after start of the initial treatment for early rheumatoid arthritis.

*Van der Elst K, Meyfroidt S, De Cock D, et al. Unraveling Patient-Preferred Health and Treatment Outcomes in Early Rheumatoid Arthritis: A Longitudinal Qualitative Study. Arthritis Care Res (Hoboken) 2016;68(9):1278-87.

Supplementary file 2 EQPERA Data collection template

Enrollment and interview logistics (t_1 and t_2)	
Respondent ID	ID number
Date of birth	dd/mm/yyyy
Gender	man, woman, X
Respondents' place of residence	postal code, location
Responsible recruiter	function, name, contact details
Rheumatology center	name, location
Type of rheumatology center	academic hospital, general hospital, private practice
Treating rheumatologist	name
Date of diagnosis	dd/mm/yyyy
Symptom duration	in months, [date of diagnosis - date of symptom onset]
Disease duration	in months; calculated with date of diagnosis
Comorbidity	no severe comorbidities present [yes/no]
Date of RA treatment initiation	dd/mm/yyyy
Months of treatment experience at t_1	date interview t_1 - date treatment initiation = between 3-6 months
Initial treatment	the local treatment protocol for early RA: free text, no details on dosages
Initial treatment allocated according to clinical prognostic factors	yes/no
Step-down strategy	yes/no (as initial treatment strategy)
MTX-only step-up	yes/no (as initial treatment strategy)
MTX + early bridging glucocorticoids	yes/no (as initial treatment strategy)
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs with glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs without glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
Biologicals as a first hit	yes/no (as initial treatment strategy)
Responder to initial treatment (at moment of t_1 recruitment)	yes/no
Patient obliged or deciding to discontinue RA treatment (at moment of t_1 recruitment; e.g., because of safety reasons, patient's decision)	yes/no
Reason to not recruit patient	free text or N/A (not applicable)
Date of study invitation	dd/mm/yyyy (sharing of invitation letter)
Reason in case not interested in study (if shared)	free text
Invitation for t_1 by phone (if interested)	dd/mm/yyyy (first contact between patient and researchers)

Verbal consent for t_1 after phone call	yes/no
Contact details patient	address/phone number/email
Patient-preferred contact method	by phone or email
Date and timing of individual interview t_1	dd/mm/yyyy; hour
Location of individual interview t_1	home or rheumatology practice/clinic
Reminder for t_1 sent	dd/mm/yyyy
Reason in case interview t_1 was cancelled (if shared)	free text
Respondent gave written informed consent t_1	yes/no
Interviewer t_1	name
Interviewer is involved as participant's health professional in daily practice	yes/no
t_1 respondent gave consent at t_1 to be contacted again for second part of study (t_2)	yes/no
Reason in case not interested in t_2 (at t_1) participation (if shared)	'Not interested to share own experiences in group', 'Feeling uncomfortable to talk in group', 'Fear for seeing other patients', 'Not interested in the story of other patients', 'Other'
Months of treatment experience at t_2	date focus group - date treatment start= at least 1 year (between 12-18 months) after treatment initiation
Invitation letter t_2 sent by post	dd/mm/yyyy (by researchers)
Invitation for t_2 by phone	dd/mm/yyyy (by researchers)
Verbal consent for t_2 after phone call	yes/no
If not interested in group interview, interested in individual interview instead?	yes/no
Reason in case not interested in t_2 (if shared)	'Not interested to share own experiences in group', 'Feeling uncomfortable to talk in group', 'Fear for seeing other patients', 'Not interested in the story of other patients', 'Other'
Date and timing of focus group t_2	dd/mm/yyyy; hour
Location of focus group t_2	clinical or non-clinical setting
If applicable: Date and timing of individual interview t_2	dd/mm/yyyy; hour
If applicable: Location of individual interview t_2	home or rheumatology practice/clinic
Reminder for t_2 sent (focus group or individual interview)	dd/mm/yyyy
Reason in case focus group (or individual interview) t_2 was cancelled (if shared)	free text
Respondent gave written informed consent t_2	yes/no
Moderator t_2	name
Observer(s) t_2	name(s)
If applicable: Interviewer t_2	name
Are the (interviewers/) moderators/observers involved as health professionals in the participants' daily clinical care	yes/no
Socio-demographic data: patient-reported t_1	
Date of birth	dd/mm/yyyy
Gender	man, woman, X
Educational level t_1	low, moderate, high

Currently employed t_1	yes/no
Employment status t_1	employed, not employed, retired, housewife/houseman, student
Marital status t_1	single, together unmarried, married, widower, other
Living status t_1	alone, with partner and/or kids, with other persons
Socio-demographic data: patient-reported t_2	
Educational level t_2	low, moderate, high
Currently employed t_2	yes/no
Employment status t_2	employed, not employed, retired, housewife/houseman, student
Marital status t_2	single, together unmarried, married, widower, other
Living status t_2	alone, with partner and/or kids, with other persons
Clinical data: patient-reported data t_1	
VAS general health t_1	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS pain t_1	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS fatigue t_1	100-mm visual analogue scale from best (0/100) to worst (100/100)
Key words in preparation of t_1 interview	Key words describing: - the impact of RA on their life - which outcomes of their illness and treatment they considered most important
Clinical data: patient-reported data t_2	
VAS general health t_2	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS pain t_2	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS fatigue t_2	100-mm visual analogue scale from best (0/100) to worst (100/100)
Key words in preparation of t_2 focus group (/interview)	Key words describing which outcomes of their illness and treatment they considered most important
Clinical data: health professional-reported data t_1 and t_2 (to be extracted from database/patient file)	
Date of diagnosis	dd/mm/yyyy
Symptom duration	in months, [date of diagnosis - date of symptom onset]
Disease duration	in months; calculated with date of diagnosis
Comorbidity	no severe comorbidities present [yes/no]
Start of treatment	dd/mm/yyyy
Months of treatment experience at t_1	date interview t_1 - date treatment start = between 3-6 months
Months of treatment experience at t_2	date focus group t_2 - date treatment start = at least 1 year

Initial treatment	the local treatment protocol for early RA, free text, no details on dosages
Initial treatment allocated according to clinical prognostic factors	yes/no
Step-down strategy	yes/no (as initial treatment strategy)
MTX-only step-up	yes/no (as initial treatment strategy)
MTX + early bridging glucocorticoids	yes/no (as initial treatment strategy)
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs with glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs without glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
Biologicals as a first hit	yes/no (as initial treatment strategy)
Treatment failure in the first year	yes/no
Treatment failure after 1 year	yes/no
Patient who discontinued treatment (t_1 or t_2; e.g., because of safety reasons, patient's decision)	yes/no

Note. RA: Rheumatoid Arthritis; MTX: Methotrexate; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; VAS: Visual Analog Scale; t_1: time point 1= 3-6 months after start of the initial treatment for early rheumatoid arthritis; t_2: time point 2= 12-18 months after start of the initial treatment for early rheumatoid arthritis.

Supplementary file 3 EQPERA data quality assurance reporting tool

Domain 1: Research team and reflexivity	
Item	Guide questions/description
Researcher characteristics	
1. Interviewer / moderator/observer	Who conducted the interviews/ focus groups? (who observed the focus groups?) ►Maximum 2 interviewers at t_1 and t_2 /country and maximum 1 moderator at t_2/country ►Preferably the same observer(s) for each focus group
2. Credentials / background	What were the researcher's credentials? (e.g., PhD, RN)
3. Occupation	What were the researcher's occupation at the time of the study?
4. Gender	Was the researcher male or female?
5. Experience and training	What experience or training did the researcher have?
Relationship with participants	
6. Relationship established	Was a relationship established prior to study commencements? (e.g., health professional)
7. Participant knowledge of the interviewer	What did the participant know about the researcher? (e.g., personal goals, reasons for doing the research)
8. Interviewer characteristics	What characteristics were reported about the interviewer/moderator/observer? (e.g., bias, assumptions, reasons and interest in the research topic)
Domain 2: Study design (a longitudinal, qualitative, explorative study)	
Participant selection	
9. Sampling	How were participants selected (e.g., purposively) Mono or multicenter sampling? Type of recruitment center(s)? (i.e., academic hospital, general hospital or private practice)
10. Method of approach	Who invited the participants? How were participants approached? (e.g., face to face, telephone, mail, email)
11. Sample size	How many participants were in the study? ♦at t_1: number of individual interviews ♦at t_2: number of participants per focus group / number of individual interviews
12. Non-participation	How many eligible patients could potentially be recruited? How many people were approached and how many of them refused to participate or dropped out? Reasons? (if shared) ♦Not interested in participation (refusal) ♦Drop out (type 1): in case t_1 interview was scheduled and cancelled ♦Not interested in participation at t_2 (drop out, type 2) ♦Not interested in participation in a focus group, but willing to participate in an individual interview instead at t_2 ♦Drop out (type 3): in case t_2 interview was scheduled and cancelled

Setting	
13. Setting of data collection	Where was the data collected?
14. Presence of non-participants	Was anyone else present besides the participant and researchers?
15. Description of sample	What are the important characteristics of the sample? (e.g., demographic data)
Data collection	
16. Interview guide	Were questions, prompts, guides provided by the authors? Was the interview guide pilot tested? Is it being made available?
17. Focus group guide	Were questions, prompts, guides provided by the authors? Was the interview guide pilot tested? Is it being made available?
18. Audio / visual recording	Did the research use audio or visual recording to collect the data?
19. Data collection method	How were the data collected? (t_2: focus group or individual interview?) Were repeat interviews carried out at t_2?
20. Field notes	Were field notes made during and/ or after the interview or focus group? ►if yes, please record them in the descriptive or methodological interview report. Were short reports prepared after each interview?
21. Duration	What was the duration of the interviews or focus groups?
22. Data saturation	Was data saturation discussed? After how many interviews was data saturation reached? (Definition in EQPERA: “if the last 3 interviews do not provide new information, insights or additional understanding to accomplish the study aims”)
Domain 3: Analysis and findings	
Data analysis	
23. Number of data coders	How many data coders coded the data? Who coded the data?
24. Independent coding	Was the analysis repeated by more than 1 researcher to ensure reliability?
25. Data analysis method	How were themes and concepts identified from the data? (e.g., Were themes identified in advance (framework-based) or derived from the data (data-driven)?)
26. Patient research partners	Did patient research partners provide feedback on the findings, and in which part(s) of the data analysis were they involved?
27. Software	What software was used to manage the data?
Reporting	
28. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quote identified? (e.g., participant number, gender, age)
29. Data and findings consistent	Was there consistency between the data presented and the findings?
30. Clarity of themes	Were themes clearly presented in the findings?

Domain 4: Data management strategies	
Data recording	
31. Recording changes and decisions	Were changes to the interview guide, the evolution in themes, deviations from the research protocol, and major local project decisions carefully documented along with the rationale for change? ►to recall decisions ►the use of a research log book is recommended
32. Recording interview data	Did you record the data with at least 2 audio recorders? ►to prevent missing data
Data storing	
33. Routinely storing of data	Was the data (e.g., audio files, transcripts, interview reports and field notes, patient-reported and clinical data, informed consents) or the project database routinely submitted to a central data repository or a secured cloud storage system? ►to avoid missing data and to easily manage large amounts of data like in qualitative research ►a uniform transcript header and file name could facilitate data storing (e.g., T1.number of interview.ddmmyyyy.initials of interviewer)
Data check	
34. Internal audit	Could the evidence (field notes, interview transcripts, recordings, reasons for interview guide adaptations,…) be inspected by others?
35. Preventing missing data	Did the principal investigator routinely check for missing data?
Data collection	
36. Recruitment flow	Was the recruitment flow carefully documented? ►the use a research log book (enrollment spread sheet) is suggested
37. Templates	Did you check the data collection templates and the Excel spread sheet?
38. Local interview guide	Translation/cultural adaptation interview guide: Did you use the proposed framework to translate the interview guide into the source language? Were cultural adaptations needed? ►please, record these in your research log book, together with the timing and the reason for adjustment
39. Avoiding and handling the presence of a third person	Focus of attention during interview scheduling: Was the purpose of a one to one interview mentioned to the participant? If someone else was present, did this affect the interview/data collection? ►please, reflect on this in the descriptive interview report
40. Introducing the interview	Did you prepare and practice the interview introduction? ►to maximize the interview return ►key words: welcoming the participant; introducing yourself; clarifying the purpose and importance of research, the importance of participant contribution, expectations regarding the participant (e.g., no good or wrong answers), role of the interviewer/moderator/observer, (t_2: “rules” regarding group discussion), ethical aspects; “Any questions?”; mobile phone on silent mode)

41. Interview burden	It is recommended to conduct 1 individual interview/day, with a maximum of 2 interviews/day ►to avoid interview burden and to have sufficient time to reflect on each interview
42. Interview reports	Did you write for each interview/focus group 3 short reports? (i.e., content report, descriptive report, methodological report)
43. Iterative process	Did you use an iterative process of data collection and analysis? ►to support data saturation
Data analysis	
44. Analysis guide	Did you use Qualitative Analysis Guide of Leuven (QUAGOL) to guide your data analysis? Did you use Saldaña's guiding questions for analyzing the longitudinal data?
45. Peer debriefings	Were regular peer debriefings held? ►time for reflection (in team): to discuss the interview return, the development of new themes, and to question and confirm saturation of themes ►early in de coding and interviewing process, more frequent meetings are suggested ►please make a short report of each debriefing to recall discussions
46. Team analysis	Was looked at the data in team (from different perspectives looking at the data)
Transcription	
47. Transcription guidelines	Who transcribed the data? ►>1 person: did you apply a uniform transcription method? (e.g., agreements about the level of details, to obtain confidentially, to reproduce the exact words spoken) ►external transcriber: was the interview transcript reviewed by the interviewer on data quality and accuracy of transcribing? How did you approach this quality check?
Team approach	
48. Patient research partners	What was the exact role of the patient research partners in the study
49. Interdisciplinary team	Who joined the interdisciplinary team, and what was their contribution?
Initiation session	
50. Project initiation	Did the local research team (at least the principal investigator) followed the initiation session lead by the project leader at t_1 and at t_2?

t_1: time point 1= 3-6 months after start of the initial treatment for early rheumatoid arthritis; t_2: time point 2= 12-18 months after start of the initial treatment for early rheumatoid arthritis.

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European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA): rationale, design and methods of a multinational, multicenter, multilingual, longitudinal qualitative study

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European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA): rationale, design and methods of a multinational, multicenter, multilingual, longitudinal qualitative study

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ABSTRACT

Introduction: Including the patient perspective is important to achieve optimal outcomes in the treatment of rheumatoid arthritis (RA). Ample qualitative studies exist on patient outcomes in RA. A Belgian study recently unraveled what matters most to patients throughout the overwhelming and rapidly evolving early stage of RA. The present study, European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis (EQPERA) was created to contribute to a more universal understanding of patient-preferred health and treatment outcomes by integrating the perspectives of patients with early RA from three European countries.

Methods and analysis: In EQPERA, a qualitative, explorative, longitudinal study will be implemented in The Netherlands and Sweden, parallel to the methods applied in the previously conducted Belgian study. In each country, a purposive sample of patients with early RA will be individually interviewed 3-6 months after start of the initial RA treatment and subsequently, the same participants will be invited to take part in a focus group 12-18 months after RA treatment initiation. Data collection and analysis will be independently conducted by the local research teams in their native language. A meta-analysis of the local findings will be performed to explore and describe similarities, differences and patterns across countries.

Ethics and dissemination: Ethics approval was granted by the responsible local ethics committees. EQPERA follows the recommendations of the Declaration of Helsinki. Two main papers are foreseen (apart from the data reporting on the local findings) for peer-reviewed publication.

Key words: Rheumatoid Arthritis, Qualitative research, Longitudinal study, Patient Preference

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The specific nature of the study, in which qualitative studies are carried out in different countries and languages using a uniform methodology, is novel, and we report in a transparent way about our approach and challenges.
- As no formal meta-analysis method was present in literature applicable to our study, we developed a method based on established techniques for the synthesis of qualitative research, which can guide other researchers interested in conducting this type of research.
- Several quality enhancing strategies are applied to yield sound results in this multinational, multilingual, longitudinal qualitative study.
- The participating countries might have rather similar cultural views and healthcare systems, which would strengthen the Belgian findings, however, the study protocol offers a methodological framework for research in different parts of the world.

INTRODUCTION

In rheumatoid arthritis (RA), the outcome landscape dramatically changed over the past decades. RA is the most prevalent chronic, auto-immune inflammatory joint disease. It was typically described as an inevitably progressive disease with a destructive and disabling natural course. The continuous growth in effective pharmacological treatments contributed to this change, but the introduction of early therapy was one of the main drivers of transformed health outcomes of patients with RA.[1] Nowadays, remission or at least low disease activity have become realistic treatment targets for a notable proportion of the population.[2]

Nevertheless, the burden of disease and unmet needs remain considerable.[3 4] For example, most of the patients are at working age upon diagnosis, but work disability rates remain high.[5] Furthermore, patients with RA indicated the need for greater emotional support, and greater psychological support to manage the impact of disease on domains such as pain, fatigue, work and leisure.[6 7] Hence, it seems that patient preferences are not sufficiently understood and met by health professionals. In a recent report, patient-centered care was identified as a recurrent unmet need across rheumatic diseases, including RA.[8] Patient-centered care can be translated as care that is guided by the values and preferences of the patients,[9] with patient preferences referring to the perspective, beliefs and expectations of patients regarding their health and life.[10] As patient-centeredness is acknowledged as one of the key dimensions of high-quality care,[11] integrating the patient perspective in outcome assessment is increasingly advocated to achieve optimal outcomes in the treatment of RA.[12 13]

Qualitative studies shed light on the different views that patients with RA have on outcome compared to health professionals. These studies revealed the importance of fatigue and independence, among others,[14-16] to consider in daily practice on top of the traditional measures of disease activity, i.e., the swelling of joints and laboratory parameters of inflammation. Remarkably, limited attention has been given to the perspective of recently diagnosed patients. The early disease stage is probably the most daunting period for patients,

indicating specific needs and preferences.[17 18] The Belgian qualitative study of Van der Elst et al. provided new insights into patient-preferred outcomes in early RA, concluding that returning to 'normality' as soon as possible was the core preferred outcome, which related to aspects of disease control and participation, physical and mental aspects.[19] However, understanding is lacking about the transferability of these local findings to other settings and cultures.

Despite recommendations for RA management, literature shows that there are differences in how rheumatology services are viewed and practiced across countries.[20 21] These differences may be attributable to characteristics of the national healthcare systems, local customs, practices and values. Such cultural differences may consequently influence how patients evaluate their disease. For example, the survey study of Van Tuyl et al. demonstrated that the country in which patients were sampled resulted in slightly different key domains on how they perceived remission of disease.[22] Hifinger et al. showed that country of residence had an important influence on how patients with RA experienced fatigue.[23] It can thus be questioned whether patients in other countries would bring out other preferred outcomes.

To examine the transferability of the Belgian findings and to contribute to a more universal understanding of patient-preferred outcomes, we initiated the EQPERA consortium. EQPERA is the acronym for European Qualitative research project on Patient-preferred outcomes in Early Rheumatoid Arthritis. It is a multicenter, multilingual, longitudinal qualitative study across Belgium, The Netherlands and Sweden. The present paper reports about the international study protocol, based on the Belgian study procedures.

Objectives

The overall research objective in EQPERA is to explore how local context influences patient-preferred health and treatment outcomes throughout the early disease course by integrating the perspectives of patients with early RA from three European countries.

The objective is twofold:

(i) to describe patient-preferred outcomes in early RA and how they change throughout the early disease course (national objective);

(ii) to identify differences, similarities and patterns in patient-preferred outcomes across the three European countries (international objective).

METHODS AND ANALYSIS

The Belgian study was conducted during 2012-2013.[19] Based on the lessons learned and after multiple discussion rounds with the EQPERA steering group, an improved research protocol was written with the aim to implement a protocol as similar as possible in the other countries. Start of patient inclusion was 2016 in The Netherlands and 2017 in Sweden. We intend to publish the final results by the end of 2019.

Study design

A qualitative, explorative, longitudinal research design will be applied within a European context. As we study a research domain still lacking evidence, the use of qualitative methods is justified because we will learn from the rich descriptions of participants being shaped in their local contexts.[24 25] Longitudinal designs are relevant for studying complex phenomena and are specifically applicable in the context of a recent diagnosis since patients' perceptions and expectations may change during the overwhelming and rapidly evolving early disease stage. Previous research also suggests that the way patients experience and evaluate their disease can differ depending on disease duration.[15 26 27]

Patients with early RA will be invited to participate at two time points (Figure 1). At t_1, participants will be individually interviewed 3-6 months after they have started their initial treatment for RA. At t_2, participants will be invited to take part in a focus group 12-18 months after RA treatment initiation. To address a potential dropout of participants at t_2, those who decline to participate in a focus group will be invited for a repeated individual interview instead.

However, the preferred interview method at t_2 remains the focus group method to align with the original design of the Belgian study.

The reason for selecting different interview methods at t_1 and t_2 is based on the input of patient research partners and aims to match with patient preference in the context of a recent diagnosis. At t_1, the individual interview method is chosen because adjusting to a recent diagnosis can be seen as a primarily individual matter. Consequently, sharing personal experiences and opinions in a group setting can be too confronting at that stage of disease. A timeframe of 3-6 months after initiation of the initial RA treatment is chosen to not interfere with the diagnostic and therapeutic procedures, however, still including patients' earliest views on preferred outcomes. Furthermore, it is assumed that a few months of experience with the disease and treatment would help patients to communicate more easily about their outcome preferences.

At t_2, focus groups are chosen above the individual interview method for two reasons. Firstly, compared to the first interview moment, participants may probably feel more comfortable in a group setting, because of a grown disease perspective and the potential interaction with other patients (e.g., in the waiting room) by then. Secondly, group interactions potentially help participants to remember significant events and bring out personal thoughts, which in turn may result in more and diverse data.[25 28] It is reasoned that after 12-18 months of treatment experience, participants have had sufficient time to develop their view on the disease, with perhaps an observable change in their preferences accordingly.

Research context

EQPERA involves three countries in Northwest Europe: Belgium, The Netherlands and Sweden. These countries have a comparable organized healthcare system including a comprehensive social security system, however, differences exist in for example their reimbursement and referral system.

Participants will receive usual care according to local standards. Across countries, a comparable early RA management is implemented in respect of current international guidelines:[29 30] patients should be treated (i) early: as soon as the diagnosis is made; (ii) intensively, with methotrexate in the first treatment if possible; (iii) to target: treatment adjustments according to a predefined target of sustained remission or low disease activity. In addition, there is a common culture across the countries regarding interdisciplinary team care as key in disease management, but diversity can be expected concerning implementation aspects. For example, it has been shown that there is a wide variation in the role of nurses in the management of patients with chronic inflammatory arthritis[20], and in the composition of rheumatology multidisciplinary teams.[31]

In each country, an early RA cohort is available, the local teams include experienced qualitative researchers with a good command of the English language, and funding possibilities are available to work out their national project. The EQPERA steering group consists of team members with different disciplinary backgrounds: nurses (KE, IL, EM, YH), physiotherapists (AB, AG), a psychologist (JV), a patient representative (AG) and a rheumatologist (RW).

Level of collaboration between countries

Individual projects will be conducted in each country. The studies in Sweden and The Netherlands will be led by the local principal investigator (IL and EM, respectively) and supervised by the EQPERA project leader (KE), who designed and completed the Belgian qualitative study.[19]

Considering qualitative studies, potential language issues can be approached in two ways: either translate the transcripts and do the analysis in one place, or have the analysis done at each location and combine the data afterwards. After consideration, the project team decided that (i) data will be collected in the local settings by the local teams in their native language;

(ii) interviews will be transcribed in the original language and the transcripts will be analyzed by the local teams; (iii) only the results of the local analysis (i.e., interpreted data) will be combined for EQPERA purposes, and this after ending the analysis procedures and writing up the findings and conclusions in every country.

Original data will thus not be reviewed by the other teams (Figure 1). Centralizing data would mean translation of local transcripts to the common language in EQPERA (English). Translation holds the risk of losing the real meaning of words,[32] and would be expensive and time consuming because of the mountains of words that will be produced in every country. Above and beyond translation issues, we assumed that local data should ideally be analyzed by the people who are familiar with the local culture and context in order to get the most appropriate interpretations.

Collaboration with patient research partners

As EQPERA aims to capture the patient perspective, the project would benefit from active collaboration with patient representatives, or those who have the lived experience of RA. Following the recommendations of the European League Against Rheumatism for the inclusion of patient representatives in scientific projects,[33] each local team will preferably collaborate with two patient research partners.

The local principal investigators will be responsibility for coordinating this research partnership, being guided by the FIRST (i.e., Facilitate, Identify, Respect, Support and Train) framework of Hewlett and colleagues.[34] The exact level of the patient researchers' contribution will depend on local agreements (feasibility). In general, they will help by reflecting on the methods, formulating clear and understandable interview questions, interpreting and explaining data, and providing feedback on the readability of the patient information leaflet and informed consent form.

Participants

Eligible patients will have to meet the following inclusion criteria: (i) confirmed diagnosis of RA, in accordance with the American College of Rheumatology/European League Against Rheumatism 2010 criteria;[35] (ii) time between diagnosis and start of RA treatment of less or equal than 1 year; (iii) minimum age of 18 years; (iv) speak, read and write the local language; (v) started the initial RA treatment 3-6 months ago.

Sampling

Every country will strive to include a broad range of perspectives in their sample. To ensure this variation, participants will be purposively sampled based on their (i) age/life phase; (ii) gender; and (iii) treatment progress/treatment experience. Moreover, every country will apply a multicenter recruitment to account for possible variation in region.

Sampling in qualitative research corresponds to the assumption that collected data is of sufficient depth, i.e., representing the various views and opinions of the population with no added value of including more participants for answering the research question.[36 37] As there is no standardized definition of data saturation, we decided that data collection can be stopped if three consecutive interviews do not result in new themes or additional understanding (local team decision).

At t_1, we estimate that around 20 participants in every country will be needed to reach data saturation. At t_2, the sample sizes will foremost depend on the interest and willingness of participants to participate again. We aim for 4-8 participants in each focus group, which seems an appropriate number to keep the discussions manageable and stimulate contribution of every group member.[36 38] If possible, patient characteristics will be taken into account to create a mix of perspectives in the groups.

Recruitment

In each country, patients are recruited from multiple centers across different geographic locations, including academic and non-academic rheumatology centers. In Belgium, patients were sampled from nine centers across Flanders. The participating centers in The Netherlands are located in Nijmegen and Woerden, and in Sweden these are located in Lund, Malmö and Halmstad. A recruitment template will help the local teams to consider the main variables for creating heterogeneity in their samples.

Data collection

The interview guides

The semi-structured interview guides include pre-defined topics, with open-ended questions, and probing questions to reach a higher level of detail. All questions relate to the central interview question: 'Which outcomes of your illness and antirheumatic treatment are important to you at this moment?'. In every country, the interview guides will have the same content at start, and main questions will be fixed across countries. Data collection and analysis will be performed simultaneously, making it possible to adapt the interview guides if necessary to increase participants' understanding or to reach data saturation (local team decision). If adaptations are needed, these will be documented in the local research journal.

The content of the interview guides is inspired by previous qualitative studies on outcomes from the patient perspective.[14 16 39] In EQPERA, Dutch and Swedish versions of the Belgian interview guides (Flemish language) will be prepared by the local teams. Given similarities between the Flemish and Dutch language, minor adaptations will be applied after discussion and consensus with the Belgian team. Forward and backward translation will be used to prepare translations into English, which then will serve as a source to translate the interview guides into Swedish. The procedure of the translation from English into Swedish is presented

in Figure 2.[40 41] The main interview questions and the interview procedures are elucidated in Supplementary file 1.

Individual interviews (t_1)

At t_1, individual, face-to-face interviews will be conducted by maximum 2 interviewers per country, who are not involved in participants' clinical care. As the patient research partners noted that patients are in general not used to talk about outcome preferences, they will be asked to prepare written key words regarding the central interview question. The interviewer will start by elaborating on these key words. It is anticipated that interviews will last no longer than 60 minutes.

Focus groups (t_2)

Focus groups will be facilitated by one of the interviewers of t_1 in assistance of at least one participating observer. The focus groups will consist of three rounds: Round 1: preparatory phase; Round 2: (i) round-robin listing, (ii) developing a group list of patient-preferred outcomes, (iii) eliciting personal preferred outcomes, (iv) eliciting preferred outcomes in the actual stage of RA; Round 3: exploring the view of participants on the evolution of their patient preferred outcomes over the past year. The second round of the focus groups was inspired by the Nominal Group Technique methodology (NGT).[42] NGT is a consensus method that creates two types of data: (i) written ideas and prioritization, and (ii) the wider discussion, generating and clarifying ideas.[43] Our interest for using a prioritizing methodology is firstly, to create discussion between participants about a potential inconvenient topic; and secondly, to capture participants' underlying reasoning regarding preferences in outcomes. It is anticipated that focus groups will last about 60 minutes.

Individual interviews *(t_2)*

If necessary, the interviewer of t_1 will conduct individual interviews at t_2. The interview guide for these interviews is slightly adapted compared to t_1 in order to question participants about their view on changes in their preferred outcomes over time.

Procedures at both time points

Both individual interviews and focus groups will be held at a neutral and convenient location, and will be audio-recorded and transcribed verbatim according to transcription guidelines.[44]

At both time points, the following information will be obtained. Prior to the (focus group) interview, participants will document socio-demographic information. They will report about their general health, level of pain and fatigue during the past week on a visual analog scale after the interviews to avoid influencing patient opinion in advance. Clinical information will be extracted from the medical records by the local health professionals and shared with the local principal investigator. A detailed overview of all collected variables can be found in Supplementary file 2.

Data analysis

Data analysis will be conducted at two levels: (i) the local analyses of t_1 and t_2 data, followed by the longitudinal analysis; (ii) the meta-analysis with locally interpreted local data. The process of data analysis was based on several frameworks, which is summarized in Figure 3.

The local analyses

In every country, the analysis process will be a team activity involving patient representatives. Preferably two researchers, including at least the local lead investigator, will independently code the interview transcripts. Data analysis will start after the first interview or focus group.

The local researchers will follow the steps that are presented in Qualitative Analysis Guide of Leuven (QUAGOL) to analyze the interview data of t_1 and t_2.[45] The central activity in QUAGOL is the constant comparison process: between researchers' interpretations and the actual participant story, as well as to check new ideas for their presence in previous interviews. QUAGOL divides data analysis into two phases.

The first phase suggests five steps of preparation, implying only paper and pencil work: 1) rereading of the transcript to get knowledge of what the interview is about, and highlighting the relevant fragments; 2) preparing a narrative summary by describing the key story lines close to participants' words; 3) schematically describing the key ideas of the interview in a conceptual scheme; 4) fitting test and adaptation of the conceptual scheme by going back to the transcript; 5) looking for common ideas/concepts across conceptual schemes as a first comparison with the other interviews.

The second phase comprises another five steps, representing the actual coding process: 6) creating a common code list, without hierarchical structure and based on the insights from the refined conceptual schemes; 7) coding of each significant passage in a qualitative software program, while critically reviewing and refining the introduced code list; 8) defining the concepts by looking across-cases and reviewing all citations connected to a concept; 9) integration of all concepts in one story line that answers the research question, followed by verification of this overarching framework against all interviews and interview schemes; 10) describing the results.

QUAGOL is not specifically developed for focus group analysis. Therefore, the group process will also be analyzed (i.e., how the conversation in the group is organized, developing and changing), as well as the differences within and between the groups will be taken into account.[25]

For the longitudinal analysis, the local teams will merge their data of t_1 and t_2, in which meaningful individual statements will be extracted and compared between time points. There

are no universal frameworks for analyzing longitudinal qualitative data. The local teams will be guided by the method described by Saldaña,[46 47] who developed a 16-question template including (i) framing questions to help focusing on the context and conditions that influence changes over time; (ii) descriptive questions to describe what kinds of changes occur; and (iii) analytic and interpretive questions to reach richer levels of analysis.

The meta-analysis

The findings of the three independently performed qualitative studies will be combined in a meta-analysis. Several methods for synthesizing qualitative studies have been developed,[48] with some studies also using a combination of methods.[49] The methodology developed for EQPERA is inspired by the principles of meta-ethnography as practiced by Britten et al.,[50] and by the coding process of QUAGOL (preparatory phase) that is based on grounded theory principles.[45] We combined key methodological elements of both approaches and summarized these into four steps: 1) describing each case; 2) recognizing differences, similarities and patterns across cases; 3) disentangling differences and similarities across cases; 4) fitting-test of the meta-interpretations.

The findings of the participating countries will be integrated by face to face interaction between the different local teams about their data in a consensus meeting. Local findings will be translated into English. The local teams of Belgium, The Netherlands and Sweden will at least consist of the principal investigator, a patient research partner and a rheumatologist to achieve an interdisciplinary view and prevent bias due to solo interpretations. A senior researcher of the EQPERA team (YH), who is not linked to the local teams and data, will moderate the meeting. Below, we describe our stepwise approach.

Step 1: Describing each case

In step 1, the aim is to understand the course and results of each study on its own. Each country will be viewed as a case, with each case reflecting the overarching story of all local participants.

The lead investigators (KE, IL, EM) will present their findings (including quotes) and conclusions, covering: (i) the name and description of the patient-preferred outcomes; (ii) when, where, why, and in which circumstances they were put forward by the participants; (iii) the change through time of the description participants attached to the different outcomes. Furthermore, they will report about study details, using three short reports:[45] 1) a descriptive report, including what is specific to the participants, the treatment strategy, the research group and the healthcare system; 2) a methodological report, including deviations from the protocol, such as modifications to the interview guide, recruitment problems and level of data saturation; 3) a content report, including the main message derived from the data. A standard form will be used to enhance uniformity across presentations. The three cases will be presented one by one without immediate cross-comparison. After the case description, local teams will have familiarized with the other team's data and the particular context in each country.

In preparation of step 2, each team will individually reflect upon the following questions to stimulate the across-case analysis: 'What do I hear in every case?', 'What do I only hear in our case?', 'What do I not hear in our case?'. Furthermore, they will write down the patient-preferred outcomes they identified (codes and concepts) on color-coded sticky notes, each country representing another color, to support visually the comparison of the local findings in step 2.

Step 2: Recognizing differences, similarities and patterns across cases

In step 2, the aim is to translate concepts from one study to another,[50] to determine how studies are related (i.e., what emerges across cases) and to recognize what is typical for each case.

An affinity diagram will be created to organize the multinational data.[51] The patient-preferred outcomes of the three studies will be displayed side by side (using the color-coded sticky notes). Their meaning will constantly be compared from one country to another in order to

identify common and recurring, as well as conceptually different outcomes. We will start with a small set of concepts including the higher level concepts of each study, after which we will refine our first interpretations by discussing the lower-level codes.[45] During this process similar outcomes will be grouped if possible (by replacing the sticky notes), and we will look specifically for subtle differences between grouped outcomes.

After reaching consensus on similarities and differences, a 'saturation grid' will be completed in preparation of step 3. This is a technique used in qualitative studies to identify covered (sub)themes in each interview and decide on data saturation.[52] However, we will use a prespecified grid to identify the coverage of outcomes across the three studies.[50] Firstly, the grouped outcomes will be renamed. Secondly, all outcomes will be listed, meaning that each outcome of each local study is encompassed by one of the renamed outcomes in the grid. The main explanation of each outcome will be added. Thirdly, each country will represent a column and their sticky notes will be pasted next to the outcome in the grid that fits best the description on the sticky note. Hence, the empty cells will represent the outcomes that do not emerge across countries. By completing the grid, an overview will be developed of differences and similarities across cases.

Step 3: Disentangling differences and similarities across cases

In step 3, the aim is to explain the recognized differences and similarities by discussing why (or why not) certain outcomes emerge in a particular country or across countries.

Starting from the saturation grid (step 2), we will first go back to the methodological considerations and contextual features (step 1), before looking for possible cultural explanations. The group discussion will be an essential element in this step. For this reason we will view this discussion as a focus group, producing data that will be audio recorded and transcribed verbatim. After step 3, we will have obtained consensus on cross-cultural variation in patient-preferred outcomes in early RA.

In preparation of step 4, the local teams will separately draft a written summary of the discussion immediately after the focus group and with special attention to how their case was similar or different to the other cases.

Step 4: Fitting-test of the meta-interpretations

In step 4, the aim is to verify the appropriateness of the interpretations made during the focus group (step 3) regarding similarities and differences across countries.

Each local team will perform a fitting-test of common and own meta-interpretations with their local data. The local researchers will go back to their data, after rereading the focus group transcript and with their written summary in mind. Two questions will need to be answered: (1) Do the contextual interpretations actually reflect what is seen in our data? Is certain context information overlooked in the focus group? (2) Can we support the meta-interpretations with quotes that typically describe the perspective of our participants? During conference call meetings, the meta-interpretations will be adapted, completed or refined based on the fitting-test in each country.[45]

Patient and Public Involvement

Patients were involved in every step of the research project, as described throughout the paper. Research findings will be disseminated at Patient and Public Engagement events where appropriate.

Enhancing data quality and methodological rigor

Quality assurance

EQPERA is a large, multicountry, multicenter, multilingual, longitudinal qualitative research project. To yield sound results, several strategies are applied to ensure trustworthiness. These are: (i) recruitment of a qualified and motivated team; (ii) use of forward-backward translation

procedures; (iii) uniformity in recruitment, conducting the interviews and focus groups, transcription of audio files, data coding, data storing, and reporting; (iv) interdisciplinary team analysis (v) training of local staff to the protocol and hands-on guidance by the project leader. In Table 1, a detailed description is provided of the used strategies according to four quality criteria (i.e., credibility, dependability, confirmability, and transferability).[53 54]

Quality appraisal

As the findings of independently performed primary studies will be combined, quality is an important aspect to consider requiring a formal system for appraisal. The local teams will use a quality reporting tool to support a consistent use of methods and documentation across studies. Johnson et al. provided a useful template,[51] based on the consolidated criteria for reporting qualitative research,[55] and the quality criteria suggested by Mays and colleagues.[56] In EQPERA, several items were added regarding data management and quality appraisal in qualitative research.[32 44 57-59] Our tool comprises 50 items regarding four domains: 1) research team and reflexivity; 2) study design; 3) analysis and findings; 4) data management strategies (Supplementary file 3).

Table 1 Applied quality assurance strategies in EQPERA, described for each research stage, according to Lincoln and Guba's framework for evaluating trustworthiness.[53]

Research stage		Employed strategies for supporting trustworthiness	Assessing quality: (1) How congruent are the findings with reality? (2) Would the research findings be the same if the study would be replicated in essentially the same way? (3) Do the research findings emerge from the context and the respondents and not solely from the minds of the researchers? (4) Can the research be applied in other contexts?			
			(1) **Credibility** (internal validity)	(2) **Dependability** (reliability)	(3) **Confirmability** (objectivity)	(4) **Transferability** (generalizability)
Study design	-	developed around the patient perspective and in collaboration with patient representatives	●			
	-	triangulation of interview methods	●			
	-	addressing potential drop-out at t_2	●			
Establishment of the EQPERA team	-	recruitment of a qualified team, with a passion for the topic: ○ skilled in conducting qualitative research ○ familiar with the patient population ○ including patient research partners	●	●	●	●
Protocol development and implementation	-	a clear understanding of the overall project objective by all co-workers		●		●
	-	use of detailed study protocol, including a methods and analysis plan, an interview protocol, a data management plan, and templates	●	●		
	-	training of local staff to the protocol (project leader) prior to patient recruitment of t_1 and data collection of t_2	●	●		
	-	monitoring of local progress and hands-on guidance (project leader)		●		●
	-	documentation of local decisions (use of a research journal): ○ when, why, what changes, and who was involved in making this decision (e.g., modifications to the interview guide) ○ personal and/or practical comments	●	●	●	●
Sampling and recruitment	-	purposive sampling informed by simultaneous data collection and analysis	●			●
	-	multicountry and multicenter recruitment	●			●

	-	applying a definition for data saturation	●				●
	-	use of an enrollment template to support heterogeneity in the local samples and systematically keep records		●			
Data collection	-	semi-structured interview guides: ○ the same main interview questions in every country ○ collaboration with patient research partners to support clarity and understandability of interview questions ○ forward-backward translation ○ the same key points in the introduction	●	●	●		
	-	use of a data collection template and at least 2 audio recorders/interview to prevent missing data		●			
	-	verbatim transcription of the audio-recorded data		●			
	-	use of transcription guidelines		●			
	-	neutral and convenient interview location	●				
t_1	-	maximum 2 interviewers/country		●			
	-	maximum 2 interviews/day per interviewer to avoid interview burden and take time to reflect upon each interview					
t_2	-	the interviewer of t_1 is moderator of the focus groups		●			
	-	1 moderator/country and the same observer(s) for each focus group					
Data analysis	-	independent coding by at least 2 researchers	●		●		
Local level	-	data collection and analysis in parallel	●				
	-	constant comparison method	●				
	-	use of field notes	●		●		
	-	reflection after each interview/focus group: descriptive, content and methodological report	●		●		
	-	use of a qualitative software program		●			
	-	peer debriefings: more frequently early in de coding process	●		●		
	-	looking at data from multiple perspectives, including collaboration with patient researchers to help understand and describe the data	●		●		
	-	uniform procedure across countries based on established frameworks		●			●
International level	-	translation of the local findings and conclusions using a structured forward-backward procedure, supported by professional translators		●			
Reporting	-	use of guidelines for reporting the synthesis of qualitative research[60]					●

t_1: time point 1= three to six months after start of the initial treatment for early rheumatoid arthritis; t_2: time point 2= at least one year after start of the initial treatment for early rheumatoid arthritis.

ETHICS AND DISSEMINATION

Ethical considerations

EQPERA will apply the principles established in the Declaration of Helsinki.[61] Participants will provide written informed consent before data collection of t_1 and t_2. Only coded and interpreted data will be shared between the local teams for the meta-analysis. Ethics approval for the original studies were granted by the responsible institutional review boards.

Dissemination of results

Every country will prepare a publication on their national findings. Two EQPERA main papers are foreseen: 1) the present paper describes the rationale, design and methods of EQPERA; 2) a publication on the results of the meta-analysis. Next to peer-reviewed publications, we will also disseminate our findings in (inter)national research presentations, and also patient organizations will be updated about the study findings.

CONCLUSION

In EQPERA, the aim is to confirm the Belgian findings on patient-preferred outcomes in early RA in a European context, and provide a study protocol that has the potential to offer a methodological framework for further exploration of transferability in other contexts. Ultimately, study findings will be used to inform and optimize current care initiatives in early RA in order to address the unmet need of patient-centered care in RA.

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Author contributions

The following authors were involved in this study: Kristien Van der Elst (KE), Ann Bremander (AB), An De Groef (AG), Ingrid Larsson (IL), Elke Mathijssen (EM), Johanna Vriezekolk (JV), René Westhovens (RW), Yvonne van Eijk-Hustings (YH). KE and RW had the main idea of the study. KE, AB, AG, IL, EM, JV, RW and YH contributed to the design of the study. KE, YH and RW drafted the manuscript. KE, AB, AG, IL, EM, JV, RW and YH were involved in the editing of the manuscript. All authors read and approved the final version of the manuscript. Apart from the first and last author, the other authors are listed in alphabetical order.

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Competing interest statement

None declared.

Patient consent

Will be obtained.

Ethics approval

The Netherlands: the Medical Research Ethical Committee of Arnhem-Nijmegen waived ethical approval since the medical research involving human subjects act did not apply to this study; Sweden: ethical approval was obtained from the Regional Ethical Review Board at Lund University, Sweden; Belgium: ethical approval was obtained from the Human Research Ethics Committee of the University Hospitals Leuven.

Data sharing statement

Not applicable.

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Figure 1 Overview of the European, longitudinal, multimethod qualitative research design. *t*: time point

Figure 2 Forward-backward translation framework applied to translate the interview questions and procedures

Figure 3 Simplified outline of the used frameworks,[25 45-47 50] and the included steps in the local analyses and the meta-analysis

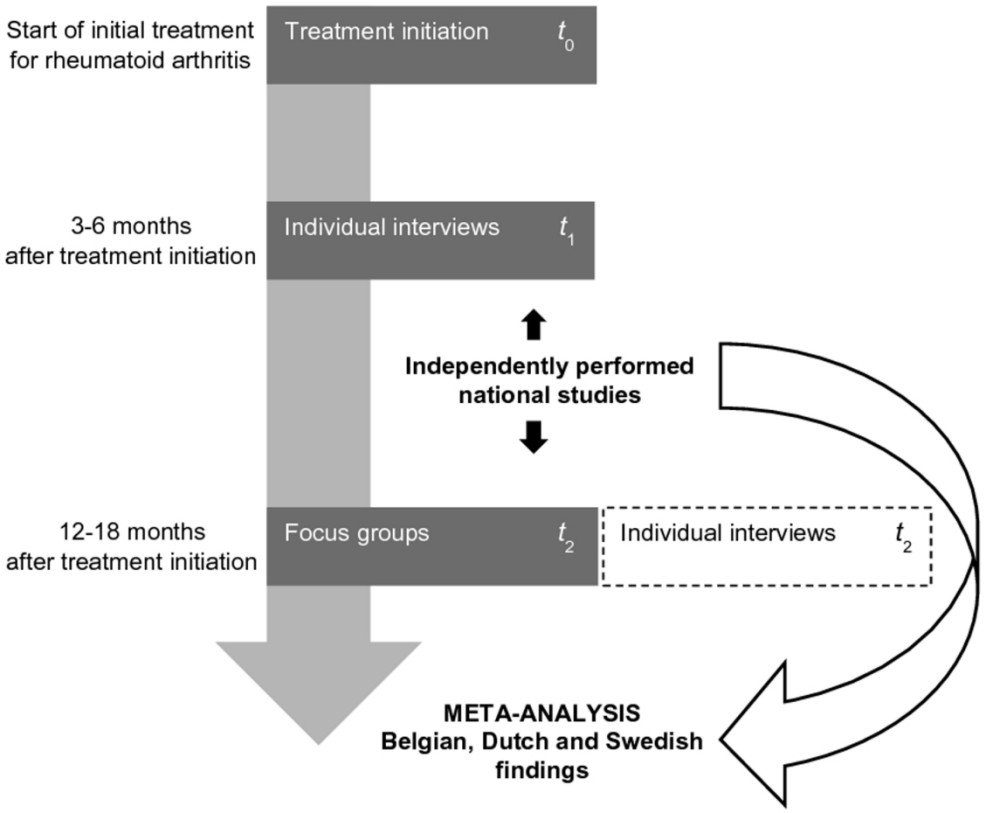

Figure 1 Overview of the European, longitudinal, multimethod qualitative research design. *t*: time point.

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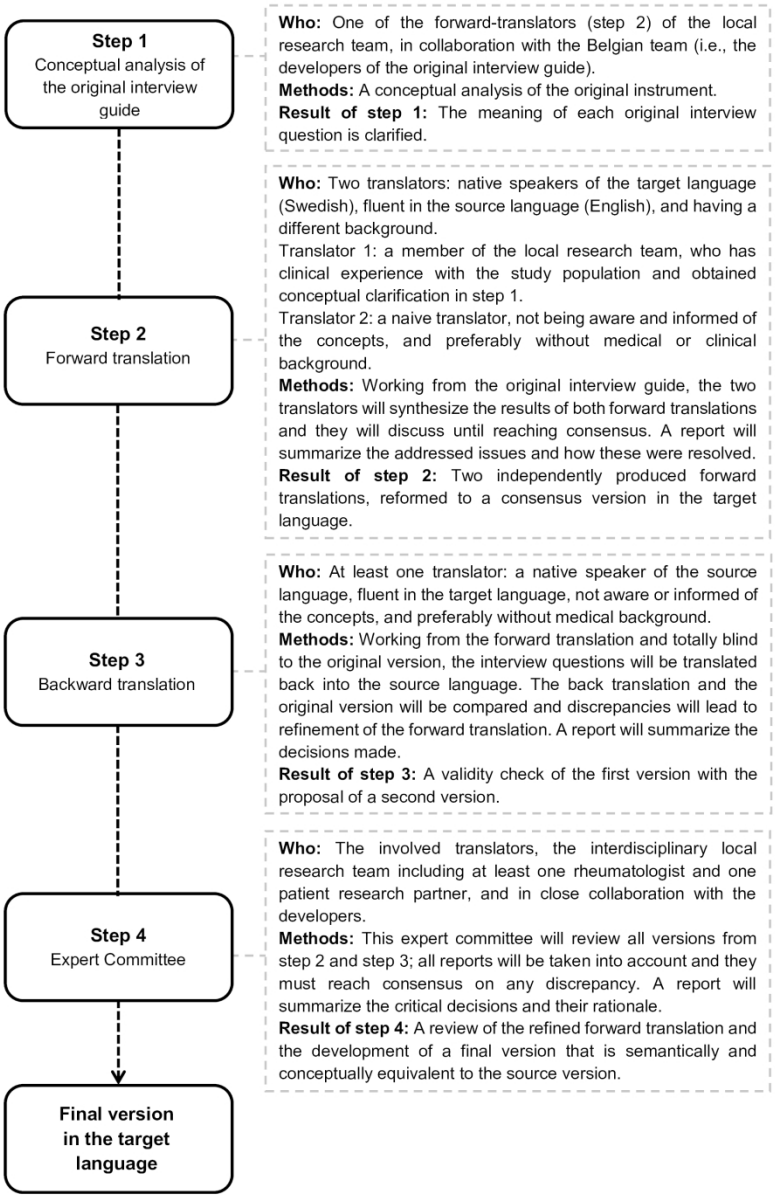

Figure 2 Forward-backward translation framework applied to translate the interview questions and procedures.

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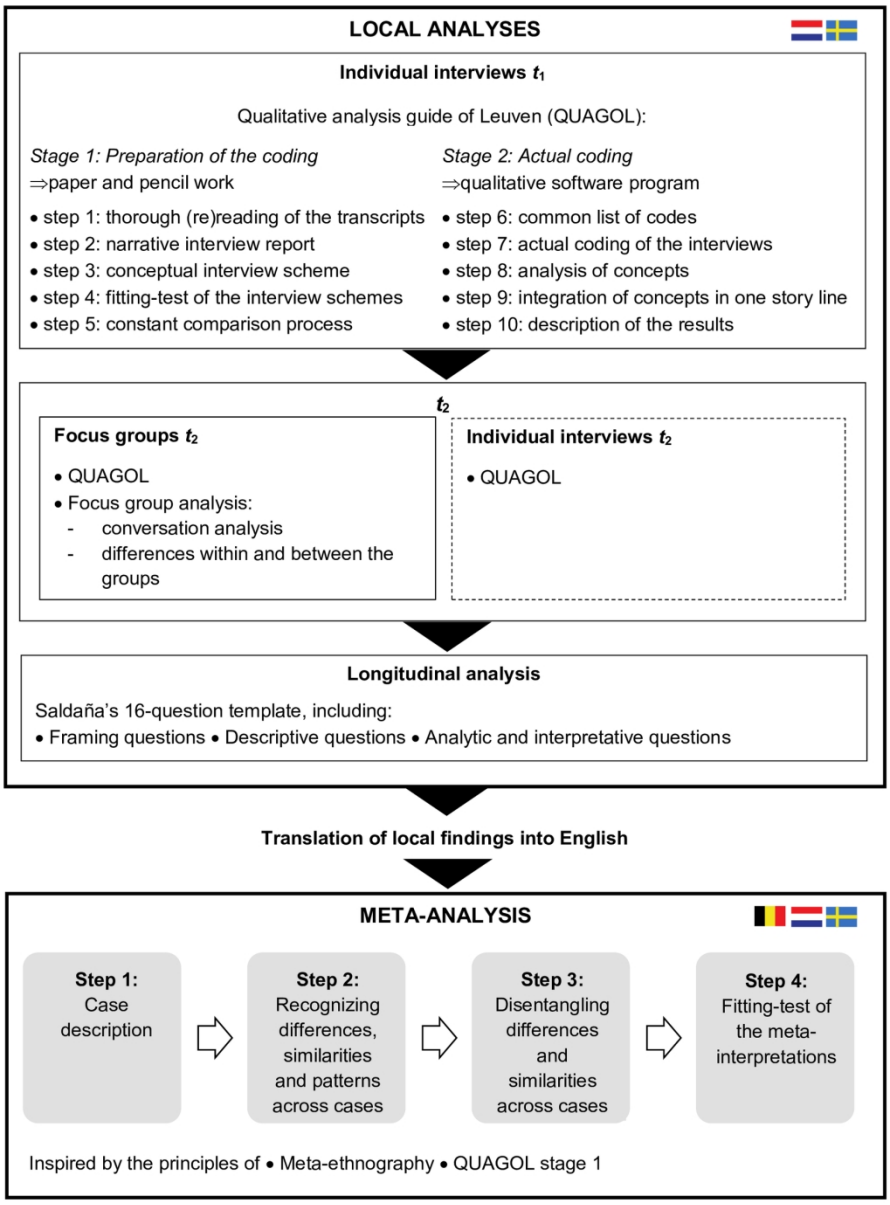

Figure 3: Simplified outline of the used frameworks,[25 45-48] and the included steps in the local analyses and the meta-analysis.

146x197mm (300 x 300 DPI)

Supplementary file 1 Main interview questions and procedures for the individual interviews (t_1 and t_2) and focus groups (t_2). Most aspects of the methods of t_1 and t_2 are adopted from the original Belgian study*

Context questions
- What type of treatment are you currently receiving? - Have there been any changes in your treatment plan? If so, why and what type of changes?
Individual interviews at t_1
Preparatory phase (5 to 10 minutes) To set the scene for the interview, participants were asked to write down as many keywords describing: - the impact of rheumatoid arthritis (RA) on their life - which outcomes of their illness and treatment they considered most important. *Start of the interview* The interviews began by discussing participants' written answers to those 2 questions. Participants were asked to elaborate on their keywords: - Can you tell me how RA affects your daily life? - Which outcomes of your illness and antirheumatic treatment are important to you at this moment? *Proceeding of the interview* The order of the other interview questions was determined by the participants' answers during the interview. - How has the treatment been working for you so far? - How do you decide whether or not your treatment is working? - What made you decide to start treatment? - What were your expectations of your antirheumatic treatment at the start of treatment? - To what extent do the expectations you had at the start of your treatment match your current expectations? Three questions were added after the first interviews: Other patients talked about 1) taking less medication, 2) returning to a normal life, 3) feeling better. Is this something you recognize? What do you feel about that? Probing questions: Could you tell me more about that? Could you give an example? *End of the individual interview* Is there anything else you would like to add?
Focus groups at t_2
Round 1: preparatory phase (5 to 10 minutes) The moderator introduced the phenomenon of interest, after which each group member was asked to independently prepare answers to the question below by writing down as many keywords as possible. Each answer was written on a separate sticky note. - Which outcomes of your illness and antirheumatic treatment are important to you at this moment? Next, participants were asked to try to order their sticky notes on a vertical scale, from most important (top) to least important (bottom). Participants were simultaneously asked to think about the following questions: - What important treatment results have already been achieved? - At present, is there anything you would like to change or improve regarding your disease or treatment?

Round 2, step 1: round-robin listing

All group members were asked to reveal and clarify, one by one, their personally preferred outcomes in order of importance. Meanwhile, the observer wrote these outcomes on a flipchart in front of the group.

- Who would like to share your personally valued outcomes with the group, in order of importance?
- Could you please clarify why these outcomes of your disease and antirheumatic treatment are important to you?
- Why did you designate that specific outcome to be the most important?
- Is there anything else you would like to add?

Round 2, step 2: developing a group list of patient-preferred outcomes

The group was asked to generate a consensus list by reviewing and merging all recorded outcomes and agreeing on the name and properties of each outcome on the list.

- Could any of the individual expectations be grouped?
- Who would like to suggest a name and meaning for this outcome?
- Do you think all the important outcomes are mentioned on the group list?
- Is there anything else you would like to add?

Round 2, step 3: eliciting personal preferred outcomes

Starting from the consensus list of patient-preferred outcomes that resulted in step 2, each group member was asked to independently try to select his or her 5 top outcomes from this list, using the sticky note ordering scheme.

Round 2, step 4: eliciting preferred outcomes in the actual stage of RA

The group was then asked to discuss a collective top 5 outcomes and to consider influencing factors.

- Looking at the group list, what outcome would you order as most important?
- What outcome would you order second…fifth?
- Can you tell us why this outcome is either important to you or not?

End of round 2

That is it for the second round. Is there anything else to add?

Round 3: exploring the view of participants on the evolution of their patient-preferred outcomes over the past year

The focus groups ended by exploring the participants' views on potential changes in personally preferred outcomes over time. During the individual interview of last year, you were asked for your preferred illness and treatment outcomes. In the meantime, you have gained more experience with your disease and treatment and the critical disease stage has passed.

- Do you feel that other results are now more important to you than the ones you identified at the start or during your interview last year?
- Could you explain why this has or has not changed?
- Are there outcomes that are now more, less, or no longer important to you?
- Why do you think that these are now more or less important than a year ago, or are no longer important? What may have caused this change in importance?
- Do you have an example of an outcome that has changed in importance compared to that outcome in the early disease stage? Why do you think this has changed? Could you clarify this in more detail?
- In general you mention (more or less) similar/different outcomes of importance compared to last year (in the early disease stage). What is your opinion on this observation?

End of round 3

This is the end of the third round. Is there anything else to add?

Probing questions: Is this outcome also important or not important to other group members? Are there any suggestions from other group members? Is there anyone who has a different opinion on the matter? Is it difficult for you to share your opinion on this? Does everyone agree? Who agrees or disagrees and why? Who would like to add something?

End of the focus group

- What is your general conclusion about today's focus group on preferred and important outcomes of disease and treatment in the actual disease stage?
- To summarize, you talked about […]. Do you agree with this summary of today's focus group?

Individual interviews at t_2

Preparatory phase (5 to 10 minutes)

Please, consider the next 5 to 10 minutes the question below by writing down as many keywords as possible. The interviews will begin by discussing your written answers to this question:

- Which outcomes of your illness and antirheumatic treatment are important to you at this moment?

Start of the interview

- Can you tell me what you have written down? So, which outcomes of your illness and antirheumatic treatment are important to you at this moment?

Proceeding of the interview

Exploring patient-preferred outcomes

- How has the treatment been working for you so far?
- To what extent do the expectations you had at the start of your treatment match your current expectations?

Exploring the view of participants on the evolution of their preferred outcomes over the past year

Last year, during the interview, you mentioned that the following outcomes of your treatment were important: ..... (t_1 keywords of the t_2 participant).

- Do you feel that other results are now more important to you than the ones you identified at the start or during your interview last year? Could you explain why this has or has not changed?
- Are there outcomes that are now more, less, or no longer important to you?
- Why do you think that these are now more or less important than a year ago, or are no longer important? What may have caused this change in importance?
- Do you have an example of an outcome that has changed in importance compared to that outcome in the early disease stage? Why do you think this has changed? Could you clarify this in more detail?

Patient-preferred outcomes compared to the focus groups at t_2

During the focus groups the following 5 treatment outcomes were found to be most important: 1) preferred outcome; 2) preferred outcome; 3) preferred outcome; 4) preferred outcome; 5) preferred outcome.

- I wonder if you recognize yourself in this? Could you explain why this is or is not the case?

End of the individual interview

Is there anything else you would like to add?

t_1: time point 1= 3-6 months after start of the initial treatment for early rheumatoid arthritis;

t_2: time point 2= 12-18 months after start of the initial treatment for early rheumatoid arthritis.

*Van der Elst K, Meyfroidt S, De Cock D, et al. Unraveling Patient-Preferred Health and Treatment Outcomes in Early Rheumatoid Arthritis: A Longitudinal Qualitative Study. Arthritis Care Res (Hoboken) 2016;68(9):1278-87.

Supplementary file 2 EQPERA Data collection template

Enrollment and interview logistics (t_1 and t_2)	
Respondent ID	ID number
Date of birth	dd/mm/yyyy
Gender	man, woman, X
Respondents' place of residence	postal code, location
Responsible recruiter	function, name, contact details
Rheumatology center	name, location
Type of rheumatology center	academic hospital, general hospital, private practice
Treating rheumatologist	name
Date of diagnosis	dd/mm/yyyy
Symptom duration	in months, [date of diagnosis - date of symptom onset]
Disease duration	in months; calculated with date of diagnosis
Comorbidity	no severe comorbidities present [yes/no]
Date of RA treatment initiation	dd/mm/yyyy
Months of treatment experience at t_1	date interview t_1 - date treatment initiation = between 3-6 months
Initial treatment	the local treatment protocol for early RA: free text, no details on dosages
Initial treatment allocated according to clinical prognostic factors	yes/no
Step-down strategy	yes/no (as initial treatment strategy)
MTX-only step-up	yes/no (as initial treatment strategy)
MTX + early bridging glucocorticoids	yes/no (as initial treatment strategy)
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs with glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs without glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
Biologicals as a first hit	yes/no (as initial treatment strategy)
Responder to initial treatment (at moment of t_1 recruitment)	yes/no
Patient obliged or deciding to discontinue RA treatment (at moment of t_1 recruitment; e.g., because of safety reasons, patient's decision)	yes/no
Reason to not recruit patient	free text or N/A (not applicable)
Date of study invitation	dd/mm/yyyy (sharing of invitation letter)
Reason in case not interested in study (if shared)	free text
Invitation for t_1 by phone (if interested)	dd/mm/yyyy (first contact between patient and researchers)

Verbal consent for t_1 after phone call	yes/no
Contact details patient	address/phone number/email
Patient-preferred contact method	by phone or email
Date and timing of individual interview t_1	dd/mm/yyyy; hour
Location of individual interview t_1	home or rheumatology practice/clinic
Reminder for t_1 sent	dd/mm/yyyy
Reason in case interview t_1 was cancelled (if shared)	free text
Respondent gave written informed consent t_1	yes/no
Interviewer t_1	name
Interviewer is involved as participant's health professional in daily practice	yes/no
t_1 respondent gave consent at t_1 to be contacted again for second part of study (t_2)	yes/no
Reason in case not interested in t_2 (at t_1) participation (if shared)	'Not interested to share own experiences in group', 'Feeling uncomfortable to talk in group', 'Fear for seeing other patients', 'Not interested in the story of other patients', 'Other'
Months of treatment experience at t_2	date focus group - date treatment start= at least 1 year (between 12-18 months) after treatment initiation
Invitation letter t_2 sent by post	dd/mm/yyyy (by researchers)
Invitation for t_2 by phone	dd/mm/yyyy (by researchers)
Verbal consent for t_2 after phone call	yes/no
If not interested in group interview, interested in individual interview instead?	yes/no
Reason in case not interested in t_2 (if shared)	'Not interested to share own experiences in group', 'Feeling uncomfortable to talk in group', 'Fear for seeing other patients', 'Not interested in the story of other patients', 'Other'
Date and timing of focus group t_2	dd/mm/yyyy; hour
Location of focus group t_2	clinical or non-clinical setting
If applicable: Date and timing of individual interview t_2	dd/mm/yyyy; hour
If applicable: Location of individual interview t_2	home or rheumatology practice/clinic
Reminder for t_2 sent (focus group or individual interview)	dd/mm/yyyy
Reason in case focus group (or individual interview) t_2 was cancelled (if shared)	free text
Respondent gave written informed consent t_2	yes/no
Moderator t_2	name
Observer(s) t_2	name(s)
If applicable: Interviewer t_2	name
Are the (interviewers/) moderators/observers involved as health professionals in the participants' daily clinical care	yes/no
Socio-demographic data: patient-reported t_1	
Date of birth	dd/mm/yyyy
Gender	man, woman, X
Educational level t_1	low, moderate, high

Currently employed t_1	yes/no
Employment status t_1	employed, not employed, retired, housewife/houseman, student
Marital status t_1	single, together unmarried, married, widower, other
Living status t_1	alone, with partner and/or kids, with other persons
Socio-demographic data: patient-reported t_2	
Educational level t_2	low, moderate, high
Currently employed t_2	yes/no
Employment status t_2	employed, not employed, retired, housewife/houseman, student
Marital status t_2	single, together unmarried, married, widower, other
Living status t_2	alone, with partner and/or kids, with other persons
Clinical data: patient-reported data t_1	
VAS general health t_1	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS pain t_1	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS fatigue t_1	100-mm visual analogue scale from best (0/100) to worst (100/100)
Key words in preparation of t_1 interview	Key words describing: - the impact of RA on their life - which outcomes of their illness and treatment they considered most important
Clinical data: patient-reported data t_2	
VAS general health t_2	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS pain t_2	100-mm visual analogue scale from best (0/100) to worst (100/100)
VAS fatigue t_2	100-mm visual analogue scale from best (0/100) to worst (100/100)
Key words in preparation of t_2 focus group (/interview)	Key words describing which outcomes of their illness and treatment they considered most important
Clinical data: health professional-reported data t_1 and t_2 (to be extracted from database/patient file)	
Date of diagnosis	dd/mm/yyyy
Symptom duration	in months, [date of diagnosis - date of symptom onset]
Disease duration	in months; calculated with date of diagnosis
Comorbidity	no severe comorbidities present [yes/no]
Start of treatment	dd/mm/yyyy
Months of treatment experience at t_1	date interview t_1 - date treatment start = between 3-6 months
Months of treatment experience at t_2	date focus group t_2 - date treatment start = at least 1 year

Initial treatment	the local treatment protocol for early RA, free text, no details on dosages
Initial treatment allocated according to clinical prognostic factors	yes/no
Step-down strategy	yes/no (as initial treatment strategy)
MTX-only step-up	yes/no (as initial treatment strategy)
MTX + early bridging glucocorticoids	yes/no (as initial treatment strategy)
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs with glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
○ glucocorticoids starting dose <30mg/day	yes/no
○ glucocorticoids starting dose ≥30mg/day	yes/no
Early combination therapy classical DMARDs without glucocorticoids	yes/no (as initial treatment strategy)
○ number of DMARDs included	number
Biologicals as a first hit	yes/no (as initial treatment strategy)
Treatment failure in the first year	yes/no
Treatment failure after 1 year	yes/no
Patient who discontinued treatment (t_1 or t_2; e.g., because of safety reasons, patient's decision)	yes/no

Note. RA: Rheumatoid Arthritis; MTX: Methotrexate; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; VAS: Visual Analog Scale; t_1: time point 1= 3-6 months after start of the initial treatment for early rheumatoid arthritis; t_2: time point 2= 12-18 months after start of the initial treatment for early rheumatoid arthritis.

Supplementary file 3 EQPERA data quality assurance reporting tool

Domain 1: Research team and reflexivity	
Item	Guide questions/description
Researcher characteristics	
1. Interviewer / moderator/observer	Who conducted the interviews/ focus groups? (who observed the focus groups?) ►Maximum 2 interviewers at t_1 and t_2 /country and maximum 1 moderator at t_2/country ►Preferably the same observer(s) for each focus group
2. Credentials / background	What were the researcher's credentials? (e.g., PhD, RN)
3. Occupation	What were the researcher's occupation at the time of the study?
4. Gender	Was the researcher male or female?
5. Experience and training	What experience or training did the researcher have?
Relationship with participants	
6. Relationship established	Was a relationship established prior to study commencements? *(*e.g., health professional)
7. Participant knowledge of the interviewer	What did the participant know about the researcher? (e.g., personal goals, reasons for doing the research)
8. Interviewer characteristics	What characteristics were reported about the interviewer/moderator/observer? (e.g., bias, assumptions, reasons and interest in the research topic)
Domain 2: Study design (a longitudinal, qualitative, explorative study)	
Participant selection	
9. Sampling	How were participants selected (e.g., purposively) Mono or multicenter sampling? Type of recruitment center(s)? (i.e., academic hospital, general hospital or private practice)
10. Method of approach	Who invited the participants? How were participants approached? (e.g., face to face, telephone, mail, email)
11. Sample size	How many participants were in the study? ♦at t_1: number of individual interviews ♦at t_2: number of participants per focus group / number of individual interviews
12. Non-participation	How many eligible patients could potentially be recruited? How many people were approached and how many of them refused to participate or dropped out? Reasons? (if shared) ♦Not interested in participation (refusal) ♦Drop out (type 1): in case t_1 interview was scheduled and cancelled ♦Not interested in participation at t_2 (drop out, type 2) ♦Not interested in participation in a focus group, but willing to participate in an individual interview instead at t_2 ♦Drop out (type 3): in case t_2 interview was scheduled and cancelled

Setting	
13. Setting of data collection	Where was the data collected?
14. Presence of non-participants	Was anyone else present besides the participant and researchers?
15. Description of sample	What are the important characteristics of the sample? (e.g., demographic data)
Data collection	
16. Interview guide	Were questions, prompts, guides provided by the authors? Was the interview guide pilot tested? Is it being made available?
17. Focus group guide	Were questions, prompts, guides provided by the authors? Was the interview guide pilot tested? Is it being made available?
18. Audio / visual recording	Did the research use audio or visual recording to collect the data?
19. Data collection method	How were the data collected? (t_2: focus group or individual interview?) Were repeat interviews carried out at t_2?
20. Field notes	Were field notes made during and/ or after the interview or focus group? ►if yes, please record them in the descriptive or methodological interview report. Were short reports prepared after each interview?
21. Duration	What was the duration of the interviews or focus groups?
22. Data saturation	Was data saturation discussed? After how many interviews was data saturation reached? (Definition in EQPERA: “if the last 3 interviews do not provide new information, insights or additional understanding to accomplish the study aims”)
Domain 3: Analysis and findings	
Data analysis	
23. Number of data coders	How many data coders coded the data? Who coded the data?
24. Independent coding	Was the analysis repeated by more than 1 researcher to ensure reliability?
25. Data analysis method	How were themes and concepts identified from the data? (e.g., Were themes identified in advance (framework-based) or derived from the data (data-driven)?)
26. Patient research partners	Did patient research partners provide feedback on the findings, and in which part(s) of the data analysis were they involved?
27. Software	What software was used to manage the data?
Reporting	
28. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quote identified? (e.g., participant number, gender, age)
29. Data and findings consistent	Was there consistency between the data presented and the findings?
30. Clarity of themes	Were themes clearly presented in the findings?

Domain 4: Data management strategies	
Data recording	
31. Recording changes and decisions	Were changes to the interview guide, the evolution in themes, deviations from the research protocol, and major local project decisions carefully documented along with the rationale for change? ►to recall decisions ►the use of a research log book is recommended
32. Recording interview data	Did you record the data with at least 2 audio recorders? ►to prevent missing data
Data storing	
33. Routinely storing of data	Was the data (e.g., audio files, transcripts, interview reports and field notes, patient-reported and clinical data, informed consents) or the project database routinely submitted to a central data repository or a secured cloud storage system? ►to avoid missing data and to easily manage large amounts of data like in qualitative research ►a uniform transcript header and file name could facilitate data storing (e.g., T1.number of interview.ddmmyyyy.initials of interviewer)
Data check	
34. Internal audit	Could the evidence (field notes, interview transcripts, recordings, reasons for interview guide adaptations,…) be inspected by others?
35. Preventing missing data	Did the principal investigator routinely check for missing data?
Data collection	
36. Recruitment flow	Was the recruitment flow carefully documented? ►the use a research log book (enrollment spread sheet) is suggested
37. Templates	Did you check the data collection templates and the Excel spread sheet?
38. Local interview guide	Translation/cultural adaptation interview guide: Did you use the proposed framework to translate the interview guide into the source language? Were cultural adaptations needed? ►please, record these in your research log book, together with the timing and the reason for adjustment
39. Avoiding and handling the presence of a third person	Focus of attention during interview scheduling: Was the purpose of a one to one interview mentioned to the participant? If someone else was present, did this affect the interview/data collection? ►please, reflect on this in the descriptive interview report
40. Introducing the interview	Did you prepare and practice the interview introduction? ►to maximize the interview return ►key words: welcoming the participant; introducing yourself; clarifying the purpose and importance of research, the importance of participant contribution, expectations regarding the participant (e.g., no good or wrong answers), role of the interviewer/moderator/observer, (t_2: “rules” regarding group discussion), ethical aspects; “Any questions?”; mobile phone on silent mode)

41. Interview burden	It is recommended to conduct 1 individual interview/day, with a maximum of 2 interviews/day ►to avoid interview burden and to have sufficient time to reflect on each interview
42. Interview reports	Did you write for each interview/focus group 3 short reports? (i.e., content report, descriptive report, methodological report)
43. Iterative process	Did you use an iterative process of data collection and analysis? ►to support data saturation
Data analysis	
44. Analysis guide	Did you use Qualitative Analysis Guide of Leuven (QUAGOL) to guide your data analysis? Did you use Saldaña's guiding questions for analyzing the longitudinal data?
45. Peer debriefings	Were regular peer debriefings held? ►time for reflection (in team): to discuss the interview return, the development of new themes, and to question and confirm saturation of themes ►early in de coding and interviewing process, more frequent meetings are suggested ►please make a short report of each debriefing to recall discussions
46. Team analysis	Was looked at the data in team (from different perspectives looking at the data)
Transcription	
47. Transcription guidelines	Who transcribed the data? ►>1 person: did you apply a uniform transcription method? (e.g., agreements about the level of details, to obtain confidentially, to reproduce the exact words spoken) ►external transcriber: was the interview transcript reviewed by the interviewer on data quality and accuracy of transcribing? How did you approach this quality check?
Team approach	
48. Patient research partners	What was the exact role of the patient research partners in the study
49. Interdisciplinary team	Who joined the interdisciplinary team, and what was their contribution?
Initiation session	
50. Project initiation	Did the local research team (at least the principal investigator) followed the initiation session lead by the project leader at t_1 and at t_2?

t_1: time point 1= 3-6 months after start of the initial treatment for early rheumatoid arthritis; t_2: time point 2= 12-18 months after start of the initial treatment for early rheumatoid arthritis.