Chapter 2: Qualitative research in rheumatology: a review of methods and contributions to practice and policy

This chapter introduces methodology, methods and appraisal of qualitative research as a background to the qualitative studies presented in the thesis.

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405. I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

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2.1 Abstract

Patient-centred care is widely advocated in rheumatology. This involves collaboration among patients, caregivers and health professionals and is particularly important in chronic rheumatic conditions because the disease and treatment can impair patients' health and wellbeing. Qualitative research can systematically generate insights about people's experiences, beliefs and attitudes which patients may not always express in clinical settings. These insights can address complex and challenging areas in rheumatology such as treatment adherence and transition to adult healthcare services. Despite this, qualitative research comprises one per cent of studies published in top-tier rheumatology journals. A better understanding about the impact and role, methods and rigor of qualitative research is needed. This overview highlights recent contributions of qualitative research in rheumatology, summarises common approaches and methods used, and outlines key principles to guide appraisal of qualitative studies.

2.2 Introduction

The need for patient-centred care is widely recognised in rheumatology, with shared decision-making being one of the cornerstone attributes in this paradigm (17, 131, 132). Clinical guidelines for rheumatic conditions have consistently emphasised that decision-making should explicitly consider the patients' values, preferences and needs (17, 18, 32). In addition, the World Health Organisation recommends that qualitative evidence is incorporated into the development of guidelines (133). This is particularly relevant because the interventions for patients with rheumatic conditions may have associated risks of complications and side-effects, and other impacts on the social, work-related and personal facets of their lives. Evidence on patients' experiences, attitudes and goals is thus needed to inform practice and policy.

Qualitative research methods can generate rich and detailed data to provide explanations and insights into the complexity of human behaviour and decision-making (134). Qualitative methods are used to generate hypotheses and address questions of 'how' and 'why'; whereas quantitative research methods are usually designed to test a hypothesis, and to answer questions of 'how much' or 'how often' (135, 136). Over the

past decade, there appears to have been a growing number of publications of qualitative studies in biomedical journals across medical specialties, including rheumatology (137-140) (Appendix B.1). However, qualitative studies remain a small percentage of published rheumatology research.

Between January 2015 to December 2019, qualitative studies comprised only 94 (1%) of the 8,484 original research articles published in the ten rheumatology journals with the highest impact factors in 2018 [Journal Citation Reports Social Science Edition (Clarivate Analytics, 2018)] (Annals of the Rheumatic Diseases, Arthritis & Rheumatology, Rheumatology, Seminars in Arthritis and Rheumatism, Therapeutic Advances in Musculoskeletal Disease, Osteoarthritis and Cartilage, Arthritis Care & Research, Arthritis Research & Therapy, Current Rheumatology Reports and Journal of Rheumatology. Only journals that publish original research articles have been listed.) (Appendix B.1) In part, this may be because health professionals and researchers have little training and experience in conducting and appraising qualitative research methods or are uncertain as to how it can inform or impact upon practice and policy (141).

This review will highlight recent contributions of qualitative research to care and policy in rheumatology and introduce qualitative research, including key methodologies and appraisal of qualitative work.

2.3 Contribution of qualitative research to clinical practice and policy

In this section, we summarise the insights that qualitative studies have provided in clinically-relevant areas affecting multiple rheumatic conditions in adult and paediatric rheumatology: medication adherence, transition from paediatric to adult care and the experience and management of fatigue. We have also summarised additional, selected qualitative studies in selected rheumatic conditions (gout, rheumatoid arthritis, systemic lupus erythematosus) that are commonly managed by health professionals in rheumatology in Table 2.1.

Medication adherence

Non-adherence to medications is common across many rheumatic conditions with consequent impacts on patient morbidity and even mortality (104, 142-144). Qualitative studies have been conducted in patients with rheumatic conditions to elucidate their experiences of and attitudes towards medications (145, 146). For example, patients with inflammatory arthritis are motivated to take disease modifying anti-rheumatic drugs in an attempt to return to their normal life and avoid future disability, though many often view their medications as a "necessary evil" with "toxic" side effects and uncertain efficacy (145, 147, 148). Medications may be perceived as a confronting reminder of their sickness and a threat to their health and well-being (145, 147, 149). For this reason, patients may decide not to take medications in order to regain control of their health and minimise lifestyle intrusions (149, 150). Patients can also be overwhelmed by the burden of deciphering multiple and sometimes conflicting information sources in order to make informed decisions about medications (145, 149, 151, 152). Studies have suggested that physicians can mitigate fears by facilitating shared decision-making and providing a supportive environment that allows them to voice their concerns about their medications (145, 152-154).

Transition from paediatric to adult healthcare

As young patients with rheumatic conditions transition from paediatric to adult care they must establish relationships with new clinicians, navigate different health care facilities and an adult model of care during a turbulent time of physical, social, vocational and psychological growth and change (155, 156). This is particularly relevant in rheumatology as many young people with juvenile-onset rheumatic diseases continue to have disease activity or significant sequelae in adult life (157). Qualitative studies in adolescents transitioning to adult rheumatology care highlight the challenges they face. They describe feeling abandoned and ill-prepared to face a health care setting that is perceived to be sterile, de-personalised and uninviting (158-160). The transition process could be isolating if healthcare staff in the adult clinic focused only on medical aspects of care, with little consideration of psychosocial impacts of the condition (158, 161, 162). Patients can feel overwhelmed by the expectations to attend clinic appointments without their parents or to handover their own clinical information to new adult providers (160). In contrast, they felt more confident and secure when given an opportunity to become familiar with the adult physician and clinic, if information on the patient's knowledge and understanding of their disease was clarified, documented and handed over, and if they

had the support of a specialist nurse in an adult clinic (156, 161). Patients undergoing transition to adult care appreciated a flexible approach that was tailored to their willingness and ability to take on more responsibilities and involvement in adult care (160, 161). Qualitative research has been used to help design and evaluate a transitional care program that incorporates the need for gradual and prepared transfer, regulated parental involvement and an adapted setting for adolescents (94, 160). Qualitative studies demonstrate the importance of transitional care programs to include familiarisation, joint clinics, nursing support, adequate transfer of information and the provision of care that addresses the psychosocial priorities of young people.

Experience and management of fatigue

Fatigue is a common and debilitating symptom, and is of high priority to patients with rheumatoid arthritis (RA) (163). Previously it was rarely addressed in clinical practice as a treatment target in long-term care of patients with RA (164). However, in the last few years rheumatologists have become more aware of fatigue in the clinical setting for example with the increasing use of patient-reported outcomes that evaluate fatigue (165). A semi-structured interview study with patients with RA found that fatigue permeated multiple aspects of life including work, leisure, family roles and led to feelings of uselessness and loss of self-esteem (166). The frustration, irritability and loss of control from fatigue negatively impacted on relationships. Fatigue was overwhelming, unpredictable and much more intense than the tiredness they felt prior to the onset of RA. Participants felt their fatigue was dismissed by health professionals, assumed that it was not treatable and that they had to manage it on their own. The findings from this study were used to develop a conceptual model of fatigue (167), a patient-reported outcome measure for fatigue (168), and a randomized controlled trial of cognitive behavioural approaches taught to nurses and occupational therapists in rheumatology care teams in order to improve fatigue (169). These studies highlighted the need for health professionals to address fatigue and ways to involve a multi-disciplinary team in supporting patients with this debilitating symptom.

2.4 Common methodologies and methods used in qualitative health research

Qualitative research is inherently subjective as the purpose is to elicit opinions and understand human behaviour. The data are co-constructed between the researcher and participants. Theory may be used to inform the design and approach of the study. For some approaches, including grounded theory, the study is designed to generate theory from the findings. There are several specific approaches (i.e. strategies of inquiry, theoretical frameworks) that are used as a basis of conducting qualitative research (170, 171). These approaches can guide the procedures for participant selection, data collection and analysis. Although many approaches exist, five of the most common approaches in health research (172) are grounded theory (173), ethnography (174, 175), phenomenology (176-178), case studies (179), and narrative research (180). The differences in these approaches are summarised in Figure 2.1 with illustrative examples of qualitative research in rheumatology (181-185). General characteristics of participant selection, data collection and data analysis that can apply to several qualitative approaches are described below. Researchers may design their study based on a single specific qualitative approach, or not specify a single approach but still use procedures that may be encountered within multiple approaches (170). Qualitative methods can also be used as part of mixed methods research and is discussed below.

Participant selection

Qualitative research typically involves an in-depth inquiry within a selected population. Purposive sampling is often used, which involves selecting participants who are relevant to the research question with the aim of including a diversity of relevant perspectives (135). Other sampling strategies include snowballing, which requires participants to identify other potential participants (97). This approach may be useful for including individuals who are hard to access, or with specific expertise or divergent opinions. These sampling methods are preferred to convenience sampling, which involves recruiting participants who are the most easily accessible (135) (e.g. consecutive patients from a single rheumatology clinic who are willing to participate in the study), because it is less likely to capture a broad range of perspectives.

Sample sizes are guided by the methodological approach, study design, participant population, research question and available resources. As a guide, semi-structured

interview studies may have 30-60 participants depending on the amount of data obtained per interview (186). In grounded theory, 20-30 participants of each population included in the study is generally reported to be adequate. For phenomenological studies that require interviewing each person multiple times, 6-10 participants may be sufficient (186). For focus groups 6 to 8 participants is recommended to optimise group interaction, with 3 to 5 groups for each characteristic of interest (e.g. based on a clinical diagnosis) (187). Rather than having pre-specified sample sizes, recruitment in qualitative research may cease when saturation is achieved (97). This is defined as when the collection and analysis of new data no longer elicits new insights.

Data collection

Semi-structured interviews and focus groups are commonly used in qualitative health research (95). These methods are effective in eliciting individual experiences, preferences and values to inform clinical practice. Focus groups capitalise on group interaction and allow participants to talk to each other, compare points of view, brainstorm ideas, and can be used to capture interpersonal language, culture and dynamics (95, 135). The facilitator keeps the group on task, asks probing questions, and encourages participation of all members of the focus group. Semi-structured interviews may be particularly useful when discussing sensitive issues or if participants are concerned about maintaining their confidentiality (95). The interview guide includes open-ended questions pertinent to the research questions (95). The guide is designed to encourage participants to openly pursue their perspectives in detail. Audio or visual recording and transcription of interviews and focus groups ensures that data is comprehensively captured for further analysis and can be complemented by field notes that capture contextual details, non-verbal communication and interactions within a group setting as well as initial reflections of the qualitative researcher (135).

Data may also be collected through observations or documents. Observations are a way of gathering data by systematically watching events and people to study their relationships and routine behaviours and is frequently applied in studies using ethnographic methodology (95). In qualitative health research this is particularly suited to understand how organisations work or how different members in the healthcare environment interact with each other (95). Observations may be covert or overt, and may involve the researcher as a participant or non-participant in the environment (95).

Documents include printed and electronic material such as diaries, newspaper articles and organisational and institutional reports. These may be used for historical or policy studies or to evaluate health care organisations or programs (135, 188).

Data analysis

The analysis of qualitative data generally seeks to develop a comprehensive understanding and description of the phenomenon being investigated. The output of qualitative research differs depending on the methodology. For example, thematic analysis will yield themes (patterns of shared meaning that together give a comprehensive picture of the population of interests' experience) (96), ethnographic studies are designed to provide insights into the behaviours and perceptions of a sociocultural group (174), phenomenology seeks to describe a phenomenon from the lived experience of individuals (189) and grounded theory develops a theory arising from the data (173). The processes used in qualitative data analysis involve data reduction (by coding and identifying meaningful sections of the data into labels), data organisation (in which codes are collected and sorted) and interpretation (where data are analysed to understand meaning, and codes are categorised, compared and emerging themes or theories are developed) (95). Data analysis should be an iterative process which involves cycles of data collection, analysis and then resumption of data collection again to further explore and challenge emerging themes or theories (97).

Qualitative analysis software manages qualitative data and provides efficient methods for storing, organising and retrieving qualitative data (135). These programs however, cannot conduct the analysis of the data. Investigators must create their own codes and interpret their data. The interpretive nature of qualitative research inevitably means that the researcher's background, knowledge and values can influence the analysis of the data. Several methods can be used to ensure the results accurately reflect the spectrum of the participants' perspective. These include member checking (sharing preliminary findings with participants to check whether their viewpoints are accurately captured), investigator triangulation (incorporating input from team members in the analysis, especially from different backgrounds) and reflexivity (reflecting on personal experiences and biases using a diary or field notes in relation to the data analysis) (97, 135).

Combining qualitative and quantitative research methods

A study may also use a mixed methods approach, which is a distinct research methodology where both qualitative and quantitative data are collected. Mixed methods research requires an integrated analysis and the use of rigorous qualitative and quantitative research methods (190). Mixed methods research can be classified into three core mixed methods designs: convergent (where qualitative and quantitative data are collected and analysed simultaneously within a single phase) (191-193); sequential explanatory (where quantitative data is collected first, then qualitative data collected to explain the quantitative findings) (194); and sequential exploratory (where qualitative data is collected, a feature such as a new instrument or intervention is built, and then the feature is tested quantitatively) (168, 195, 196). These core mixed methods designs can be built into more complex research designs such as within a randomised controlled trial (166, 169, 197, 198) and is recommended for process evaluations of complex interventions (199). Before a trial, qualitative studies could generate hypotheses for examination, help develop and refine the intervention or outcome measures (200, 201) or enhance patient recruitment (202, 203). During a trial, qualitative methods could examine whether the intervention was delivered as intended, explore the participants' responses to the intervention and understand processes of implementation and change. After a trial, qualitative research can explain reasons for positive or negative findings of the trial, variations in effectiveness amongst trial participants, assess the acceptability of the intervention or be used to generate further questions or hypotheses (204).

2.5 Reporting and appraisal of qualitative research

The Enhancing Quality of Transparency of Health Research (EQUATOR) network recommends using the Consolidated Criteria for Reporting Qualitative Health Research (COREQ) as a guideline for reporting of qualitative research using interviews and focus groups (100). There are several other guides available for the conduct and evaluation of qualitative research (95, 97, 100, 135, 205, 206) including the American Psychological Association's Journal Article Reporting Standards for Qualitative Research (JARS-Qual) (207) which also provides guidance on how to structure a qualitative manuscript. However, the appraisal of qualitative research remains contentious, and there is debate as to how and even whether quality can be legitimately judged (95, 208, 209). There is no empirical evidence to indicate which

criteria are critical and how to assess them (95, 209). The framework by Lincoln and Guba, addresses the rigor of qualitative research based on four criteria: credibility, confirmability, dependability and transferability (210). The links between the COREQ reporting items and these constructs of rigor are shown in Table 2.2.

Credibility – Are the findings trustworthy?

Credibility refers to having confidence in the truth of the findings (analogous to internal validity in quantitative research) (206). Readers may be confident that the findings are credible if the researcher provides a comprehensive and sensible explanation of the data. Comprehensiveness includes ensuring that the true breadth and depth of the phenomena in question were explored. Breadth of data can be captured using purposive sampling, continuing to sample until data saturation and the final sample size. Depth of data may be gauged by reviewing the question guide and duration of the interview or focus group to determine if they allow the participant to discuss the topic of interest in detail, and whether efforts were made to provide a setting that allowed participants to feel comfortable to express their opinions. In addition, triangulation in qualitative research allows a generation of deeper and richer insights. This includes using multiple data sources (data triangulation), data collection methods (methodological triangulation) or involving multiple researchers (investigator triangulation) in the analysis of data (135). Involving multiple researchers in coding can ensure that findings adequately capture all aspects of the data. A clear and insightful presentation of major and minor themes provides a final check on the comprehensiveness of data findings. Member checking allows participants to provide feedback on preliminary findings and ensures that findings are a sensible interpretation of their experiences.

Confirmability – Are the findings linked to the data?

Confirmability refers to the extent to which findings of the study are shaped by the data and are not a misinterpretation of findings by the researcher (analogous to objectivity in quantitative research) (206). This can be demonstrated by showing raw data such as quotations and linking them to findings from the study. The researcher may describe self-reflexivity whereby they recognise and reduce any undue influences on their

interpretations of the data. Interpretations of data can also be confirmed using multiple data coders, triangulation and member checking, as noted in relation to credibility (206).

Dependability – Is the process auditable?

Dependability is analogous to reliability in quantitative research (206). Due to the nature of qualitative research it is not possible for another researcher to fully replicate a qualitative study. However, a rigorous and systematic approach to qualitative research can be followed with a coherent link formed between the findings and methods used in the study. Audio or video recordings, transcription of data and the use of qualitative software for coding allows transparent and auditable documentation of the research process (135). The raw data and analysis can thus be reviewed by others.

Transferability – Are the findings relevant to other contexts?

Transferability describes the degree to which themes or concepts from a qualitative study can be applicable to other contexts (analogous to external validity in quantitative research) (206). By providing details about participants' characteristics and study setting in enough detail (termed 'thick description'), readers of qualitative research can determine whether the findings may be applicable to their own setting. In addition, comparing the results of the study with other studies in different populations or to existing theory can also help demonstrate the broader relevance of the study findings.

2.6 Conclusions

Qualitative studies have the potential to generate a deep understanding of people's motivations, beliefs, goals, expectations and needs. In rheumatology, evidence from qualitative studies has made a unique and valuable contribution to practice and policy. Qualitative research can be systematic, rigorous, and evaluated using the principles of credibility, confirmability, dependability and transferability. We suggest that further qualitative research is needed in rheumatology to address evidence gaps regarding patient priorities in the management of rare rheumatic conditions, co-ordination and

integration of care amongst health care professionals and education about psychosocial impacts of disease. Incorporating insights from qualitative studies into clinical care, policies and trials can help promote patient-centred care to improve outcomes for patients with rheumatic conditions.

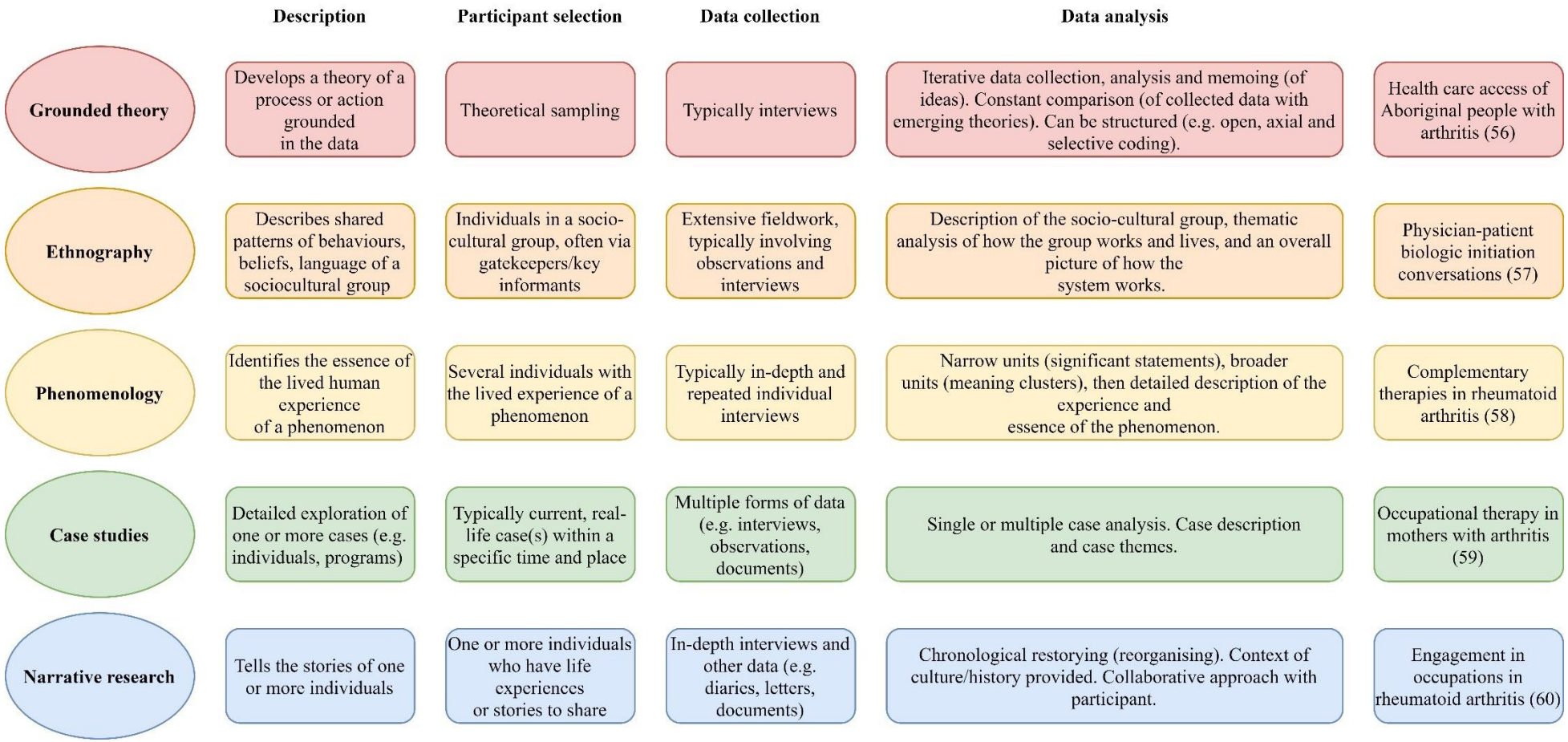

Figure 2.1. Five key qualitative approaches in health research

Table 2.1. Selected examples of qualitative studies in rheumatology

Reference	Topic	Approach	Data collection	Data analysis	Main findings	Implications for clinical care or policy
Singh et al. (200)	Gout self-management among African American male veterans with high medication adherence	NR	Semi-structured interviews	Thematic analysis and content analysis	Fear of the severe and debilitating pain of gout and self-confidence from having a military-like discipline helped veterans adhere to medications and lifestyle changes. Maintaining a positive outlook and accepting the diagnosis of gout allowed participants to embrace changes in their daily routines.	Emphasising self-discipline, positivity and disease acceptance through patient narratives could facilitate better gout-self management.
Flurey et al. (211)	Experiences and coping styles of men with RA	NR	Focus groups	Thematic analysis	Men with RA felt angry, embarrassed and helpless by their reduction in strength, ability to work, perform household duties or play with children. Participants coped by being stoic or reacted by engaging in destructive behaviours, withdrawing and concealing their arthritis.	Health professionals should ask men explicitly about their psychological and emotional well-being and be aware that RA can threaten masculine roles and identity. Support could take the form of purposeful information-oriented sessions with other patients with RA.
Hart et al. (212)	How young people (aged 16-25) with inflammatory arthritis evaluate the risks and benefits of treatment	Grounded theory	Semi-structured interviews, recorded consultations, focus groups	Grounded theory analysis	Young people aspired to live a “normal” life. However, treatment schedules and side effects could be highly intrusive, diminish well-being, and compound feelings of being different. Changes to treatment could force young people to confront their illness and heighten distress about uncertainties of the future. Participants wished for a relatively simple and stable treatment regimen that improved symptoms and had side effects that posed minimal restrictions.	Health professionals should elicit young people’s priorities and concerns regarding their treatment and address the impact of treatment on their ideas of a “normal” life such as relationships, education, work and physical appearance.

Reference	Topic	Approach	Data collection	Data analysis	Main findings	Implications for clinical care or policy
Shaw et al. (152)	The development of resilience among patients with RA	Ethnography/ Narrative inquiry	Semi-structured interviews and observations of participants' living environment and routines	Narrative analysis	Resilience was cultivated through internally directed emotional management strategies and externally directed behaviours. This included adopting a mindset of being in control of their RA, remaining calm during challenges such as medication-related complications, and positive reframing and focus on abilities rather than limitations. Offering support to others through community service, engaging in enjoyable hobbies and activities, or using humour in social interactions about limitations posed from RA allowed patients to feel valuable, satisfied and connected to others.	Behavioural interventions or social support programs can promote resilience by utilising externally and internally directed management strategies identified in the study.
Tunnicliffe et al. (192)	Healthcare and research priorities of adolescent and young adults with SLE	Mixed methods study	Semi-structured interviews and focus groups	Thematic analysis, descriptive statistics for votes	Service shortfalls including timely diagnosis of SLE worsened symptoms and caused anxiety, lack of culturally relevant educational materials made it difficult for participants to understand and explain their illness to family and friends. Participants strongly emphasised the impact of SLE on psychological health including reduced self-esteem, social withdrawal and fear of being unable to achieve future vocational and family goals. Participants also wanted to reduce the psychological, emotional and financial burden SLE imposed on their family, friends and other patients with life disrupting manifestations of SLE.	Research and clinical resource allocation should address gaps in service provision and incorporate strategies to alleviate anxiety and efficient use of resources to minimise the impact of SLE on family, friends as well as the wider population of patients with SLE.

Reference	Topic	Approach	Data collection	Data analysis	Main findings	Implications for clinical care or policy
Sumpton et al. (213)	Patients' perspectives of systemic sclerosis	NR	Semi-structured interviews	Thematic analysis	Systemic sclerosis imposes major physical and social restrictions that impair patients' identity and self-esteem. Insecurities and anxiety in care arise from ambiguities about the cause, diagnosis and prognosis of the disease.	Clinical care for patients with systemic sclerosis can be optimised by providing psychosocial care and improving communication and education around the concerns regarding disease prognosis and management.
Hewlett et al. (214)	RA patients' perspectives of flare	NR	Focus groups	Thematic analysis	Flare incorporated an individual cluster of symptoms including severe, unrelenting and multi-joint pain, dramatic and extreme level of stiffness, fatigue that was unlike normal RA fatigue, systemic flu-like symptoms and cognitive shut down. The symptoms profoundly compromised simple daily functions and caused emotional distress to the point of wanting to cut off joints or die for some. Patients increased their usual level of self-management and would seek professional help when they were still unable to control their multiple symptoms or run their normal lives.	Assessment of flare that includes these patient experiences can help patients and clinicians recognise early warning signs and enhance communication between patients and professionals.

NR, Not reported; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus

Table 2.2. Appraisal of qualitative studies

Qualitative criteria	Quantitative criteria	Aspect of quality	Examples from COREQ domains and items
Credibility: Are the findings trustworthy?	Internal validity	Truth value	Purposive sampling Data saturation Final sample size Interview guide Duration Repeat interviews Setting of data collection Relationship with participant Presence of non-participants Multiple data coders Participant checking Clarity of themes
Confirmability: Are the findings linked to the data?	Objectivity	Neutrality	Reflexivity Multiple data coders Participant checking Quotations Data and findings consistent
Dependability: Is the process auditable?	Reliability	Consistency	Audio/Visual recording Transcription Description of coding tree Software
Transferability: Are the findings relevant to other contexts?	Generalisability	Applicability	Thick description of sample and setting of data collection

Appraisal of qualitative studies using the Lincoln and Guba framework linked to examples from Consolidated Criteria for Reporting Qualitative Health Research (COREQ) items

Chapter 3: Scope of outcomes in trials and observational studies of interventions targeting medication adherence in rheumatic conditions: a systematic review

This chapter assesses the scope of outcomes in interventional studies of medication adherence in rheumatic conditions.

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405. I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

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3.1 Abstract

Objective Non-adherence to medications is common in rheumatic conditions and associated with increased morbidity. Heterogeneous outcome reporting by researchers compromises the synthesis of evidence of interventions targeting adherence. We aimed to assess the scope of outcomes in interventional studies of medication adherence.

Methods We searched electronic databases to February 2019 for published randomised controlled trials and observational studies of interventions with the primary outcome of medication adherence including adults with any rheumatic condition, written in English. We extracted and analysed all outcome domains and adherence measures with pre-specified extraction and analysis protocols.

Results Overall, 53 studies reported 71 outcome domains classified into adherence (1 domain), health outcomes (38 domains) and adherence-related factors (e.g. medication knowledge) (32 domains). We subdivided adherence into three phases: initiation (n=13 studies, 25%); implementation (n=32, 60%); persistence (n=27, 51%); phase unclear (n=20, 38%). Thirty-seven different instruments reported adherence in 115 unique ways (this includes different adherence definitions and calculations, metric and method of aggregation). Forty-one studies (77%) reported health outcomes. The most frequently reported were: medication adverse events (n=24, 45%); disease activity (n=11, 21%); bone turnover markers/physical function/quality of life (each n=10, 19%). Thirty-three studies (62%) reported adherence-related factors. The most frequently reported were: medication beliefs (n=8, 15%); illness perception/medication satisfaction/satisfaction with medication information (each n=5, 9%); condition knowledge/medication knowledge/trust in doctor (each n=3, 6%).

Conclusion The outcome domains and adherence measures in interventional studies targeting adherence are heterogeneous. Consensus on relevant outcomes will improve the comparison of different strategies to support medication adherence in rheumatology.

3.2 Introduction

Many rheumatic conditions require the long-term use of medications, yet adherence may be suboptimal. Adherence may be defined as *"the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* (34). In rheumatoid arthritis (RA), medication adherence ranges from 14% to 80% and non-adherence can lead to poorer health outcomes such as increased disease activity, poorer quality of life and radiological progression (63, 87). In osteoporosis (OP), less than 70% of patients start prescribed treatment and approximately 50% discontinue therapy within one year, which is associated with an increased risk of fracture (88). Researchers are increasing efforts to develop and test strategies to improve medication adherence in rheumatology. However, differences in the design of these interventional studies, including outcome selection and reporting, hamper the comparison of these strategies.

Adherence studies to date have used heterogeneous adherence outcome measures, definitions and thresholds, and often have not assessed clinically meaningful health outcomes (75). If researchers omit important outcome domains, or use different measures, end-users of the research are unable to judge the relative effectiveness of interventions or understand the clinical relevance of research findings. Core domain sets, which are defined as the minimum set of outcome domains that should be measured and reported in specific clinical trials, reduce inconsistent reporting, reporting bias and can help ensure the measurement of outcomes that are important to patients and decision-makers (76). The Outcome Measures in Rheumatology (OMERACT) initiative has developed core domain sets for many rheumatic conditions (76).

The aims of this study were to describe the scope and consistency of outcome domains and adherence measures in studies (including both randomised controlled trials and observational studies) of interventions to improve medication adherence in adults with rheumatic conditions.

3.3 Materials and Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to report this systematic review (Appendix C.1). We have published the original protocol and protocol amendments (102, 215).

Search and selection criteria

The inclusion criteria is described with the PICOS framework (Participant/Intervention/Comparator/Outcome/Study design): 1) Participants: Adults aged 18 or older with any rheumatic condition; 2) Intervention: Any strategy to improve adherence; 3) Comparator: Management as usual (if a comparator arm was included in the study); 4) Outcomes: All outcome domains, including only studies with medication adherence as the primary outcome; 5) Study design: Randomised controlled trials (RCTs) and observational studies (non-randomised comparison studies, including pilot studies, which incorporated an intervention targeting adherence). We included both RCTs and observational studies as we anticipated a limited number of informative RCTs of adherence interventions in rheumatic conditions.

We searched MEDLINE, PsycINFO, Embase, CINAHL and CENTRAL from inception to 25th February 2019 to identify all studies of interventions designed to improve medication adherence in any rheumatic condition. The search strategy included MESH terms ('Rheumatoid arthritis', 'Spondyloarthritis', 'Osteoporosis', 'Systemic lupus erythematosus', 'Systemic scleroderma', 'Vasculitis', 'Connective tissue diseases', 'Medication adherence', 'Treatment adherence and compliance', and 'Treatment refusal') (See Appendix C.2 for the full search strategy). We also hand searched the reference list of selected systematic reviews of adherence studies (93, 216, 217) and Google Scholar. We excluded conference reports, protocols and abstracts given the limited information provided, however we searched for the full publications of these and contacted authors if needed. We included only English language articles. Two reviewers (AK and LCS) independently screened abstracts and full texts of all identified studies. A third reviewer (KT) resolved any disagreements on included studies.

Data extraction

For each study, two reviewers (AK, KT) independently extracted the following study characteristics: first author, year of publication, participating countries, study design, type of intervention, sample size, study duration, and participants' mean age, sex, medication, rheumatic condition, and disease duration. In addition, two reviewers (AK, LCS)

independently extracted all outcome domains, measures and the instrument, metric, method of aggregation and time points of all adherence measures

Data synthesis and analysis

Two reviewers (AK, LCS) grouped all outcome domains into three overarching groups: adherence, health outcomes and adherence-related factors. We calculated the number of studies reporting each outcome domain. The two reviewers discussed any discrepancies between the extracted outcomes and outcome domain grouping until agreement was reached and consulted a third reviewer (KT) when necessary.

We subdivided adherence into phases: (1) initiation defined as when the patient takes the first dose of prescribed medication; (2) implementation defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing; or (3) persistence defined as the length of time between initiation and the last dose immediately preceding discontinuation (35).

We categorised each adherence measure into subjective and objective measures. Subjective measures included all self-report questionnaire/diary/interview and clinician judgment (i.e. clinician estimate of adherence). Objective measures included: direct observation; drug concentration in body fluid; electronic monitoring (e.g. medication event monitoring systems [MEMS]); pharmacy refill record; and pill count. We also recorded the name of each instrument used to measure adherence, e.g. different self-report measures and drug levels were recorded separately. Finally, to demonstrate the heterogeneity in adherence measure reporting, we recorded a unique adherence measure which included the instrument, details on the adherence calculation/cut-off determined for adherence, metric (e.g. reporting adherence measures as change from baseline, end value or time to event) and method of aggregation (categorical, or use of means or medians when reported as a continuous measure). We recorded the time points for all adherence measures.

Health outcomes included any condition-specific outcome domain that informed the impact of the intervention on any clinical aspect of the condition including pathophysiological manifestations (e.g. fracture, pain), life impact (e.g. quality of life), death, or resource use (e.g. utilisation costs) as defined in the OMERACT handbook (76). In order to evaluate whether studies reported important health outcome domains,

we assessed whether existing studies of adherence interventions reported on medication adverse events. We also compared the health outcome domains in the included studies with existing condition-specific core domain sets via OMERACT (https://omeract.org/) and Core Outcome Measures in Effectiveness Trials websites (http://www.comet-initiative.org/), noting whether these core domain sets were available at least five years before publication of the adherence trial for feasible inclusion within the trial.

Adherence-related factors included any factors that could influence adherence behaviour using the COM-B ('capability', 'opportunity', 'motivation' and 'behaviour') framework described by Michie et al (38), reported as an outcome, e.g. medication knowledge. Appendix C.3 includes examples of adherence-related factors within the COM-B framework.

3.4 Results

Study characteristics

We included 53 studies (41 RCTs, 77%) with a total of 26,361 participants (Fig 3.1). Interventional studies in adherence in rheumatology have exponentially increased over the last two decades (Appendix C.4). Table 3.1 provides the characteristics of included studies. Appendix C.5 includes a descriptive summary of all studies. The review included studies conducted in 33 countries (four studies in multiple countries) with participants with nine rheumatic conditions (OP, RA, gout, systemic lupus erythematosus, psoriatic arthritis, 'systemic rheumatic diseases', 'early inflammatory arthritis', 'inflammatory polyarthritis', 'degenerative joint disease'). Studies had a mean follow-up duration of 13 months (range four weeks to two years for RCTs, ten days to five years for observational studies) and mean sample size of 497 participants (range 18 – 2,382 for RCTs, 18 – 5,413 for observational studies).

Adherence as an outcome domain and its measurement

The phases of adherence measured included initiation (n=13 studies, 25%), implementation (n=32, 60%) and persistence (n=27, 51%). The phase of adherence was unclear in 20 studies (38%). Self-report questionnaires which assessed more than one

phase of adherence were used in most of the studies with an unclear phase of adherence.

We categorised all adherence measures into subjective and objective measures. Studies used objective measures more often overall (n=28, 53%). This included pharmacy refill records, pill count, MEMS and drug concentration in body fluid. Subjective measures included all self-report questionnaires/interviews/diaries (n=25 studies, 47%). Five studies combined subjective and objective measures to report a single value for adherence (e.g. combining pharmacy refill record and self-report, n=5, 9%). RCTs used more objective measures (n=20, 49% of RCTs) compared with observational studies (n=5, 42% of observational studies). OP studies used more objective measures (n=20, 61% of OP studies) compared with RA studies (n= 4, 33 % of RA studies).

In total, studies used 37 different instruments to measure adherence (mean 1.5 instruments per study, range 1-5). The five most frequently reported instruments were pharmacy refill record (n=20 studies, 38%), pill count (n=7, 13%), 4-item Morisky (n=6, 11%), Compliance Questionnaire in Rheumatology (CQR) (n=4, 8%) and MEMS (n=4, 8%). Six studies (11%) did not specify the instrument used to measure adherence. Twenty-nine instruments appeared in one study only. These were predominantly self-report questionnaires or interviews created specifically for the study. Figure 3.2 depicts the range of all adherence instruments and their time points.

When combining the instrument, definition/calculation for adherence, metric and method of aggregation, studies reported adherence in 115 unique ways (Fig 3.3). The most frequent were: pharmacy refill record, adherence defined as filling an initial prescription, reported as an end value, categorical method of aggregation (n=8 studies, 15%); pharmacy refill record, adherence defined as no discontinuation of therapy, reported as an end value, categorical method of aggregation (n=5 studies, 9%); pill count, adherence calculated as the percentage of tablets taken, reported as an end value, continuous method of aggregation (mean) (n=4, 8%). Ninety-four (82%) appeared in one study only. Appendix C.5 includes the unique adherence measurement approaches for each study.

Health outcomes

Forty-one studies (77%) reported 38 health outcomes. Twenty-four studies (45%) reported on medication adverse events. We reviewed the compatibility of the reported

health outcomes in the included adherence studies against the existing condition-specific core domain sets. We excluded five studies from this analysis as they included conditions for which no core domain set currently exists or existed at least five years prior to the date of the publication of the respective study. Of the remaining 48 studies, only one study reported all outcome domains in the existing condition-specific core domain set, 32 studies (67%) reported at least one domain and 16 studies (33%) did not use any outcome domains from the existing condition-specific core domain set (Table 3.2).

Thirty-three studies (including 28 RCTs) with participants with osteoporosis-related conditions assessed the impact of the adherence intervention on a total of 10 health outcomes. The five most frequently reported health outcomes were: adverse events (n=17 studies, 52%), bone turnover markers (n=10, 30%), bone mineral density (n=5, 15%), fractures (n=5, 15%), quality of life (n=4, 12%). None of the studies reported on pain or height, which are outcome domains in the existing core domain set for osteoporosis (218).

Studies including participants with RA (12 studies in total, including 8 RCTs), reported 26 health outcomes. The five most commonly reported health outcomes were: disease activity (n=7 studies, 58%), physical function (n=7, 58%), pain (n=5, 42%), quality of life (n=4, 35%), adverse events (n=3, 25%), erythrocyte sedimentation rate or C-reactive protein (n=3, 25%). In RA, only one study reported on all outcome domains from the existing RA core domain set (219).

Adherence-related factors

Thirty-three studies (62%) reported 32 adherence-related factors. Table 3.3 outlines the proportion of studies reporting each factor. The most frequently reported factor was reasons for adherence/non-adherence (n=12 studies, 23%), where studies would list a variety of reasons elicited from participants. The next four most commonly reported factors were: medication beliefs (including necessity, concerns, harms, overuse) (n=8, 15%); illness perception, medication satisfaction, and satisfaction with medication information (each in n=5, 9%).

3.5 Discussion

This systematic review of 53 studies shows that researchers are conducting an increasing number of studies, especially RCTs to evaluate strategies to improve adherence in rheumatic conditions. There is considerable heterogeneity in the outcome domains and adherence measures that assess the impact of these interventions. A third of studies had an unclear phase of adherence and the review identified 37 different instruments that measured and reported adherence in 115 unique ways. Although adherence was linked to health outcomes in 77% of studies, the 38 reported health outcome domains were varied. Studies rarely used the existing disease-specific core domain sets and only half of studies reported medication adverse events. Studies evaluated multiple adherence-related factors. However, the review did not find any specific factor in more than 15% of studies.

Studies included in this systematic review assessed medication initiation least frequently compared to other phases of medication adherence. This may be due to difficulty in patient recruitment, as patients who are not intending to start treatment are unlikely to agree to participate in an adherence trial. In previously published studies, medication adherence dramatically drops in the first year after initiation (104). The step prior to this – the actual rate of initiation of prescribed medications is still poorly characterised in rheumatology studies.

Adherence measures varied at many levels: instrument, definitions for the calculation of adherence, metric and method of aggregation. There are many adherence measures available, with no gold standard of adherence measurement. Measures may differ for different phases of adherence and require differing amounts of time, expertise and costs associated with their use. Variability in medication dosing, route and polypharmacy further complicates how adherence is measured and reported in rheumatic conditions.

Health outcomes are dependent on both the efficacy of the medication and adherence. Patients and health professionals may perceive health outcomes to be important outcome domains of medication adherence studies. Despite this, 23% of studies in this review did not report on any health outcomes. Furthermore, the condition-specific core domain set includes outcome domains that are mandatory in all clinical trials (76) and represent the minimum set of outcome domains of highest importance to multiple stakeholders. However, only one adherence study in this review used the entire condition-specific core domain set to assess health outcomes. There may be some

explanations for this including considerations of study power and duration of follow-up, or the added participant burden and study costs when researchers incorporate health outcomes into their studies. Qualitative studies indicate that concerns about medication adverse effects and experience of side effects influences adherence behaviour (145). Conversely, adherence can also affect the occurrence of side effects. However, only half of studies reported on this.

This review identified many adherence-related factors. Members of the OMERACT-Adherence group found it difficult to delineate which factors should be considered candidate domains for a core domain set to be used for interventional studies targeting adherence. These factors may be better classified as intervention targets or explanatory variables for adherence (i.e., in the causal pathway to adherence) and not true outcome domains (215). Some of the same factors could be considered to be potential contextual factors (a covariate that could be measured at baseline that could serve as an effect modifier of the outcome, e.g. trust in the doctor). No specific adherence-related factor was reported frequently, this may be because factors influencing adherence are complex and numerous and some factors are tied directly to theories of adherence used to design the intervention (e.g. medication beliefs). Therefore, any single factor may not have relevance across all potential adherence interventions in different rheumatic conditions and is unlikely to be in the core domain set for adherence interventions.

Many systematic reviews in rheumatic conditions and a broader range of chronic conditions have noted the difficulty of combining adherence results because of the inconsistency in adherence measurement (75, 93). This review adds an in-depth analysis of different points at which heterogeneity exists at the level of instrument, definition/calculation of adherence, metric and method of aggregation. A previous systematic review and meta-analysis of medication adherence interventions across multiple health conditions showed a positive impact of adherence interventions on some patient-centred outcome domains including quality of life, physical function and symptoms (220). However, it remains unclear which outcome domains are of most importance to patients in trials targeting adherence in rheumatic conditions, which is needed to inform the design of patient-centred adherence interventions.

This review provides a detailed analysis of the scope and consistency of outcome domains, including adherence measures across a large number of adherence interventions in rheumatic conditions from 33 countries. However, there are some limitations. We included studies published in English and did not include studies

published in other languages. The majority of studies in this systematic review focused on osteoporosis. The findings are likely to differ in other rheumatic conditions and may therefore not be generalisable.

This review provides a broad understanding of the outcomes reported in interventional studies across multiple rheumatic conditions. The evidence from this review informs the next phases in the OMERACT-Adherence five-phase project which includes qualitative research with patients and researchers, a Delphi survey and consensus voting (102). The OMERACT-Adherence group aims to develop a core domain set that includes outcome domains that are important to patients and health professionals and also feasible for researchers. A core domain set for adherence interventions can enhance the quality of adherence research conducted in rheumatology and ensure studies lead to improvements for patients in outcomes that are important and relevant to them.

This systematic review also demonstrates the need for clear guidance of the method for measuring and reporting adherence in interventional studies targeting adherence in rheumatic conditions. A consensus-based recommendation for adherence measures in adherence trials should be specific for the phase of adherence, applicable to the different frequencies, modes of administration and combinations of medications used in rheumatology and consider the time, resources and expertise needed for their use.

In summary, studies of adherence interventions in adults with rheumatic conditions measure and report a broad range of adherence outcomes, health outcomes and adherence-related factors. Adherence measures are highly heterogeneous and there is no consistency in which health outcomes are reported. A significant portion of outcome domains were not true outcomes and are better classified as determinants of adherence whose improvement may lead to better adherence (i.e. a time-dependent contextual factor). A core domain set will enhance the ability to compare results across adherence studies on outcomes of significance to patients and other stakeholders.

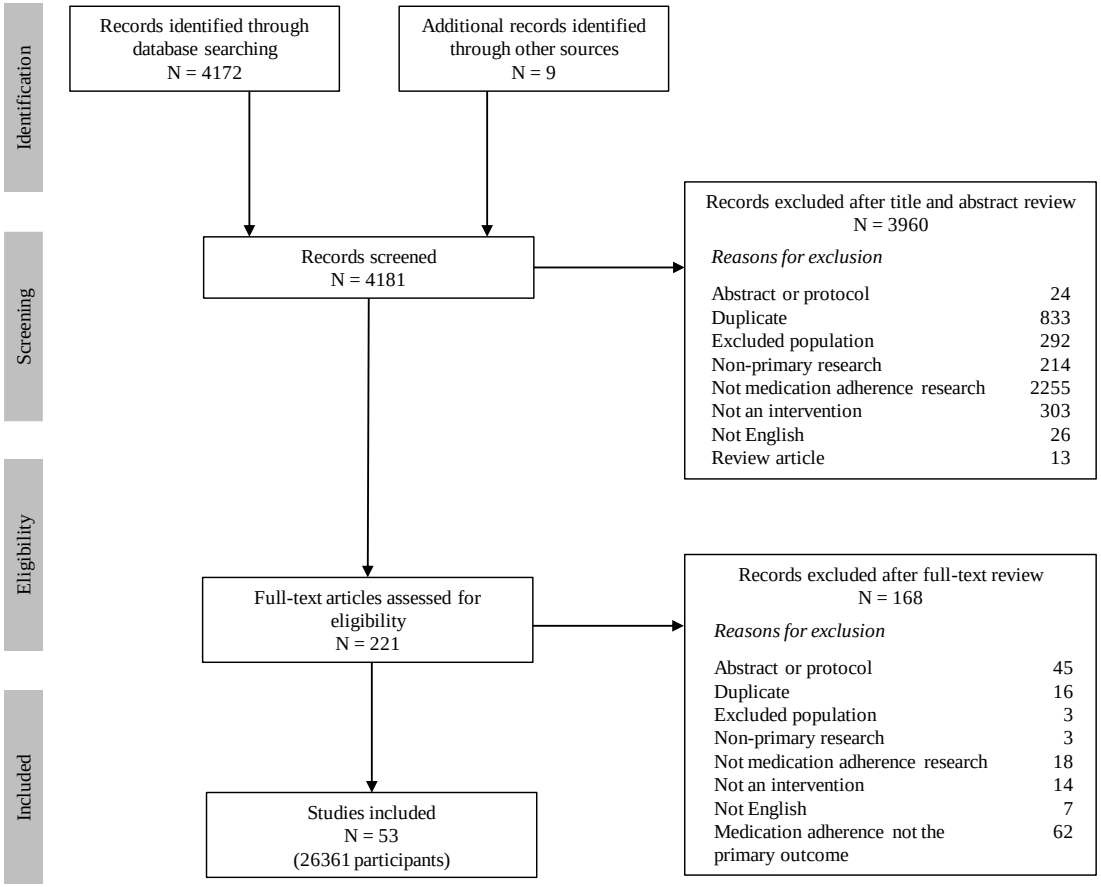

Figure 3.1. Search results

Figure 3.2. Frequency and timepoints of instruments measuring adherence

NS, Not specified; CQR, Compliance Questionnaire in Rheumatology; MEMS, Medication Event Monitoring System; MARS, Medication Adherence Report Scale; MASRI, Medication Adherence Self-Report Inventory; MTB-Thai, Medication Taking Behaviour measure for Thai patients; ULT, Urate lowering therapy.

115 unique ways of measuring and reporting adherence					
Top 6				**Studies**	**(%)**
Pharmacy refill record	Filled initial prescription	End value	Categorical	6	(11)
Pharmacy refill record	Persistent if no discontinuation of therapy	End value	Categorical	5	(9)
Pill count	Percentage of tablets taken	End value	Continuous (Mean)	4	(8)
Pharmacy refill record	Medication Possession Ratio >80%	End value	Categorical	3	(6)
Pharmacy refill record	Medication Possession Ratio	End value	Continuous (Mean)	3	(6)
Pharmacy refill record	Medication Possession Ratio	End value	Continuous (Median)	3	(6)

Instrument | Adherence definition and calculation | Metric | Method of aggregation

Figure 3.3. Unique ways of measuring and reporting adherence

Table 3.1. Characteristics of included studies

Study Characteristic	No. of Studies	(%)
Type of study		
Randomised controlled trial	41	(77%)
Observational studies	12	(23%)
Year of publication		
1981-2000	2	(4%)
2001-2010	17	(32%)
2011-2019	34	(64%)
Country		
United States	16	(30%)
United Kingdom	6	(11%)
Other*	27	(51%)
Multinational studies	4	(8%)
Sample size		
1-100	14	(26%)
101-300	19	(36%)
>300	20	(38%)
Duration of study		
≤6 months	14	(26%)
>6-12 months	29	(55%)
>12 months	10	(19%)
Condition		
Osteoporosis/osteopenia/fracture/at risk of osteoporosis	33	(62%)
Rheumatoid arthritis	12	(23%)
Gout	2	(4%)
Systemic lupus erythematosus	1	(2%)
Systemic rheumatic diseases	1	(2%)
Early inflammatory arthritis	1	(2%)
Multiple †	3	(6%)

* 1-3 studies: Australia, Canada, Denmark, Egypt, France, India, Italy, Japan, Korea, Malaysia, Netherlands, New Zealand, Spain, Thailand, Turkey
† Rheumatoid arthritis (RA) and degenerative joint disease; RA and psoriatic arthritis (PsA); RA, PsA and inflammatory polyarthritis

Table 3.2. Reporting of health outcomes, core domain set and medication related adverse events

	Osteoporosis/osteopenia/fracture/at risk for osteoporosis																
Study	(221)	(222)	(223)	(224)	(225)	(226)	(227)	(228)	(229)	(230)	(231)	(232)	(233)	(234)	(235)	(236)	(237)
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1
Adverse events	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	×	×

	Osteoporosis/osteopenia/fracture/at risk for osteoporosis															
Study	(238)	(239)	(240)	(241)	(242)	(243)	(244)	(245)	(246)	(247)	(248)	(249)	(250)	(251)	(252)	(253)
Health outcome	✓	✓	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×
No. CDS items	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adverse events	×	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×

	Rheumatoid arthritis											
Study	(219)	(254)	(255)	(256)	(257)	(258)	(259)	(260)	(261)	(262)	(263)	(264)
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	7	6	6	5	5	4	4	3	1	1	1	0
Adverse events	×	✓	✓	×	×	✓	×	×	×	×	×	✓

	Gout		SLE	Other or multiple conditions				
Study	(265)	(266)	(91)	(267)	(268)	(269)	(270)	(271)
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	5	2	2	NA	NA	NA	NA	NA
Adverse events	✓	✓	×	✓	✓	×	×	×

Table 3.3. Adherence related factors

Adherence related factor	No of studies	(%)
Reasons for adherence/non-adherence	12	(23%)
Medication beliefs (Necessity/Concerns/Overuse/Harms)	8	(15%)
Illness perception	5	(9%)
Medication satisfaction	5	(9%)
Satisfaction with medication information	5	(9%)
Condition knowledge	3	(6%)
Medication and condition knowledge	3	(6%)
Trust in doctor	3	(6%)
Decisional conflict	2	(4%)
Illness risk	2	(4%)
Intervention satisfaction	2	(4%)
Intervention's influence on adherence	2	(4%)
Involvement in decision making	2	(4%)
Medication initiation decision	2	(4%)
Medication knowledge	2	(4%)
Satisfaction with medical care	2	(4%)
Anxiety	1	(2%)
Drug interactions	1	(2%)
Duplication of prescriptions	1	(2%)
Duplication of therapeutic class	1	(2%)
Health and medication information source	1	(2%)
Helpfulness of pharmacist's recommendation	1	(2%)
Intention to adhere	1	(2%)
Medication bother	1	(2%)
Medication cost	1	(2%)
Medication preference	1	(2%)
Medication problems	1	(2%)
Patient activation (engagement with therapy)	1	(2%)
Prescription documentation	1	(2%)
Safety of pharmacist's recommendations	1	(2%)
Self-efficacy	1	(2%)
Unmet treatment needs	1	(2%)

Chapter 4: Patients' attitudes and experiences of disease modifying anti-rheumatic drugs in rheumatoid arthritis and spondyloarthritis: A systematic review of qualitative studies

This chapter describes the attitudes and experiences of patients with rheumatoid arthritis and spondyloarthritis regarding disease modifying anti-rheumatic drugs.

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405. I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Patients' attitudes and experiences of disease modifying anti-rheumatic drugs in rheumatoid arthritis and spondyloarthritis: A systematic review of qualitative studies.

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Senior author or collaborating author's endorsement: Kathleen Tymms

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Endorsed

Kathleen Tymms	18/11/20	**Diana Perriman**	19/11/20
Primary supervisor	Date	Delegated authority	Date

4.1 Abstract

Objectives: Non-adherence to disease-modifying anti-rheumatic drugs (DMARDS) in rheumatoid arthritis (RA) and spondyloarthritis (SpA) results in increased disease activity and symptoms and poorer quality of life. We aimed to describe patients' attitudes and experiences of DMARDs in RA and SpA to inform strategies to improve medication adherence.

Methods: Databases (MEDLINE, Embase, PsycINFO, CINAHL) were searched to January 2016. Thematic synthesis was used to analyse the findings.

Results: From 56 studies involving 1383 adult patients (RA [n=1149], SpA [n=191], not specified [n=43]), we identified 6 themes (with subthemes): intensifying disease identity (severity of sudden pharmacotherapy, signifying deteriorating health, daunting lifelong therapy); distressing uncertainties and consequences (poisoning the body, doubting efficacy, conflicting and confusing advice, prognostic uncertainty with changing treatment regimens); powerful social influences (swayed by others' experiences, partnering with physicians, maintaining roles, confidence in comprehensive and ongoing care, valuing peer support); privilege and right of access to biologics (expensive medications must be better, right to receive a biologic, fearing dispossession); maintaining control (complete ownership of decision, taking extreme risks, minimising lifestyle intrusion); and negotiating treatment expectations (miraculous recovery, mediocre benefit, reaching the end of the line).

Conclusions: Patients perceive DMARDs as strong medications with alarming side effects that intensify their disease identity. Trust and confidence in medical care, positive experiences with DMARDS among other patients, and an expectation that medications will help maintain participation in life can motivate patients to use DMARDs. Creating a supportive environment for patients to voice their concerns may improve treatment satisfaction, adherence and health outcomes.

4.2 Introduction

Patients with rheumatoid arthritis and spondyloarthritis (including ankylosing spondylitis, psoriatic arthritis and arthritis associated with inflammatory bowel disease) can suffer progressive joint damage, deformity and disability, which can limit functioning and impair quality of life (272-275). Disease-modifying anti-rheumatic drugs (DMARDs) are recommended first-line treatment using a treat-to-target strategy, particularly for rheumatoid arthritis and psoriatic arthritis, with the aim of decreasing joint inflammation, achieving remission, and preventing permanent damage (25, 276). Yet, non-adherence to DMARDS remains a major clinical challenge.

It is estimated that only 66% of patients with rheumatoid arthritis are adherent to DMARDs (66). Non-adherence is associated with disease flares, increased disability, and health care costs in rheumatoid arthritis (68, 277). The patient-physician relationship, patients' beliefs about medications, knowledge about their disease and self-efficacy have been consistently identified as modifiable factors associated with adherence in rheumatoid arthritis (65-67, 87). However, studies have not consistently demonstrated that patient and treatment characteristics including age, gender, disease duration, number of medications and side effects are associated with adherence (87, 153).

International rheumatology guidelines emphasise shared decision making in rheumatoid arthritis and spondyloarthritis (25, 276, 278). This requires a comprehensive and detailed understanding of the patients' values, priorities and preferences. Yet there is sparse qualitative evidence for this approach in relation to DMARDs. A thematic synthesis of multiple qualitative studies can summarise and extend qualitative research in a defined field (98). A systematic review of qualitative studies has been performed in lay experiences of medicine taking across multiple conditions (279). This study aims to describe patients' attitudes and experiences of DMARDs in rheumatoid arthritis and spondyloarthritis. The findings may be used to develop strategies, models, and interventions to improve treatment adherence, satisfaction and health related outcomes.

4.3 Materials and Methods

We followed the Enhancing Transparency of Reporting the Synthesis of Qualitative research (ENTREQ) framework (99). The systematic review does not require ethics

approval by an institutional review board or ethical review board in accordance with the policy of the authors' institutions.

Selection criteria

Qualitative studies that reported the perspectives and experiences of adults (aged ≥18 years) with rheumatoid arthritis or spondyloarthritis on DMARDs were eligible. Observational epidemiological studies, non-primary research articles (letters, commentaries and reviews), and non-English articles were excluded.

Data sources and searches

We searched MEDLINE, Embase, CINAHL and PsycINFO from database inception to 12th January 2016 (Appendix D.1). We also hand searched reference lists of relevant studies and searched Google Scholar for additional studies. We screened the abstracts and examined the full text of potentially relevant studies.

Comprehensiveness of reporting

We used a modified version of the consolidated criteria for reporting qualitative health research framework (COREQ) (100) to evaluate the completeness of reporting of each interview study. Items specific to the research team, methods, setting, analysis and interpretations were assessed. Three reviewers (AK/DT/DS) independently assessed each study and resolved disagreements through a fourth reviewer AT.

Synthesis of findings

We used thematic synthesis for data analysis. We extracted all participant quotations and text under the "Results" and/or "Discussion/Conclusion" sections and imported them into HyperResearch (ResearchWare, INC 2015 version 3.7.3) software. AK inductively identified preliminary concepts. The preliminary coding framework was discussed among

authors (AK/DT/DS/KT/AT), to ensure the codes reflected the full range and depth of data. For each article, AK performed line-by-line coding into themes and subthemes and refined them iteratively. AK/DT/AT identified conceptual links amongst themes to develop an analytical thematic schema.

4.4 Results

Literature search and study descriptions

From 2113 citations, we included 56 studies involving 1383 participants (Figure 4.1). Study characteristics are provided (Table 4.1 and Appendix D.2). Participants were 26-86 years old, 851 female (62%), 423 male (31%), 109 gender unspecified (8%). 1149 had rheumatoid arthritis (83%), 191 had spondyloarthritis (14%). The type of arthritis was unspecified in 43 participants (3%). Disease duration was <1 month to 49 years. Eighteen studies had participants on biologic DMARDs (32%), three studies on conventional DMARDs (5%), eight studies on both DMARD groups (14%) and it was unspecified in 27 studies (48%).

Comprehensiveness of reporting

The comprehensiveness of reporting was variable with interview studies reporting 5-21 out of the 26 items in the modified COREQ framework (Appendix D.3). Twenty-four studies (44%) documented data saturation and 44 studies (81%) specified the use of researcher triangulation. Participant quotations were provided in 49 studies (91%).

Synthesis

We identified six themes: intensifying disease identity, distressing uncertainties and consequences, powerful social influences, privilege and right of access to biologics, maintaining control, negotiating treatment expectations. The subthemes are described in the following section with illustrative quotations in Appendix D.4. The conceptual links among themes are presented in Figure 4.2.

Intensifying disease identity

“The more medication you take. . .the more ill you feel. Maybe even more than you really are.” (149)

This theme describes how DMARDs intensified the patients’ feelings of being unwell. This occurred throughout the patient’s journey from diagnosis, during DMARD escalation and chronic maintenance therapy.

Severity of sudden pharmacotherapy: After being diagnosed with arthritis, some patients were shocked with having to take medications for the first time and how “strong” the medications were. Patients who avoided medications previously could be particularly alarmed and view DMARDs to be both unexpected and unwarranted. Some chose not to start their medications because it would mean they were “seriously ill”(149), or were frightened by the side effects of their first medication: “if this is the drug they start with (methotrexate), what will be the side effects of the next drug?” (149)

*Signifying deteriorating health**:*** Being placed on increasing numbers of medications was a sign of worsening illness and created concerns about potential drug interactions. Therefore, reducing medications could be an indicator of improving health and a primary health goal. When patients forgot to take their medications because they felt well, they interpreted forgetting their medications as a sign of good health.

Daunting lifelong therapy: Patients despaired being on lifelong medications, a reminder that their arthritis was incurable. When some patients stopped their medications, symptoms returned and their ability to function decreased. This made patients feel physically dependent on medications and provoked anxiety about long-term side effects.

Distressing uncertainties and consequences

“My orthopaedist said: ‘‘arthritis patients actually have 2 diseases, that is arthritis and methotrexate’’; I have always remembered that.” (151)

This theme describes the difficulty and fear patients experience due to uncertainty in relation to DMARD safety and efficacy. Fears can be further heightened during times of DMARD changes and from comments by other health professionals.

Poisoning the body: DMARDs were perceived to be “strong”, “toxic” (280) medications that could damage internal organs, increase mortality and the risk of having cancer because of immune suppression. Patients were aware that methotrexate was used to treat cancer, which made them feel they were taking a “very, very strong drug” (281) equivalent to chemotherapy. Patients expressed concern about both conventional and biologic DMARDs. Some reluctantly accepted the medication because of necessity – “Hate it, but can’t do without it” (148). Others preferred taking alternative medications that were perceived to be natural and harmless.

Doubting efficacy: Sometimes patients felt vulnerable, as if they were “guinea pigs” (282) trying one medication after another. They waited in anxious anticipation to see if a new medication would start working and found it difficult to cope with any delay of demonstrable effect. If patients were doing well, they questioned whether it was due to the medication, or if their disease had naturally stopped progressing.

Conflicting and confusing advice: Some patients felt they received insufficient or contradictory information from within and outside the rheumatology service. This led to confusion, mistrust and heightened medication concerns. For example, the patients’ pharmacist, family doctor or other specialists raised concerns about their DMARD. They noted that the drug information leaflets contained more information than provided by their physician.

Prognostic uncertainty with changing treatment regimens: Patients were afraid of their arthritis worsening when they switched or stopped their DMARDs. Even when patients did well on their medications, they would worry about returning "back to square one" (280). Some patients on biologic DMARDs noticed a dramatic worsening of symptoms when they stopped their medications during pregnancy, infections or for surgery.

Powerful social influences

"I feel I have a good doctor and I feel that he was doing what was best for me personally. If it wasn't for the trust I have in my doctor, then no, I wouldn't have took it." (154)

This theme describes how others including family, friends, doctors and nurses can strongly influence the experience and perceptions of DMARDs in both positive and negative ways.

Swayed by others' experiences: Experiences of others on DMARDs could influence patients' acceptance of DMARDs. One patient's mother developed gastrointestinal haemorrhage, and another patient's colleague took a day off work after taking methotrexate and cited these as reasons for never wanting to take methotrexate. In contrast, some patients were motivated to take medications by family members with arthritis who accepted and coped well with their DMARD, and from seeing older family members who had developed deformities and disability without DMARDs.

Partnering with physicians: Certain characteristics of the physician and their communication could influence patients' perception and attitudes towards DMARDs. Patients had confidence in physicians who were knowledgeable, optimistic, acknowledged their fears and needs and provided a range of treatment options. These physicians made patients feel hopeful and secure in their treatment choices. Information from their physician that was consistent with other sources (e.g. internet, drug information leaflets) was regarded as credible. Some patients valued shared decision making, whilst others preferred to relinquish their decision to their doctor who they trusted.

Maintaining roles: Being able to function in the family role as a parent or grandparent could be the main reason for patients to take DMARDs. Others wished to maintain work roles, independence, or had a general goal to be “healthy”, “normal” and “live the life (they) had before” (283). For some, side effects from DMARDs impeded their ability to fulfil these roles and would lead to DMARD discontinuation.

Confidence in comprehensive and ongoing care: Patients felt secure with the frequency of follow up in the biologic clinic and in the setting of clinical trials for intensive conventional DMARD therapy. The practical and psychosocial support nurses provide during regular biologic DMARD infusions, clinic visits and over the telephone created positive experiences. In contrast, some patients with ankylosing spondylitis found follow up in the biologics clinic unnecessary and inconvenient.

Valuing peer support: Patients valued the opportunity to share experiences with others with the same illness whilst on intravenous biologic therapy. Some developed close friendships and considered their infusions to be a social outing.

Privilege and right of access to biologics

“You sit there and try and get every single drop out of, and then you make sure that the syringe, you really press it and try to squeeze the bit down to make sure you’ve got every drop. But it does I mean it is precious because it’s expensive.” (284)

This theme describes unique attitudes and perceptions of patients towards biologic DMARDs. The expense and restricted access to these medications created a sense of privilege for some, but could also invoke anger, guilt and fear of being denied or losing access.

Expensive medications must be better: Patients felt privileged to have access to biologic DMARDs as they were “horribly expensive” (284) and were careful not to waste the medication when self-injecting.

Right to receive a biologic: Patients defended their right to receive a biologic and were angered if they did not meet the clinical requirements. They argued that they paid national insurance, and that there was a long-term economic benefit as surgery and hospitalisations would be reduced. Patients who qualified for a biologic felt guilty that others could not access these medications.

Fearing dispossession: Once on biologics, patients felt they were valued possessions, and were afraid that they would be deprived of them. Some avoided telling the doctor or nurse of side effects, in case they were taken off their biologic.

Maintaining control

“Let me have the choice that I want to be treated aggressively... Don't take that away from me.” (150)

This theme describes the desire of patients to be in control of the decision to take DMARDs and to choose a DMARD based on life priorities. Patients also emphasised the importance of maintaining disease control, occasionally despite significant medication side effects.

Complete ownership of decision: Patients advocated their right to make the final decision about taking biologic and conventional DMARDs and wanted comprehensive information including alternative treatment options. They urged physicians to be explicit about the potential effects of DMARDs on the body, including recognition that DMARDs were different to other medications that were perceived to be safer.

Taking extreme risks: Patients wished to remain in control of their disease and were willing to accept the risks of complications such as organ damage or low platelet counts to remain on their medications. Some ignored instructions to stop their medication. When DMARDs were highly effective, patients described them as something they would “kill for”. (285)

Minimising lifestyle intrusion: Patients wanted to control their choice of DMARD in order to minimise the impact on their day to day life. They wanted information that would better inform their decision-making. For example, they wanted to be informed of the need to limit their alcohol intake, the timing of methotrexate dose to decrease side effects at work and the impact of their DMARD on sexual function. Some patients preferred subcutaneous to intravenous biologics because they could do this at home with minimal disruption to their routine.

Negotiating treatment expectations

“I mean I was, you know, really hoping against hope that it would work, having been on, sort of, most of the other conventional drugs and thinking well ‘If this doesn’t work, then what?’…” (286)

Patients’ emotional response to their DMARD varied widely between joy, disappointment and hopelessness and depended on their initial and ongoing expectations of their medications.

Miraculous recovery: Patients were surprised and delighted if DMARDs exceeded their expectations and led to rapid and dramatic improvements, particularly with TNF inhibitors. Some patients felt “the healthiest I’ve been in years” (286) and described forgetting they had arthritis. One patient described methotrexate as “the elixir of life” (285). These DMARDs elevated their mood, self-esteem and relationships with their spouses and children.

Mediocre benefit: Other patients noted moderate improvements with DMARDs but still had disease flares, needed to use corticosteroids, and had functional limitations. Some accepted this and hoped for future medical advances. Others felt disappointed as they were expecting an immediate and pronounced response to DMARDs.

Reaching the end of the line: Failing multiple DMARDS had a detrimental psychological and emotional impact on patients who felt increasing desperation. Patients felt they had reached the end of the line when given the option of biologic therapy and saw these DMARDs as their last hope. They subsequently feared that if biologics did not work they had no other options.

4.5 Discussion

Dependence on DMARDs exacerbated disease identity in patients with rheumatoid arthritis and spondyloarthritis. They were alarmed about potential side effects, uncertain of treatment efficacy, and confused when they received conflicting medical advice. Concerns were alleviated through trust, confidence and support in their health environment and positive experiences of family and friends. An immediate benefit or response to DMARDs was seen as a miracle whereas others felt disappointed and hopeless from failed responses to DMARDs. The high cost and limited accessibility of biologic DMARDs increased their value.

Some experiences and perceptions were unique to biologic DMARDs. Patients felt well supported by frequent biologic clinic visits, nursing assistance and peer support during infusions. Extending these positive experiences to conventional DMARD patients may improve their DMARD experience. Biologic DMARD patients may also experience rapid and dramatic treatment benefits and can feel privileged to receive restricted medications. However, regardless of the type of DMARD, arthritis, age, gender, and duration of disease, patients had similar concerns of DMARD toxicity, loss of efficacy and desires to maintain control of their disease and social roles. Additionally, patients on either type of DMARD desired to have control of the decision to take their medications and reported experiences of mediocre benefits or recurrent failures.

Our review has shown that patients believed DMARDs increased mortality, risk of cancer and organ damage despite evidence that cardiovascular disease and mortality may be reduced with the use of methotrexate and biologic DMARDs in rheumatoid arthritis (287, 288). Explaining these benefits may help increase acceptance and reduce fears of long-term toxicity.

This study highlights the critical role of the patient-provider relationship in DMARD acceptance. By remaining optimistic, knowledgeable, validating patients' fears and understanding their practical needs, physicians can foster a trusting and more successful therapeutic relationship with their patient. Communicating potential benefits and harms of medications by using examples of other patients' experiences may improve patients' understanding. Communication also needs to be consistent between health professionals. Referring to reliable online resources may help patients feel more confident in treatment recommendations. A meta-analysis of 21 studies involving training physicians in communication skills found that all studies improved adherence (289). The use of decision aids may also improve knowledge, reduce decisional conflict and increase participation in decision making (290).

Clinicians are encouraged to follow international guidelines that recommend the early use of DMARDs, and escalating or changing treatment to aim for a target of remission or low disease activity (25, 276, 278, 291). However, patients can find commencing DMARDs at the first consultation alarming, and fear changes and escalations of therapy. This therapeutic approach may be more acceptable if patients understand that treating early and treating to target increases DMARD efficacy and results in better long-term outcomes.

A structured approach may help the clinician discuss DMARD use. The 5A approach (Ask, Assess, Advise, Assist, Arrange follow-up) to smoking cessation has been adapted to guide brief counselling interventions targeting diet and exercise (292, 293). We suggest the following 5A approach to address DMARD adherence (Figure 4.3). Ask about patients' experiences of their DMARDs, their concerns (especially those they may not mention such as mortality, cancer and organ damage) and goals (which could be to take less medications). Assess their willingness to take DMARDs. Advise on the benefits of DMARDs (using examples, include benefits on mortality, on maintaining roles and control of disease), options (including practical implications to lifestyle), and communicate with optimism and consistency (referring to reliable internet sources and drug information leaflets). Assist patients taking DMARDs so they feel supported

(including nursing, phone and peer support). Arrange adequate follow-up and continue to address the above at every stage of their disease.

Similar barriers and facilitators to medicine-taking have been identified in other chronic conditions (279, 294). The perception of medicines as “poison” was identified in systemic lupus erythematosus (295). Fear of medication dependence and long-term side effects were identified with anti-hypertensives and proton pump inhibitors (279). Medication non-adherence as a means to deny illness was reported with anti-retroviral therapies and psychotropic medications (279). Patients with cancer doubted the efficacy of their medications (296). Patients with HIV were positively influenced by trustworthy health care providers, favourable experiences of others, and were motivated to take medications in order to maintain social roles (297, 298). Unique experiences in relation to biologic DMARDs and specific ways to address barriers in our population are derived from the qualitative studies in our review.

Core themes relating to prescribed medications have been described by Horne et al using a necessity-concerns construct and Azjen et al using the theory of planned behaviour (299, 300). The necessity-concerns cognitive representation includes beliefs about necessity of medications and concerns including long-term toxicity, disruptive effects of medication and the danger of dependence. The theory of planned behaviour postulates three independent determinants of intention and behaviour. The first is “attitude toward the behaviour” and refers to a person’s favourable or unfavourable evaluation of the behaviour. The second is “subjective norm” and refers to perceived social pressures to perform the behaviour. The third is “perceived behavioural control” and refers to the perceived ease or difficulty of performing the behaviour. Our study adds a broad and in-depth understanding into the beliefs of necessity and concerns, attitudes towards medications taking behaviour and the positive and negative social pressures that influence adherence in rheumatoid arthritis and spondyloarthritis.

Multiple researchers independently assessed the transparency of reporting and triangulated findings during thematic analysis. Software was used to code the data to ensure a systematic and reproducible methodology. Our study has some limitations. Whilst we provided contextual details for the data (if reported), we acknowledge the potential for decontextualisation of the original data. Most studies were performed in high income countries with English speaking participants with rheumatoid arthritis. The type of DMARD was not recorded in half the studies. This highlights the need for qualitative studies to specify the type of DMARD and explore perspectives in non-English speaking

and spondyloarthritis patients. Successful interventions to improve DMARD adherence are needed. Exploring patients' ideas on how to improve their experience and perceptions of DMARDs may guide future interventions.

DMARDs are perceived as strong medications with frightening side effects. However, trust and security in medical care, positive DMARD experiences of others, the ability to maintain social roles can motivate patients to use DMARDs. The physician is in a unique position to acknowledge and address fears of DMARD toxicity and adjust DMARD regimes to suit individual beliefs, lifestyles and goals. The 5A approach to DMARD adherence may help structure discussions and combat barriers to medication-taking. Understanding, supporting and remaining optimistic for patients on these long-term medications can improve DMARD experience with an aim to promote quality use of medicines and maximise the benefit patients can gain from their DMARDs.

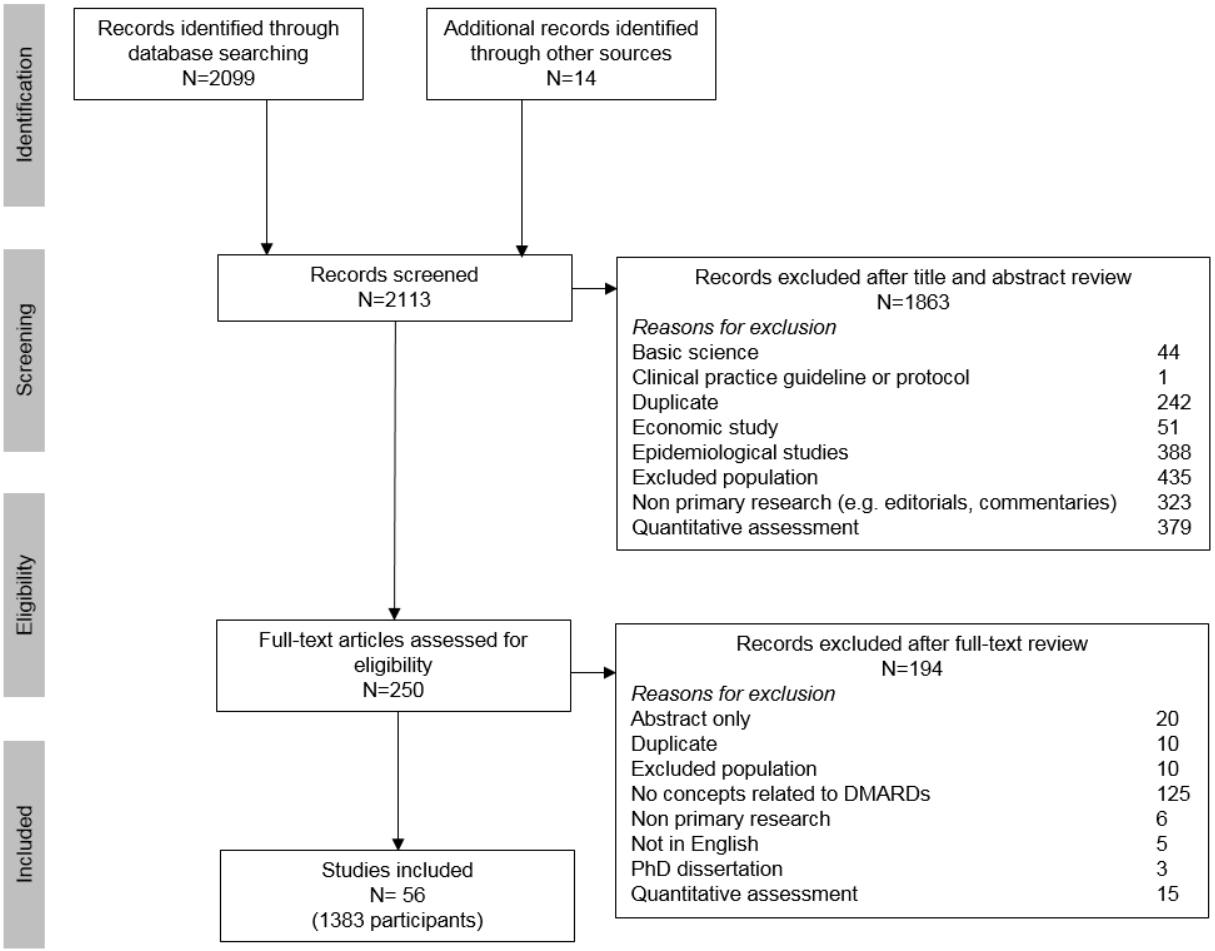

Figure 4.1. Search results

Figure 4.2. Thematic schema

Patients equate medications to being ill, and are terrified of side effects, uncertain of treatment efficacy and confused when receiving insufficient or conflicting medical advice. A trustworthy doctor, supportive health environment and positive family influences and experiences of others can mitigate patient fears, and improve their medication experience. Patients desire to maintain control of their disease, their social roles and their decision to take medications sometimes at extreme costs. Some patients are pleasantly surprised by their treatment outcomes, whilst others are repeatedly disappointed.

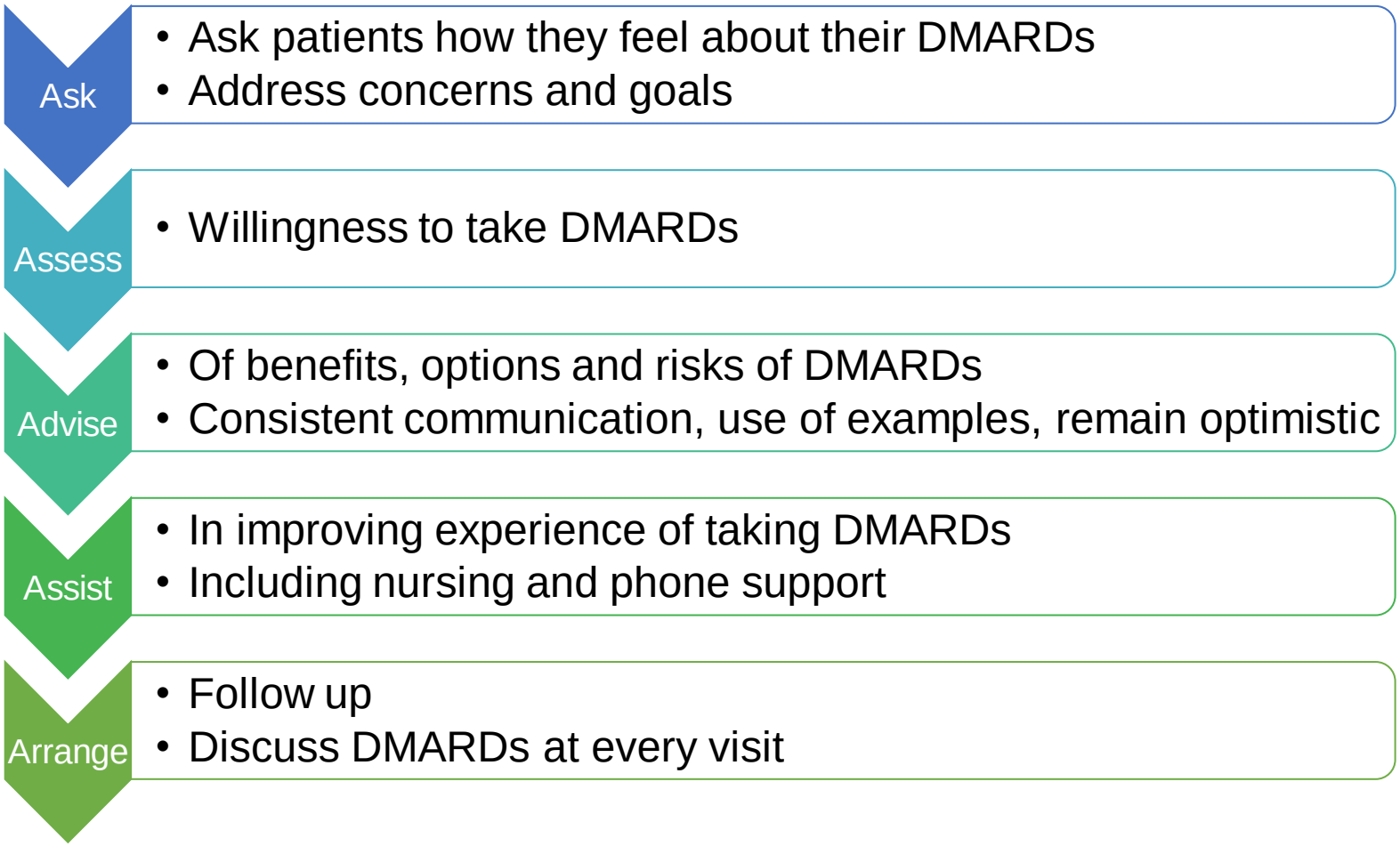

Figure 4.3. Proposed 5A approach to addressing DMARD use

Table 4.1. Characteristics of included studies (n=56)

Study characteristics	No. of studies	n (%)
Year of publication		
1990 – 2010	28	50
2011 – 2016	28	50
Country*		
United Kingdom	27	48
United States	5	9
Canada	5	9
Australia	2	4
Europe	16	29
Other†	2	4
Sample size		
1 – 20	29	52
21 – 40	21	38
41 – 60	1	2
61 – 80	0	0
>80	3	6
Not reported	2	4
Type of arthritis		
Rheumatoid arthritis	41	73
Rheumatoid arthritis and spondyloarthritis	7	13
Spondyloarthritis	4	7
Not reported	4	7
Type of DMARD		
Biologic DMARD	18	32
Conventional and biologic DMARD	8	14
Conventional DMARD	3	5
Not reported	27	48
Method of data collection		
Interviews	33	59
Focus groups	10	18
Interviews and focus groups	8	14
Other	5	9

*One study conducted in multiple countries, † Ireland, Turkey (1 study each)

Chapter 5: Patients' attitudes and experiences of transition from paediatric to adult healthcare in rheumatology: a qualitative systematic review

This chapter describes the attitudes and experiences of transition from paediatric to adult healthcare in rheumatology.

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405. I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Patients' attitudes and experiences of transition from paediatric to adult healthcare in rheumatology: a qualitative systematic review.

Authors: Kelly A, Niddrie F, Tunnicliffe DJ, Matus Gonzalez A, Hanson C, Jiang I, Major G, Singh-Grewal D, Tymms K, Tong A.

Publication outlet: Rheumatology (Oxford)

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Contribution to paper: Study design, data collection, analysis and manuscript write up.

Senior author or collaborating author's endorsement: Kathleen Tymms

Ayano Kelly Candidate	18/11/20 Date

Endorsed

Kathleen Tymms Primary supervisor	18/11/20 Date	**Diana Perriman** Delegated authority	19/11/20 Date

5.1 Abstract

Objectives: We aimed to describe patients' attitudes and experiences of transition from paediatric to adult healthcare in rheumatology to inform patient-centred transitional care programs.

Methods: We searched MEDLINE, Embase, PsycINFO, CINAHL to August 2019 and used thematic synthesis to analyse the findings.

Results: From 26 studies involving 451 people with juvenile-onset rheumatic conditions we identified six themes: a sense of belonging (comfort in familiarity, connectedness in shared experiences, reassurance in being with others of a similar age, desire for normality and acceptance); preparedness for sudden changes (confidence through guided introductions to the adult environment, rapport from continuity of care, security in a reliable point of contact, minimising lifestyle disruptions); abandonment and fear of the unknown (abrupt and forced independence, ill-equipped to hand over medical information, shocked by meeting adults with visible damage and disability, vulnerability in the loss of privacy); anonymous and dismissed in adult care (deprived of human focus, sterile and uninviting environment, disregard of debilitating pain and fatigue); quest for autonomy (controlled and patronised in the paediatric environment, liberated from the authority of others, freedom to communicate openly); and tensions in parental involvement (overshadowed by parental presence, guilt of excluding parents, reluctant withdrawal of parental support).

Conclusion: Young people feel dismissed, abandoned, ill-prepared and out of control during transition. However, successful transition can be supported by preparing for changes, creating a sense of belonging and negotiating parental involvement and autonomy. Incorporating patient-identified priorities into transitional services may improve satisfaction and outcomes in young people with juvenile-onset rheumatic conditions.

5.2 Introduction

Transition from paediatric to adult care is a complex process that presents multiple challenges for young people with juvenile-onset rheumatic diseases. These conditions often persist into adulthood, and include ongoing disease activity, comorbidities, burden of treatment and impaired psychosocial functioning (89, 92, 301-303). The transition period coincides with a vulnerable time in young peoples' lives when major biopsychosocial changes are occurring (304). Accordingly, transition is associated with discontinuity of care, medication non-adherence, increased hospital admissions, anxiety, depression and disease activity (89-91, 157).

Transition is defined as 'the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health-care systems' (305). 'Transfer' is a single event, whereas transition is a process that continues even after transfer into adult care. The need for comprehensive transitional care support is recognised by national and international societies (306-309). However, the provision of transitional care in rheumatology remains suboptimal (310, 311) with limited evidence on the perspectives of young people regarding transition (312). In rheumatology, approximately half of patients are lost to follow up after transfer (90, 157, 313). Surveys amongst paediatric and adult rheumatology health practitioners identify issues in providing adequate transition support including low provider familiarity with transition resources and recommendations, inadequate training and limited clinic time (311, 314).

A synthesis of primary qualitative studies can offer broader understanding of young people's perspectives on transition across different contexts. The aim of this study was to describe patients' attitudes and experiences of transition from paediatric to adult care in rheumatology to inform patient-centred transition services.

5.3 Methods

We used the Enhancing Transparency of Reporting the Synthesis of Qualitative research (ENTREQ) framework for this study (99).

Selection criteria

Qualitative studies that reported the attitudes and experiences of patients (aged ≥10 years) with juvenile-onset rheumatic conditions (e.g. arthritis, connective tissue disease, vasculitis) of transition from paediatric to adult care were eligible. We excluded abstracts, non-primary research (e.g. reviews) and non-English language publications to avoid misinterpretation of linguistic nuances.

Data sources and searches

We searched MEDLINE, Embase, PsycINFO and CINAHL from database inception to 30th August 2019. The search strategy is provided (Appendix E.1). We also searched Google Scholar and dissertation databases (Dart-Europe E-Theses Portal and ProQuest). AK and FN screened all titles and abstracts and reviewed potentially relevant full text articles.

Comprehensiveness of reporting

We evaluated the comprehensiveness of reporting using a modified version of the consolidated criteria for reporting qualitative health research framework (COREQ) (100). The criteria include items regarding researcher characteristics, participant selection, data collection, analysis and reporting. Each study was independently assessed by two reviewers (AK, FN, DT or CH). Discrepancies were resolved by discussion or a third reviewer if required (AT).

Synthesis of findings

We used thematic synthesis for data analysis (315). AK inductively identified concepts and discussed the preliminary coding framework with co-authors (AT/FN/DT/KT/GM). We imported all participant quotations and text from the results and discussion into HyperResearch (ResearchWare, INC 2015 version 4.0.1). AK performed line-by-line coding into themes and subthemes, refining and adding new concepts as they arose. AK/DT/CH/AT developed a thematic schema illustrating the conceptual links amongst themes.

5.4 Results

Literature search and study descriptions

From 2302 studies, we included 26 studies with 451 participants from 11 countries (Figure 5.1). The majority were female (n=315, 70%) and had juvenile idiopathic arthritis (JIA, n=302, 67%). The other conditions included were systemic lupus erythematosus (SLE), dermatomyositis, mixed connective tissue disease and scleroderma. Eight (31%) studies included adolescents (aged 10-18 years), four (15%) included young adults (aged 19-25 years), ten (38%) had both, and four (15%) did not specify participant age. Table 5.1 and Appendix E.2 summarise the characteristics of included studies.

Comprehensiveness of reporting

Studies reported between 6 to 22 of the 26 items in the modified COREQ framework (Table 5.2). Data saturation was reported in 11 (42%) studies, investigator triangulation in 23 (88%) studies, and member checking in 4 (15%) studies. Twelve studies (46%) provided broad and deep insights into patient perspectives of transitional care.

Synthesis

We identified six themes: a sense of belonging, preparedness for sudden changes, abandonment and fear of the unknown, anonymous and dismissed in adult care, quest for autonomy and tensions in parental involvement. The following section contains descriptions of each subtheme. Illustrative quotations (Table 5.3) and a thematic schema (Figure 5.2) are provided.

A sense of belonging

"He (paediatric specialist) was like another dad to me... And I knew that he wouldn't do anything for me that he wouldn't do for his own kid."(33-year-old female with SLE) (159)

Comfort in familiarity: Some young people considered their paediatric rheumatologist to be as close as family, someone who knew their "whole life" history (316). They described paediatric wards as a "second home" (158) where they met friends and enjoyed social activities. They were upset about having to leave their trusted, supportive paediatric rheumatologist who respected their opinions through a well-established relationship. They felt reassured if their paediatrician was positive and confident that the adult service would provide high quality care.

Connectedness in shared experiences: Some young people felt like "the only person on earth" (317) with their condition. Adolescents craved connection, understanding and support and looked forward to meeting people with similar experiences at transition clinics or support groups organised by their healthcare providers. Self-management programs that included videos of adolescents with JIA from different countries, or programs that included online discussion forums helped reduce isolation. Young people felt reassured by peer mentors (i.e. older patients) who gave them hope of being successful with further education and employment.

Reassurance in being with others of a similar age: Some older patients felt uncomfortable in a paediatric setting amongst "teddies and rattles and dolls" (161), and unable to be "grown up" in an environment designed for "babies and kids" (161, 318). However, they also felt misplaced in adult care amongst older adults and hoped to see young people in adolescent-focused clinics and wards.

Desire for normality and acceptance: Some people avoided taking medications in front of friends, worried about disclosing their illness, felt disappointed about missing out on social activities, and adolescents with SLE experienced being bullied because of the physical impacts of their condition and prednisone use. They lacked confidence in undertaking further education or seeking employment because of physical limitations and the experience of being discouraged by teachers, employers and careers advisers who they felt underestimated their potential. They wanted transition clinics to provide

careers advice and advocacy at work or school. Adolescents wanted to know how to discuss their illness with friends and teachers, and young adults with their partners and employers. To protect their sense of normality, some avoided illness-related websites and support groups that had been suggested in transition programs. Some older patients avoided attending rheumatology clinics or taking medications when they felt well to forget about their illness.

Preparedness for sudden changes

"..when you're jumping from pillar to post, like I was seen by six doctors in one year, then I just didn't want to talk to them, but if you stay at the same doctor you tend to get a bit closer." (Adolescent with JIA) (161)

Confidence through guided introductions to the adult environment: Young people appreciated being introduced to the adult healthcare team, clinic and ward prior to transfer through an information night, introductory folder/poster or an adult clinic visit with a nurse. They wanted to know the duration and frequency of consultations, medication and joint injection procedures including the use of sedation, changes in health insurance (some people in the United States lost health insurance coverage in adult care), service availability and access (e.g. hydrotherapy).

Rapport from continuity of care: Young people wanted to see the same adult rheumatologist and nurses to build a relationship with them. Having the flexibility to book extra consultations between appointments in adult care helped maintain continuity. During transition, young people wanted access to their paediatric rheumatologist for reassurance. They valued joint clinics with the paediatric and adult rheumatologist.

Security in a reliable point of contact: Some appreciated having a friendly transition co-ordinator, described as a "personal advisor" (94) who provided advice about alcohol, contraception, sports, self-image and medications. They preferred face-to-face contact

which was more interactive and personal than written or online materials. The co-ordinator motivated confidence in self-management, helped build an immediate connection with the adult team, and reduced confusion about who to contact when in crisis.

Minimising lifestyle disruptions: Having to contend with an uncertain prognosis (e.g. disease flares, complications) and treatment burdens, adolescents' (particularly those with SLE) wanted transition to be minimally intrusive and fit their preferences and lifestyle. They wanted flexible appointment times to reduce interruptions to school and work, and to attend family vacations and school events. They preferred receiving appointment reminders through text messaging, rather than calls or emails. Online resources for self-management or to store and share health information with healthcare providers needed to be easy, fun and visually appealing.

Abandonment and fear of the unknown

"When I turned 18, I received a letter in the mailbox. It informed me that I was to report to a completely different hospital for my next check-up. And that was it... not even a single 'good-bye' from the doctor I had had for 10 years" (26-year-old female with JIA) (158)

Abrupt and forced independence: A sudden and unprepared transfer caused young people to feel abandoned, vulnerable, lost and alone in their new environment. They wished to be informed earlier about when transfer would occur, how long it would take, and to have a say in the timing. This provided a sense of control and ensured that transfer occurred when they were emotionally and physically stable and confident in their level of independence.

Ill-equipped to hand over medical information: Young people felt unable to handover medical information to new doctors, nurses and allied health professionals. Some relied

on their parents to upkeep their health information and described themselves as being too “lazy” (319) to record and relay their medical history. Patients suggested having a written clinical summary, joint paediatric/adult clinics or providing them a copy of clinical notes. For some, poor coordination of information led to delays in transfer, cancelled appointments and discontinuation of care.

Shocked by meeting adults with visible damage and disability: People with JIA wanted to be warned about seeing older adults who had visible disabilities in adult outpatient waiting rooms. They were afraid that this was their inevitable fate. People with SLE were unsettled in sleeping alongside older patients. Although at times, sharing an inpatient room with older adults enabled supportive relationships to form.

Vulnerability in the loss of privacy: Young people were afraid to communicate online with strangers or with healthcare providers through social media as they valued privacy. During transition, they preferred meeting peers face-to-face for support groups and to use secure, credible websites affiliated with medical institutions for online transition programs that involved communicating with their healthcare team.

Anonymous and dismissed in adult care

“Everybody was very friendly when I was a child... and suddenly I was treated as an adult... it felt a bit cold and rigid.” (Adolescent with JIA) (320)

Deprived of human focus: Young people felt like “objects on a conveyer belt” (158) in an adult clinic that was “business-like” (321) and rushed. They wanted to be supported in their daily lives, aspirations, and discuss the psychological, vocational, educational and social impacts of their disease. Although some enjoyed the efficiency of adult care, others felt the sole focus was on their joints and medications and perceived lower levels of empathy, expertise and resources.

Sterile and uninviting environment: The unwelcoming and impersonal atmosphere in the adult outpatient clinic contrasted the warm and friendly paediatric clinic. Adult services were difficult and cumbersome to navigate as they were spread over different locations. Unlike the paediatric inpatient ward which had social and leisure activities, "nothing happened" on the adult ward and young people felt lonely and anonymous (158).

Disregard of debilitating pain and fatigue: Young people experienced problems with not being taken seriously when they felt fatigue or pain by adult doctors. This reduced their self-confidence and made them question the validity of their own symptoms.

Quest for autonomy

"I enjoy it [the adult service] because now I can say what I want to say and what I think is important… It felt like you were grown up." (18-year-old female with JIA) (318)

Controlled and patronised in the paediatric environment: Some young people felt that health professionals who knew them as children were unable to treat them as adults. People with SLE wanted a full explanation of their disease prognosis and treatment options to be involved in decision-making.

Liberated from the authority of others: Young people felt surprised and empowered by the freedom, responsibility and autonomy in adult care. They enjoyed being spoken to directly, making therapeutic decisions, and attending appointments alone or with their partners. Although some adolescents felt afraid and reluctant to move to adult care, after transition, some young adults felt the timing was appropriate and "no big deal" (321).

Freedom to communicate openly: Young people would seek opportunities to discuss sensitive issues with their providers without parental presence. This could include discussing medication non-adherence, relationships, alcohol, drugs and university life.

They suggested having drop in clinics to be able to do this and appreciated doctors who asked parents to sit out of the consultation.

Tensions in parental involvement

"If [my parents] are there, [the consultant] just ignores me, talks to them and I just come out and don't feel anything's been achieved" (Adolescent with JIA) (161)

Overshadowed by parental presence: Patients, especially young adults, felt frustrated and undermined if the doctor relayed information about medications and tests only to their parents. Some chose to attend the clinic alone to force their doctor to speak with them directly. Young adults emphasised the importance of adolescents practicing attending clinics independently and learning about their treatments.

Guilt of excluding parents: Young people were unsure of how to tell their parents they no longer needed them in the clinic. Some felt obliged to invite their parents to their appointment if they had driven them. They were mindful of their parents' struggles with relinquishing control and worried about hurting their feelings and appearing ungrateful of their support.

Reluctant withdrawal of parental support: Some young people were shocked and uncomfortable if parents were not allowed to attend appointments with them in the adult clinic, especially on their first visit. Parental presence helped them gain confidence in communication and build trust with their new provider. Parental support was particularly needed during medication changes, joint injections, or for people with SLE - when they felt "really, really sick" (162). Some patients completely depended on their parents for managing medications and health information.

5.5 Discussion

Some adolescents felt abandoned, disconnected and vulnerable in adult care. They were shocked to meet adults with visible damage and disabilities in waiting rooms. Some felt their debilitating symptoms were dismissed by their new clinician. A gradual introduction to the new system, including thorough explanation of differences such as joint injection procedures, continuity of care and having access to a transition co-ordinator, helped them prepare for the major changes and skills needed for independence. The transition service needed be minimally disruptive, age-appropriate and address issues young people faced with their daily lives as they already had to contend with uncertain prognosis and treatment burdens and needed a sense of connection and belonging within and outside of their healthcare setting. Young people felt conflicted between wanting autonomy and negotiating changing relationships with their parents and clinicians.

We found some differences by country, rheumatological condition and age of participants. People in the US were concerned about changes to insurance, which impacted access to emergency care and medications in the adult setting. People with SLE indicated that the unpredictable disease course, burden of multiple medications and bullying at school disrupted daily living. They emphasised the need for transition services to provide better education about disease prognosis, involvement in treatment decision-making, advocacy and education at school, and parental presence in clinics when they were very unwell. People with JIA wanted to be warned about adults with visible damage and disability in waiting rooms. Adolescents expressed a greater need to meet people with similar experiences than young adults who had established peer support groups (322).

Young people with other chronic conditions, including diabetes, chronic kidney disease, HIV, congenital heart disease, sickle cell disease and cystic fibrosis have voiced similar perspectives and experiences of transition (323-325). The familiar and friendly paediatric services are in contrast to the impersonal and disease-focused adult service. They valued continuity of care with the adult physician, continued access to the paediatrician, peer support, transfer of health information and being given control of the timing of transfer. An observational study in young people with other chronic conditions found that their satisfaction with parental involvement, promotion of health self-efficacy, and meeting the adult team before transfer were transitional care features associated with improved outcomes (326). Our findings also reflect and explain the role and impact of

these factors in rheumatology. Concepts unique to rheumatology in this review included the need for information and parental support in adult care when joint injections are required, feeling confronted in seeing adults with frightening effects of their arthritis in waiting rooms, and feeling that symptoms of pain or fatigue were dismissed in adult care.

We used a sensitive search strategy, software to facilitate a systematic and auditable approach to analysis, and investigator triangulation to ensure that the findings reflect the full range and depth of data from the primary studies. However, there are some potential limitations. The majority of studies were from high-income countries with English-speaking participants. Most participants had either JIA or SLE. The transferability of the findings to other settings and populations that were not included is therefore uncertain.

Transition from paediatric to adult health services occurs in parallel to major physiological and psychosocial developmental changes. Accordingly, transition services need to be developmentally appropriate and support the unique needs of a population undergoing pubertal, social, vocational, emotional and cognitive transitions. To address this, guidelines have recommended optimal components of transitional care programmes (306-308). The European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PReS) developed 12 standards and recommendations for transitional care of young people with juvenile-onset rheumatic diseases. This includes high-quality, holistic, multidisciplinary care starting in early adolescence, transition co-ordinator, protocols and policies, efficient and direct communication, transfer documentation, an open electronic platform with transition resources, training for paediatric and adult healthcare professionals, secure funding and the need for further research to inform best practice (307). The World Health Organisation and GRADE (Grading of Recommendations, Assessment, Development and Evaluations – a framework for grading the quality of evidence for use in clinical practice guidelines) recommend incorporating qualitative evidence synthesis to inform the values and preferences, acceptability, feasibility and equity of guideline recommendations (133, 327, 328). Incorporating findings from this qualitative systematic review could enhance future transition guidelines in rheumatology (Figure 5.3).

Some strategies highlighted in this review that are not addressed in current guidelines include: 1) Introduce – The paediatric rheumatologist introducing the adult healthcare team with confidence, 2) Inform - Providing comprehensive information on the differences in the adult setting (e.g. encountering adult patients with damage and disability in waiting rooms, joint injections procedures and changes in service availability

such as hydrotherapy), 3) Empower - Providing guidance, training and opportunities to manage parental relationships and the ability to attend adult clinics independently, 4) Transfer – Allowing the timing of transfer to be flexible, patient-controlled and avoiding times of disease flares or medication changes and 5) Support – Advocacy at school and work to reduce bullying and discrimination.

Medication adherence is particularly challenging during transition. A survey of parents of older teenagers with juvenile myositis showed that only 51% were deemed responsible enough to take medications without being reminded (329). A cross-sectional survey of people aged 13-20 years with various rheumatic conditions showed only 54% reported full adherence to medications in the previous week (330). Our review showed that some young people continue to rely on their parents' reminders to take medications in adult care and may be more comfortable discussing non-adherence with clinicians without parental presence. They wanted to be more informed and involved in treatment decision-making and be presented with information about medications face-to-face. A brief transition programme for adolescents with JIA showed no effect on medication adherence (94). However, young people develop self-management skills with increasing age (329-331), and many continue to develop these skills after the age of 18 (332). Therefore, young people need to be supported in achieving mastery of self-management including medication management even beyond the age of transfer.

Transition to adult care in rheumatology is challenging for young people who feel suddenly abandoned, ill-prepared and fearful of the differences in adult-based healthcare that can be dismissive and impersonal. Creating an environment that promotes a sense of belonging, provides person-focussed and comprehensive care, and a gradual preparation for independence could enhance the young people's experience of transitional care and lead to better health-related outcomes into adulthood.

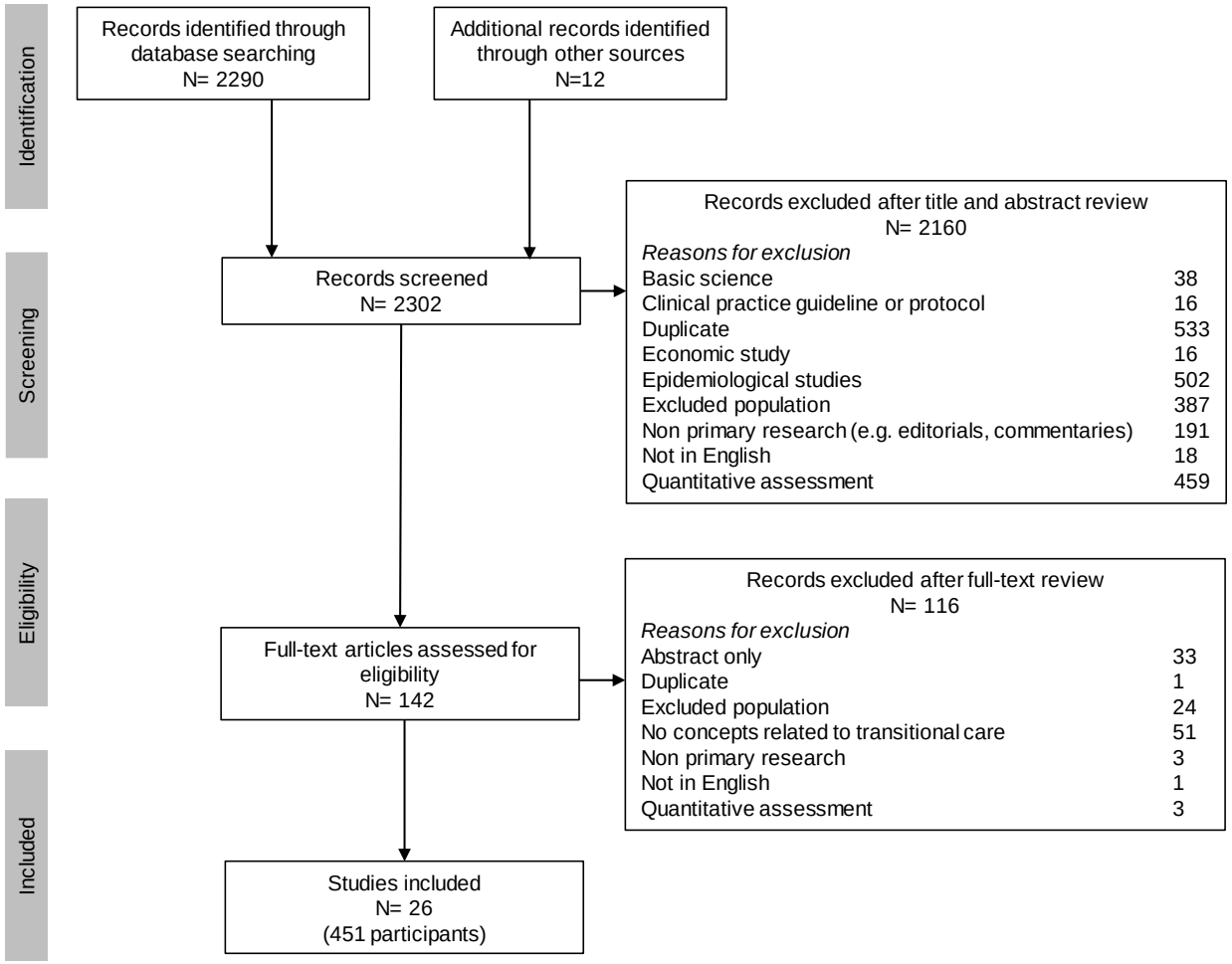

Figure 5.1. Search strategy

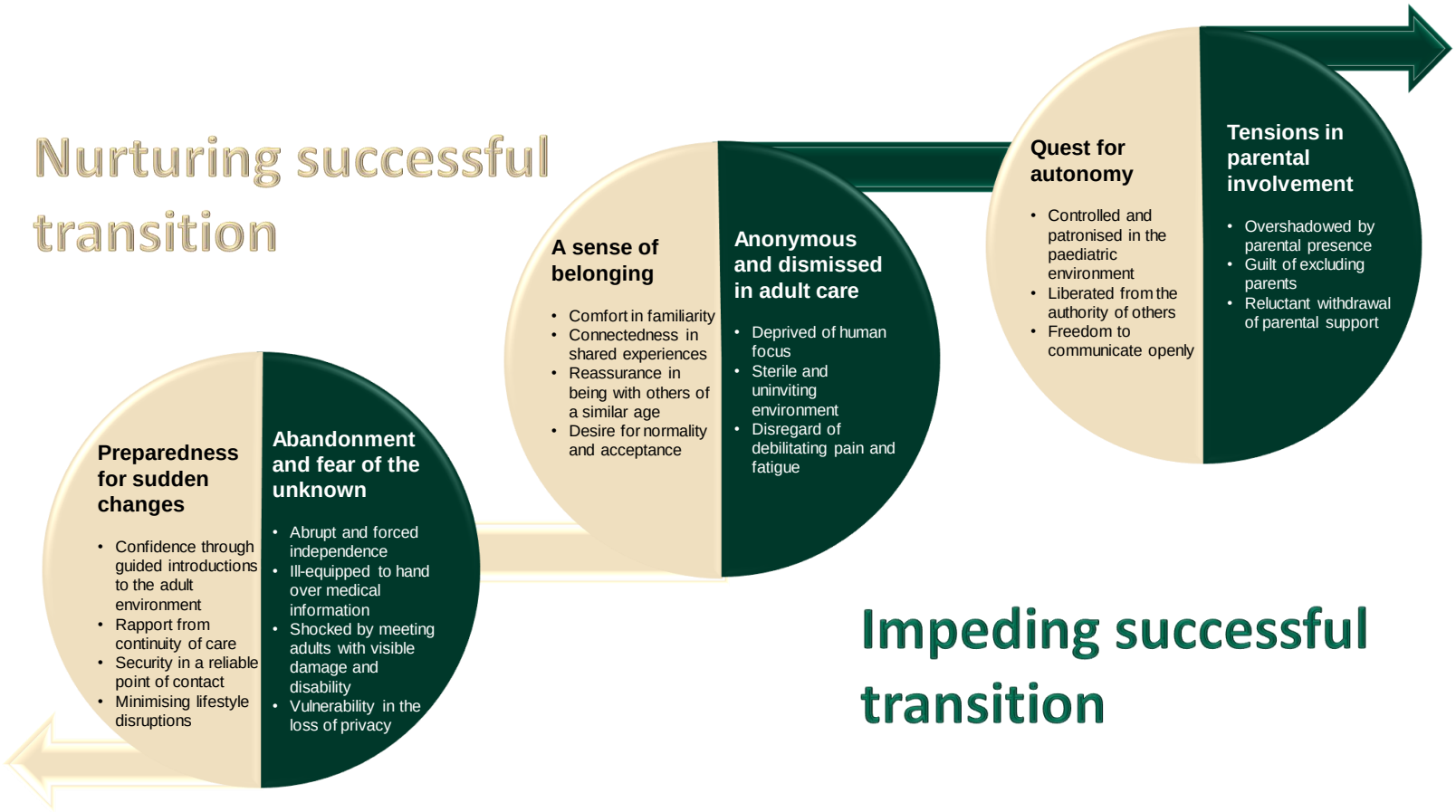

Figure 5.2. Thematic schema

Young people could feel abandoned and afraid of the unknown adult health environment and dismissed in care that was impersonal. In contrast, those that were given graded preparation, psycho-social support and an opportunity to feel a sense of belonging had a successful transition experience. Young people must contend with the tensions surrounding parental and paediatric health professional involvement in their care whilst seeking increasing autonomy.

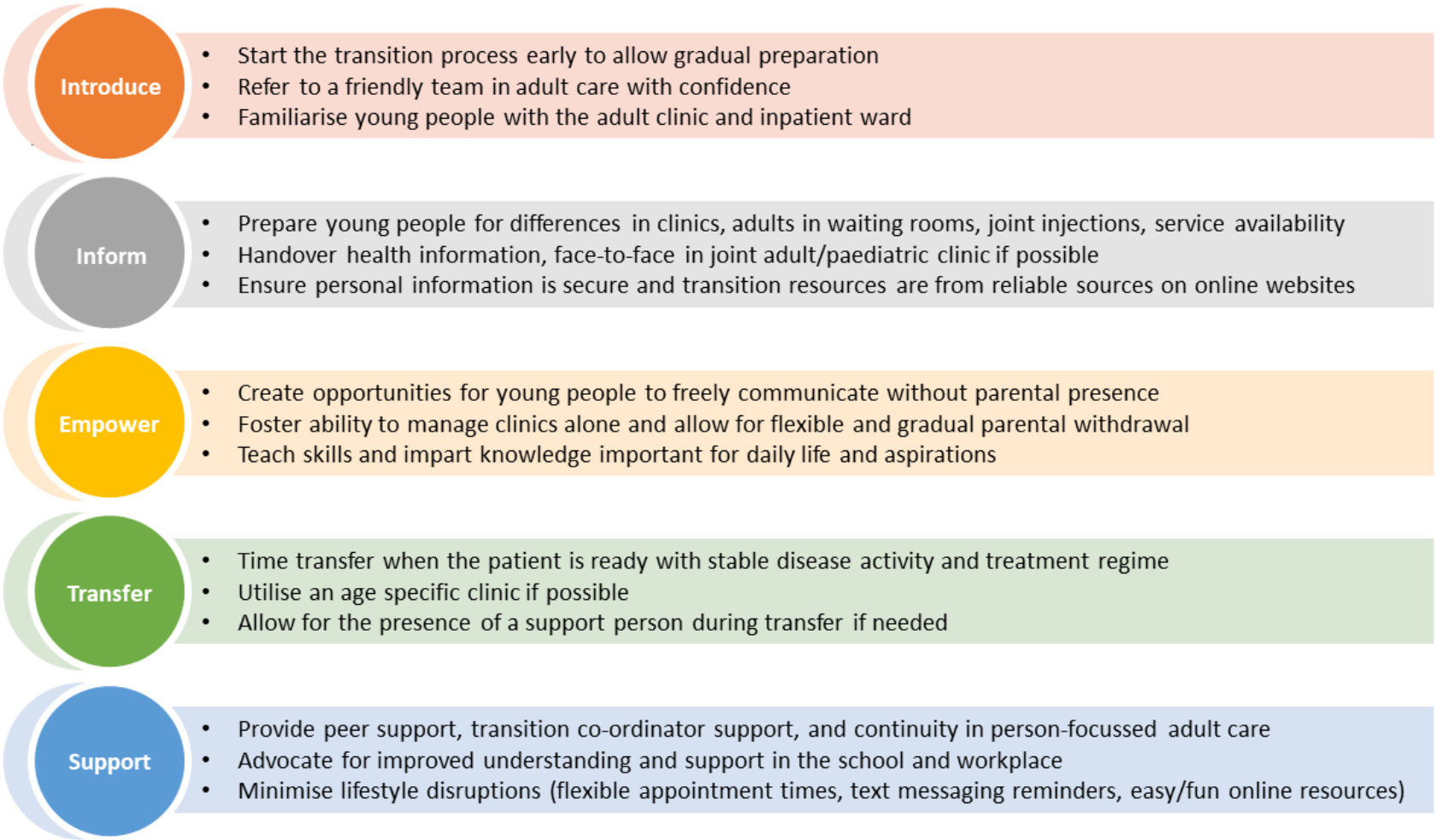

Figure 5.3. Patient-centred strategies for transitional care in rheumatology informed by qualitative evidence synthesis

Table 5.1. Characteristics of included studies

Study characteristics	No. of studies	%
Year of publication		
2001 – 2010	7	27
2011 – 2019	19	73
Country		
United States	8	31
United Kingdom	5	19
Australia	2	8
Belgium	2	8
Canada	2	8
Denmark	2	8
Other*	5	19
Sample size		
1 – 10	8	31
11 – 20	11	42
21 – 30	3	12
> 30	3	12
Not reported	1	4
Type of rheumatic condition		
Juvenile idiopathic arthritis	22	85
Systemic lupus erythematosus	7	27
Dermatomyositis	2	8
Mixed connective tissue disease	1	4
Scleroderma	1	4
Method of data collection		
Interviews	10	59
Interviews and focus groups	8	31
Focus groups	7	27
Other†	1	4

* The Netherlands, New Zealand, Norway, Republic of Ireland, Sweden (1 study each)
† Phone interviews and questionnaire with open and closed-ended question

Table 5.2. Modified consolidated criteria for reporting of qualitative health research

Item	Studies reporting each item	Studies n (%)
Personal Characteristics		
Interviewer / facilitator identified	(156, 158, 159, 161, 162, 316-318, 322, 333-338)	15 (58)
Occupation of the interview or facilitator	(156, 159, 316, 317, 321, 322, 333, 334, 339, 340)	10 (38)
Experience or training in qualitative research	(317, 321, 322, 334, 340, 341)	6 (23)
Relationship with participants		
Relationship established prior to study commencement	(159, 322, 333-336)	6 (23)
Participant Selection		
Selection strategy (e.g. snowball, purposive, convenience)	(159, 161, 162, 316, 317, 319, 321, 322, 333, 335-338, 342, 343)	15 (58)
Method of approach or recruitment	(158, 159, 161, 162, 303, 317-319, 321, 322, 333-344)	22 (85)
Sample size	(156, 158-162, 303, 316-319, 321, 322, 333-344)	25 (96)
Number and/or reasons for non-participation	(158, 162, 303, 317-319, 321, 322, 336, 338, 340, 342, 343)	13 (50)
Setting		
Venue of data collection	(156, 159, 160, 162, 317, 318, 321, 322, 335, 337-339, 341, 343)	14 (56)
Presence of non-participants (e.g. clinical staff)		0 (0)
Description of the sample	(94, 158-162, 303, 316-319, 321, 322, 333-344)	25 (96)
Data Collection		
Questions, prompts or topic guide	(158-162, 303, 317-319, 321, 334-336, 338-342)	18 (69)
Repeat interviews / observations	(156, 159, 316-318, 333, 336, 337)	8 (31)
Audio / visual recording	(94, 156, 158, 159, 161, 162, 316-319, 321, 322, 333-338, 340-344)	23 (88)
Field notes	(158, 159, 161, 162, 316, 317, 319, 333-335, 341, 342, 344)	13 (50)
Duration of data collection	(156, 159, 161, 162, 303, 317, 319, 321, 333, 335, 338, 340-344)	16 (62)
Translation and interpretation	(303, 317, 339)	3 (30)
Protocol for transcription	(94, 158-162, 316-318, 321, 322, 333-335, 337, 338, 340-344)	21 (81)
Data (or theoretical) saturation	(94, 159, 160, 162, 318, 319, 335-337, 339, 340)	11 (42)
Data Analysis		
Researcher/expert triangulation	(94, 158-160, 162, 316-319, 321, 322, 333-344)	23 (88)
Translation (language in which analysis was done, NA if English)*	(317, 339, 342)	3 (30)
Derivation of themes or findings (e.g. inductive, constant comparison)	(94, 158-162, 317-319, 321, 322, 333-344)	23 (88)
Use of software (e.g. NVivo)	(159, 162, 316, 317, 321, 322, 335, 336, 339, 341, 343)	11 (42)

Item	Studies reporting each item	Studies n (%)
Participant feedback on findings	(159, 161, 321, 336)	4 (15)
Reporting		
Participant quotations or raw data provided (e.g. picture, diary entries)	(158-162, 316-319, 321, 322, 333-335, 337-344)	22 (85)
Range and depth of insight into participant perspectives of transitional care (thick description)	(156, 158, 160-162, 317-319, 321, 335, 337, 338)	12 (46)

Table 5.3. Illustrative quotations

Theme	Quotations*	Contributing studies
	A sense of belonging	
Comfort in familiarity	He knows every single thing about me. He knows my whole family. He knows my whole life, and like, I like that he does. But I don't think with any other doctor I would be comfortable with that, because it would just feel weird. (316) I was afraid to transition to an adult rheumatologist and I waited as long as I could. I could tell him what was wrong, tell him what I needed, tell him what worked, and what didn't work. We were so in sync. I had his home phone number and I could call him up and say, "Can I get this med to get me through this or that?" At the last appointment, I cried. (159)	(156, 158, 162, 303, 316, 318, 319, 321, 322, 341, 345)
Connectedness in shared experiences	It always felt like I was the only person on earth that had arthritis, but I met a whole bunch of other kids who had it and I'm not the only one. It makes you feel a lot better. *(12-year-old female with JIA)* (317) Meeting other people with arthritis who had gone through the transition from school to tertiary education and employment was also seen to be valuable, as demonstrated by these young people: I'd like to get to know somebody that's been through the UCAS [University and Colleges Admission Services] thing for a highly competitive course and see what the outcome was like. It would really help. It would show that you can still do things. *(Adolescent with JIA)* (334)	(94, 159, 160, 162, 303, 317, 319, 334, 335, 337, 339, 342-344)
Reassurance in being with others of a similar age	I also feel that we should have been told of the risk of ending up in a group of people that were not our age. That was the only thing I was looking forward to really – people of my own age, getting to know other people. And in hindsight, it was far from it. *(Young adult with JIA)* (160) I was always sat between people of 50-60 years old, and I felt ill at ease there. Those old people give you a look as if to say, 'what are you doing here, youngster?' and, believe me, that didn't feel right at all! Then again, at the paediatric department, the reverse was true: there I sat the oldest and tallest among all those toddlers… *(Young adult with JIA)* (160)	(37, 160-162, 340)
Desire for normality and acceptance	At first it was like a secret, almost. My best friends didn't know. It was something I was almost ashamed of… I felt like the word, disease, just didn't sit well with me. I don't really understand why, but it was like I was an outcast almost. *(Person with SLE/MCTD)* (322) I think the most important would be the teachers because it's very difficult to do work when you think that you're being looked down upon by your peers and your teachers because of arthritis…So just educating the teachers and then make them do something about the bullying, because I remember the bullying being in class and like yeah. *(15-year-old female with JIA)* (335) It is like so many of them [medications]. I have 15 a day that I take... If I think some are less important then I do not take it. (319) I think it would be wise to have a careers adviser at the adolescent clinic. *(Adolescent with JIA)* (334)	(94, 156, 158, 159, 162, 317, 319, 322, 334, 335, 337, 340, 343, 344)

Theme	Quotations*	Contributing studies
	I've already had a couple of college interviews and I was alright up until they got to the disability bit and I did start backing away a bit and I think the interviewer picked up on that. *(Adolescent with JIA)* (334) I think having a disability is like a financial burden at times. I think maybe if they could give us advice on how to access some financial help to finance our way through college or uni. *(Adolescent with JIA)* (334)	
Preparedness for sudden changes		
Confidence through guided introductions to the adult environment	A polished presentation wouldn't come amiss: getting properly introduced to the adult rheumatology team, the department, etc. So that you know where stuff is and don't have to ask dumb questions on your first day. *(Young adult with JIA)* (160) It was awful. I was very sad, and it was a huge shock… In child care you are sedated when having joint injections, and you don't really get any information about the procedure in here [adult care]. And suddenly you are not sedated. *(Adolescent with JIA)* (338)	(94, 156, 160, 161, 318, 321, 337, 338)
Rapport from continuity of care	In another way, you felt secure… it's not quite the same here [adult care], because you meet different nurses and doctors and must tell your story every time. *(Adolescent with JIA)* (338) It has been different doctors; where you have to tell every time and I'm tired of it – it's a long story… and maybe you don't remember it all… it seems a bit unprofessional *(Adolescent with JIA)* (338)	(158, 160, 161, 335, 337, 338)
Security in a reliable point of contact	She (the nurse) came in and very quickly became my friend, if I can put it like that… instead of saying "I'm a nurse and I'm going to ask you a lot of medical questions", she came in and we sat and had a proper chat, like two friends. *(19-year-old female with JIA)* (337)	(94, 156, 161, 337, 338)
Minimising lifestyle disruptions	This is what your life looks like right now and these are our [medication] options. What do we think fits best into that?... it would make it easier for us to take them. *(Young adult with SLE)* (340) The main benefit [of a regional outreach program] would probably be having more time doing normal things, not time travelling and not having to spend the extra money to travel. *[15-year-old female with JIA]* (335)	(94, 156, 161, 162, 316, 317, 319, 322, 335-337, 340, 343)
Abandonment and fear of the unknown		
Abrupt and forced independence	I still feel that they should have said more to me beforehand, along the lines of: 'Look, we're going to try to move you to the adult department'. That you first get a taste of what it's like there. But it was all so immediate, straight in at the deep end. For me, personally, it was all a bit too sudden. *(Young adult with JIA)* (160)	(156, 158, 160, 161, 303, 316, 318, 321, 338)

Theme	Quotations*	Contributing studies
Ill-equipped to hand over medical information	They [the medical notes] were lost in transmission between the two hospitals, which meant cancellations of appointments… In the last 4, 5 years, I've seen Dr … once. *(Young adult with JIA)* (161) Indeed, being shunted around from one doctor to the next, made me nervous and I didn't know what to expect. But because my paediatric rheumatologist sat in on the meeting with the adult rheumatologist, I was more confident that everything would go well and that she would pass on the correct information. *(Young adult with JIA)* (160)	(156, 158, 160, 161, 316, 318, 319, 321, 338)
Shocked by meeting adults with visible damage and disability	You're sitting there looking at kids, and I can remember sitting, thinking, you know, 'you're so lucky compared to these people', and then suddenly being surrounded by these adults and thinking 'oh my God that's going to be me! This is going to be me in 20 years' time'. *(Young adult with JIA)* (161)	(158, 160-162, 338)
Vulnerability in the loss of privacy	Many expressed hesitation to use chat rooms and existing social media sites on the internet because of privacy concerns and feeling uncomfortable talking with strangers about their health. They would much rather use sites curated by the medical institution(s) and health professionals whom they already trust. (319)	(161, 317, 319)
Anonymous and dismissed in adult care		
Deprived of human focus	Yeah just be generally nice, I guess. Not just there to treat the symptoms and get you on your way. Finding out more about you as a person. *(20-year-old male with JIA)* (335) There is not as much about getting personal, which I really don't care about that. But it just seems like, they are just in and out . . . Like the nurses don't ask you as many questions and stuff. It just makes you think about things. (316)	(156, 158, 160, 161, 316, 318, 321, 322, 334-338, 340, 341)
Sterile and uninviting environment	By contrast, the youths felt more pacified, lonely and anonymous in the adult unit; no kitchen evening gatherings, no hobby activities, 'nothing happened'; they were glued to the television set in their patient rooms. (158)	(94, 158, 318, 321, 338, 341, 344)
Disregard of debilitating pain and fatigue	… I didn't feel they took me seriously, because… the clinical examination did not match what I said, and you feel a little untrustworthy – it was reflected in the conversations, when they said the examinations [physical examination and x-r ay] and my symptoms came out differently. *(Adolescent with JIA)* (338) The doctor was upset that I transferred my records; she said, "I don't need to see all this." I said, "yes you do, this is my life." She said, "Looking at your labs, I don't think you have arthritis." "What? Did you even read any of my stuff?" She said, "I don't have time for that." (159)	(158, 159, 338)
Quest for autonomy		

Theme	Quotations*	Contributing studies
Controlled and patronised in the paediatric environment	At about 15 to 16 years old, the paediatric rheumatologist and me didn't get on any more, as she mothered me too much. I wasn't allowed to make my own decisions—although I was plenty old enough to do so, I felt. I became very unruly and recalcitrant. So maybe it was a good thing to quietly contemplate a move to the adult group. After all, you're no longer that child with which they could do as they pleased. *(Young adult with JIA)* (160) You get really fed up of other people making the decisions because it is your body, and you want a say in it. *(Adolescent with JIA)* (161)	(160-162, 318, 321, 334)
Liberated from the authority of others	I really got responsibility in here [adult care], and in a way it has been good to take the plunge… But it has been hard, and you think: "You'll never make it" - but it has made me strong and I almost never bring my parents anymore. *(Adolescent with JIA)* (338) At the same time, perceived disadvantages of the children's hospital ('some treat you as if you're still a child') were compensated for in the new setting ('you take more control of your own affairs').Young adults liked it that they were 'more involved as an adult' and that consultations were more business-like. (321)	(37, 158-162, 316, 321, 337, 338)
Freedom to communicate openly	I lie to my mom about taking my medicine, but I don't lie to the doctor because they need to know. *(Person with SLE)* (340) Opportunities to be seen alone were thought to have many benefits. They not only promoted disclosure but also engendered feelings of increased independence and control: You'd feel a little bit more independent—this is good because this is my body, it's my arthritis and I'm talking about it—and you haven't got your parents there all the time. *(Adolescent with JIA)* (161)	(158, 161, 337, 340)
Tensions in parental involvement		
Overshadowed by parental presence	I think you should give the information to teenagers actually instead of talking to parents all the time… I think it is important that young people are told as soon as possible what their mediation is, what treatments are, what's happening with them because otherwise you go at 14 and 15 years old and haven't got a clue what drugs they're on or anything like that. *(Young adult with JIA)* (161) I think that has been something that's been difficult for me, the transition and to start making my own decisions, because they [parents] have been so heavily involved. Like I need to start figuring out what adult doctor I'm going to see. *(20-year-old female with SLE)* (162)	(158, 161, 162, 316, 318, 338, 340)
Guilt of excluding parents	It's quite difficult, because my mom and dad have been great, really supportive, but there's times when you've been going to speak up . . . you think I just wish I'd come on my own. I'm like 19/20 years old now, I really don't need you to come and hold my hand any more. *(Young adult with JIA)* (161)	(160, 161, 318)
Reluctant withdrawal of parental support	But for the most part, my parents still handle my whole medical thing, because it's just—it'd be like having another part-time job for me. It'd just be too much. *(Adolescent with JIA)* (344)	(94, 156, 158, 160-162, 316-318, 337,

Theme	Quotations*	Contributing studies
	I was quite young when I first got diagnosed, and basically when I am sick, I really can't speak for myself and make decisions for myself, so my parents have been very influential in the decisions around my health. *(20-year-old female with SLE)* (162) It's very important to me that my parents are present, or at least one of them… Otherwise I have to fill them in afterwards and suppose I misunderstood a part or said something I shouldn't have? (160)	338, 343, 344)

JIA, Juvenile idiopathic arthritis; SLE, Systemic lupus erythematosus

Chapter 6: Patient and caregiver priorities for medication adherence in gout, osteoporosis and rheumatoid arthritis: nominal group technique

This chapter describes patient and caregiver priorities for medication adherence in gout, osteoporosis and rheumatoid arthritis.

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405. I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Patient and caregiver priorities for medication adherence in gout, osteoporosis and rheumatoid arthritis: nominal group technique.

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Contribution to paper: Study design, data collection, analysis and manuscript write up.

Senior author or collaborating author's endorsement: Kathleen Tymms

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Endorsed

Kathleen Tymms Primary supervisor	18/11/20 Date	**Diana Perriman** Delegated authority	19/11/20 Date

6.1 Abstract

Objectives: This study aimed to identify and prioritise factors important to patients and caregivers with regard to medication adherence in gout, osteoporosis (OP) and rheumatoid arthritis (RA), and to describe the reasons for their decisions.

Methods: Patients with gout, OP and RA, and their caregivers purposively sampled from five rheumatology clinics in Australia, identified and ranked factors considered important for medication adherence using nominal group technique and discussed their decisions. An importance score (scale 0-1) was calculated, and qualitative data were analysed thematically.

Results: From 14 focus groups, 82 participants (67 patients, 15 caregivers) identified 49 factors. The top five factors based on the ranking of all participants were trust in doctor (importance score 0.46), medication effectiveness (0.31), doctor's knowledge (0.25), side effects (0.23), medication taking routine (0.13). The order of the ranking varied by participant groupings with patients ranking trust in doctor the highest whilst caregivers ranked side effects the highest. Five themes reflecting the reasons for factors influencing adherence were: motivation and certainty in supportive individualised care; living well and restoring function; fear of toxicity and cumulative harm; seeking control and involvement; and unnecessarily difficult and inaccessible.

Conclusions: Factors related to the doctor, medication properties and patients' medication knowledge and routine were important for adherence. Strengthening doctor-patient trust and partnership, managing side effects, and empowering patients with knowledge and skills for medicine-taking could enhance medication adherence in patients with rheumatic conditions.

6.2 Introduction

Gout, osteoporosis (OP) and rheumatoid arthritis (RA) are common rheumatic conditions associated with pain, reduced quality of life and premature mortality (14, 346-350). Medications can reduce symptoms, decrease flares and prevent joint damage in gout and RA, and fracture risk is roughly halved by OP treatments (278, 351-354). However, adherence is low in these conditions. For example, adherence may range from 10-46% in gout and 30-80% in RA (74, 87). Approximately 50% of osteoporotic women discontinue prescribed treatment in 1 year (88). Non-adherence is associated with increased disease activity, long-term joint damage in gout and RA and increased fractures in OP (63, 74, 109, 110, 118, 123).

Non-adherence is complex and multi-factorial (71, 74, 86, 87) and taking long-term medications for rheumatic conditions is challenging. Five dimensions of adherence are described by the World Health Organisation, factors affecting adherence can be divided into: social/economic (e.g. medication cost, health literacy); health care team and system (e.g. doctor-patient relationship); condition (e.g. symptom severity); therapy (e.g. immediacy of benefits, side effects); and patient-related factors (e.g. knowledge, beliefs, self-efficacy) (34). No adherence strategy has been effective across all patients, conditions and settings (75, 93). It remains uncertain whether existing adherence interventions address the priorities and concerns of patients with rheumatic conditions. Caregivers also offer important insight into the patient's health status and may have a role in supporting adherence including organising and administering medications (355). Because of this, the caregiver's perspective adds further to understanding adherence.

As part of the Outcome Measures in Rheumatology (OMERACT) – Adherence initiative (102), this study aimed to identify and prioritise factors influencing adherence for patients and caregivers in gout, OP and RA and to describe the reasons for these decisions. This can inform the development of patient-centred interventions for medication adherence in rheumatology and enable adequate evaluation of their effectiveness.

6.3 Patients and Methods

Participant recruitment and selection

Patients with gout, OP and RA and their caregivers (family member or friend involved in their care) were recruited from five rheumatology clinics in New South Wales, Australia. The clinics were in rural, regional and metropolitan areas in private and public practices. Participants were purposively sampled for diversity in demographic (age, sex, cultural and socio-economic backgrounds) and clinical characteristics (severity and duration of condition, type of medications), and experience with medications (level of adherence as perceived by the doctor). Participants were eligible if they were aged 18 years or older, spoke English, and were prescribed disease-modifying anti-rheumatic drugs (DMARDs), urate-lowering therapy, anti-resorptive or anabolic therapy for OP. $35 USD in local currency was offered to participants for travel expenses. Ethics approval was obtained for all participating sites. All participants provided informed consent.

Data collection

The study combined two methods: focus groups and modified nominal group technique (96, 101), an approach used to generate patient and caregiver priorities in outcomes research (356, 357). The groups were convened from February to October 2018 in rooms external to rheumatology clinics. Rheumatologist AK, with training in qualitative research, facilitated all groups with a co-facilitator (KT/MC/KM/MG/SB/AT), who took field notes. The modified nominal group technique involved structured discussion to generate a list of ideas followed by a single round of individual ranking. This takes into account each participants' opinions and encourages equal participation (101). The focus group method was used to explore participants' reasons for their choices. Each two hour session included: 1) discussion on experiences with medications, involvement in decision making, strategies used to enhance adherence, 2) group generation of factors important for adherence, which was supplemented with factors from previous groups and a literature review of adherence interventions in rheumatology (allowing participants to consider and discuss a greater number of factors), 3) individual ranking of each factor, and 4) discussion of the reasons for rankings. The question guide (Appendix F.1) was developed with patient research partners (MDW/VE/MG/MSV) and pilot tested. Groups were convened by condition when feasible (four groups) and continued until data saturation (when no new ideas or factors were identified in consecutive groups). Each patient completed the 5-item version of the Compliance Questionnaire in Rheumatology (CQR5) to estimate the level of adherence of the study population (358). Each group

was conducted in English, audio-taped and transcribed verbatim. Participants were able to review and revise their transcripts.

Data analysis

Qualitative analysis: AK recorded field notes and used thematic analysis to inductively develop preliminary themes that explained participants' rankings. Thematic analysis is a form of qualitative analysis which captures patterns of shared meaning or 'themes'. Themes that emerge unite individuals' perspectives and experiences to form a comprehensive picture of the group's experience (96). The inductive approach is a 'bottom up' approach which begins from the data without a pre-existing model or theory (96). Preliminary themes were discussed and refined with co-authors and co-facilitators KT and AT for researcher triangulation. Transcripts were entered into HyperRESEARCH software (ResearchWare Inc. Version 4.0.1, Randolph, MA). AK coded transcripts line-by-line and revised preliminary themes to ensure the full range and depth of the data was captured. Results were sent to participants for feedback. The Consolidated Criteria for Reporting Qualitative Health Research was used in the reporting of this study (100) (Appendix F.2).

Nominal group ranking: An importance score (IS) which is the average of the reciprocal rankings was calculated for each factor. The reciprocal ranking is 1 over the ranking assigned by the participant for a factor. For example, if "side effects" is ranked 1st by one participant and 3rd by another, the reciprocal rankings will be 1 and 1/3 respectively. If the factor was not ranked by the participant, the reciprocal ranking was given a value of 0. The average of these three reciprocal rankings, 0.44, is the IS. The IS ranges from 0 to 1, with higher scores reflecting factors that are more valued by the participants. The IS incorporated 1) the importance given to the factor by the rank position and 2) the consistency of being nominated by participants. The IS was calculated for the entire group and analysed in subgroups (gout/OP/RA-based on the predominant diagnosis of each participant; patients/caregivers; male/female). The analysis was conducted using statistical software R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). A detailed explanation is provided in Appendix F.3.

6.4 Results

Participant characteristics

In total, 82 people (67 patients, 15 caregivers) participated in 14 focus groups comprising of three to ten participants (Table 6.1). Sixteen (20%) participants had more than one diagnosis (OP/RA, ten participants; gout/OP, three; gout/RA, two; gout/OP/RA, one), with the predominant diagnosis of each participant being gout (n=25, 30%), OP (n=20, 24%) and RA (n=37, 45%). Participants were born in 16 countries. Patients were aged 28-85 years (mean 66 years, standard deviation 12), and 42 (63%) were female. Patients with RA and OP were taking a variety of DMARDs or anti-resorptive therapy for their conditions (Table 6.1). All participants on urate-lowering therapy were on Allopurinol (n=20, 95%). Of the caregivers, 11 (73%) were spouses/partners and four (27%) were children of a patient. Using the CQR5, ten (15%) patients were 'low adherers', 54 (81%) were 'high adherers'. Fifty-nine additional patients declined participation in the study as they were unwell, overseas, disinterested in the topic, had work or childcare commitments, difficulty with transport or poor mobility.

Ranking of factors

Participants identified 49 factors important for adherence (Figure 6.1, Appendix F.4). The top ten factors were trust in doctor (IS 0.46), medication effectiveness (0.31), doctor's knowledge (0.25), side effects (0.23), medication taking routine (0.13), medication necessity (0.13), medication satisfaction (0.13), reminders/organisers (0.12), medication knowledge (0.12) and medication monitoring (0.11). When IS was analysed for patients versus their caregivers, differences were identified. For patients (n=64) the top three factors were trust in doctor (0.51), medication effectiveness (0.30), doctor's knowledge (0.24) and for caregivers (n=15) the top three factors were side effects (0.32), doctor's knowledge (0.32), medication effectiveness (0.31) (Appendix F.5). The greatest difference between IS for patients and caregivers was for trust in doctor (0.51 vs 0.28 respectively, ranked 4th for caregivers).

By condition, participants with RA and OP had the same top three factors: trust in doctor (0.38, 0.56 respectively) medication effectiveness (0.33, 0.32), side effects (0.29, 0.25). The top three for gout were: trust in doctor (0.49), doctor's knowledge (0.28), medication effectiveness (0.26), with side effects ranked in 6th place (0.12) (Appendix F.6).

By gender, the top three factors for females were trust in doctor (0.43), medication effectiveness (0.30), side effects (0.28). For males, the top three were trust in doctor (0.51), medication effectiveness (0.31), doctor's knowledge (0.23), with side effects ranked 7th (0. 15) (Appendix F.7). Most male participants had gout (16 patients and one caregiver, 52% of all male participants), reflecting their similarities in ranking.

Qualitative analysis

Five themes explaining the participants' decisions were identified. Where themes apply to both patients and caregivers the term 'participants' has been used, otherwise themes related specifically to patients or caregivers have been specified. Illustrative quotations for each theme (Table 6.2) and a thematic schema showing the relationship between themes and factors (Figure 6.2) are provided.

Motivation and certainty in supportive and individualised care

"Where there is trust, you are bound to get on whatever the doctor says to you. If there is no trust, then there is no treatment effectively." – Mr X, 50s, caregiver for wife with RA.

Participants needed to trust the prescribing doctor to take medications. Participants developed trust if their doctor was empathetic, knowledgeable, took the time to listen, discussed options and individualised care to suit personal preferences and life circumstances. A trustworthy doctor would *"always do the right thing by you"*. Although a trustworthy doctor had good knowledge, not all knowledgeable doctors were trusted. The key difference was that participants felt the latter may lack genuine interest and care. Therefore, doctor's knowledge was ranked lower than trust. Participants had greater confidence in their medications if their specialists, general practitioners (GP) and/or pharmacists worked together to reach agreement on medications. Participants felt GPs and pharmacists had broader knowledge and responsibility for all their health conditions and medications and were reassured when they checked for drug interactions. They suggested that pharmacists and nurses could provide further medication education. Caregivers had a major role in supporting adherence as they would administer and organise medications, continually remind patients to take medications and help patients emotionally cope and accept their illness and medications.

Living well and restoring function

"It's very important for me to drink this, I don't like this sickness. I want to be fit, I don't' want to struggle like this. I'm still young. I need to work, you know what I mean?" – Mr. Y, 30s, living with gout for 3 years, on Allopurinol.

Patients with gout and RA were motivated to take medications to avoid perceptible symptoms such as severe pain and to enable performance of activities of daily living such as walking, showering, caring for children and working. The delay in medication benefit was difficult for patients with gout and RA, and during this time they could stop taking their medications. In addition, patients were not convinced of the need for long-term medications if they only had intermittent gout symptoms or were asymptomatic with OP. Patients were discouraged and confused by ongoing pain or swelling despite medications for gout or RA, or if they developed a new fracture on treatment for OP. One patient described decreasing the dose of allopurinol whenever he started to feel well, and patients with RA were tempted to stop DMARDs when they achieved remission, but would be motivated to restart if symptoms returned. Patients emphasised that their medications must have the overall effect of allowing them to live well. In addition to medications, they discussed the value of eating well, having a positive attitude and exercising. Some felt these lifestyle choices could reduce side effects and boost medication effectiveness.

Fear of toxicity and cumulative harm

"How long has the drug been on the market? Because there are side effects that maybe you only see after 40 years, but the drug has been in the market for five, so you have to wait to see what happens." – Mrs A, 30s, caregiver of husband with RA.

The potential need for lifelong medications was daunting for many patients. This was especially true for younger patients and those recently made aware of side effects such as liver toxicity with methotrexate. Even if no side effects occurred, participants had persistent fears of cumulative damage. Some caregivers felt a *"paranoia"* that long-term side effects are unknown until much later and concerns of an unhealthy dependence on medications developing. Patients would keep taking medications despite side effects

which had a significant impact on their lives such as headaches or nausea because of the duration between follow up appointments or being unaware of alternative medications. Patients were often uncertain of their medications and felt like *"guinea pigs"* with prescriptions that were *"trial and error".* When multiple medications were being taken, both patients and caregivers worried about drug interactions and whether medications were as effective, targeted the right condition, or impacted other conditions. Receiving conflicting information from different health professionals (e.g. dentists and rheumatologists on risks of OP medications) was confusing and heightened concerns. Alarming information could be found on the internet (e.g. methotrexate causing sudden death, or bisphosphonates being made from industrial cleaners) though some learned to overcome this by consulting their doctor or scrutinising the information.

Seeking control and involvement

"I needed to know the side effects, ongoing effects of what I'm taking, and an understanding of why I'm taking them, how it's going to affect me. It's those things you think of when you go home, at night, you sit in front of the telly thinking why am I doing it?" – Mr. Z, 60s, living with gout for 4 years, on Allopurinol.

Patients felt that acquiring knowledge about their medications and disease empowered them to self-manage their condition and share in decision-making. A major source of this information was their doctor or their pharmacist. Participants also used Google and Facebook but could be wary of their credibility. Monitoring in the form of blood tests for RA, gout and bone density scans for OP, helped patients feel secure in knowing whether their medications were working and were safe. Patients with established routines were confident with their adherence, especially those with longer disease duration. Patients had unique routines (e.g. keeping their medications in a visible place, having a pill box or phone reminders) and emphasised the importance of self-discipline in medication taking. When routine was compromised (e.g. weekends or overseas trips) or if their daily lives lacked routine (e.g. retirees or shift workers), patients had less control and poorer adherence.

Unnecessarily difficult and inaccessible

"Even my daughter has trouble opening them, and God bless, her hands work perfectly. She struggles with some of them, the methotrexate bottle in particular." – Ms. B, 50s, living with RA for 6 years, on Methotrexate.

Some barriers to managing medications were beyond the patient's control. Some found it difficult to be able to get a hospital appointment in time for their prescription, others were unable to afford multiple medications. Some patients with RA had difficulty with qualifying for biologics and were disheartened about having to take many medications they experienced side effects with. Patients with RA found it frustratingly difficult to open medication bottles. Pain when injecting biologics, or the taste of some medications made it unpleasant to continue with them. Patients were confused with the different names, packaging, shapes and colors that accompanied generic medications.

6.5 Discussion

For patients with gout, OP and RA and their caregivers, factors related to their doctor (trust and knowledge), medication properties (effectiveness, side effects) and patient capabilities (knowledge, routine) were important with regard to adherence. Patients and caregivers valued supportive and trustworthy doctors, the ability to achieve a balance between medication benefits and harms and being involved and in control of medication management.

Relationships with health professionals, in particular with the prescribing doctor impacted patient and caregiver willingness to take medications. "Trust in the doctor" and "doctor's knowledge" were amongst the top three factors. To build trust, patients explained that doctors needed to demonstrate genuine interest and concern, impart knowledge around medication benefits, harms, and options, and foster understanding and agreement with other health care professionals. A systematic review and thematic synthesis of qualitative studies in gout demonstrated the impact of a negative doctor-patient relationship, with patients feeling they receive inadequate information and even dismissal and ridicule from their doctor (146). This review also reported that providers themselves felt insufficiently trained and under-resourced to provide adequate care for gout patients. Qualitative studies in other rheumatic conditions including spondyloarthritis, systemic lupus erythematosus, systemic sclerosis, and vasculitis also showed that relationship with the rheumatologist and other health care professionals strongly influenced patients' perceptions and experiences of their medication (145, 359).

“Medication effectiveness”, in balance with “side effects” were important to patients and caregivers. Patients emphasised the need consider their broader health picture – that medications interacted safely and did not impact their other comorbidities, and that medication benefits balanced side effects to improve function and well-being. Participants mentioned that side effects could be better managed with closer follow-up and being able to communicate the side effects in between consultations.

“Medication knowledge”, establishing “medication taking routine”, and use of “reminders/organisers” were ranked in the top ten factors. Knowledge was important for adherence, as patients felt that it gave them better awareness and involvement in medication taking. Routine gave patients a sense of control and confidence in taking medications regularly. Reminders and organisers were tools that patients and caregivers used to maintain their routine. Although knowledge was valued by participants in this study, adherence studies suggest that education to improve knowledge alone is inadequate to change adherence (360, 361). Findings from a meta-analysis of adherence interventions echo participants’ confidence in established medication taking routines and organisation. Interventions that included habit analysis and training were more effective than interventions that did not (362).

There were differences in priorities across different conditions. For example, participants with gout ranked side effects much lower than OP and RA participants, possibly reflecting the differences in side effect profile for the medications of these conditions. Patients with RA reported a variety of DMARD related side effects and were particularly concerned about long-term medication harm. In OP, although osteonecrosis of the jaw and atypical femoral fractures are rare complications of anti-resorptive agents (363, 364), these were concerning, especially if patients felt inadequately informed. In gout, the risk of increased flares during initiation of allopurinol was worrying. However, reluctance to start allopurinol was reduced if patients were given a time frame of when this risk would be reduced. Having infrequent monitoring of uric acid levels in gout or bone density scans in OP, patients felt frustrated with the lack of positive feedback and validation of medication effectiveness as compared to RA.

Differences were also seen in rankings between patients and caregivers. Caregivers ranked side effects the highest, whereas patients ranked trust in the doctor the highest. A possible explanation is that caregivers may have less contact with the doctor than patients, whose fears may have been reduced by interactions with a trustworthy doctor.

This study included 82 patients and caregivers with diverse demographic and clinical characteristics and was conducted across five rural, regional and metropolitan centers. The use of focus groups with nominal group technique allowed prioritisation of factors influencing adherence as well as insights into the reasons for their priorities. There are potential limitations. The transferability of the findings to contexts beyond Australia and other rheumatic conditions is uncertain. However, many themes identified in our studies are consistent with those identified in qualitative syntheses across many countries and cultures in RA (145) and gout (146). Coding was undertaken by one researcher, though three researchers contributed to preliminary themes and all co-facilitators and co-authors gave feedback on themes. It is uncertain if the study included participants who were 'low adherers' as the sampling was in part based on a self-report questionnaire, which have been shown to over-estimate adherence. It is unclear what impact this may have in terms of the factors identified and prioritised.

For clinical practice, this study highlights the critical role of health professionals, particularly the doctor, in the patient's acceptance of their medications. Closer collaboration and consistency among specialists, GPs and pharmacists, creating opportunities for patients to discuss side effects between clinic appointments, checking for drug interactions, providing feedback with drug monitoring and addressing the patients' goals of living well and improving function are potential patient-centred strategies to support medication taking.

An importance score was generated to quantify the relative importance of different factors. However, this study was designed to generate hypotheses that can be explored in future studies. A quantitative study with adequate power and an accurate measure of adherence could confirm whether highly ranked factors are truly correlated with adherence. In addition, the impact of these factors on adherence would be best explored in an intervention study. In contrast to the findings of this study, the majority of adherence interventions focus on patient-related factors (e.g. forgetfulness or lack of knowledge) as the cause of problems with adherence and there is a relative neglect of provider and health system related determinants (93). In addition, qualitative studies in gout and OP show health care providers perceive poor adherence to be predominantly related to factors such as lack of patient knowledge, number of medications, cost, family support, cognitive functioning of patients, side effects or warnings from the media or friends (365, 366). The results of this study suggest testing interventions that incorporate a focus on provider-related factors. A meta-analysis reviewed correlational studies and experimental interventions involving training of doctors' communication skills in varying

conditions. In this study there was a 19% higher risk of non-adherence among patients whose doctor communicated poorly compared to a doctor who communicates well (289). The odds of patient adherence were 1.62 times higher with doctor communication training than when a doctor receives no training (289). Another meta-analysis of adherence interventions in multiple conditions found that interventions targeting the health care provider were less effective than interventions delivered directly to patients (362). However, the healthcare provider targeted interventions in this meta-analysis may have focused more on cognitive interventions (i.e. changing the patients' medication knowledge and beliefs), rather than the quality of the patient-provider relationship.

Patient and caregivers' experience with their medications is complex. Factors related to the doctor, medication properties, and patient knowledge and medication taking routine were perceived to be important regarding adherence. Enhancing doctor-patient relationships, balancing medication benefits and harms within the context of an individual's unique set of comorbidities and goals, and empowering patients with medication knowledge and skills are potential solutions that require further investigation. Understanding and addressing patient-important factors in adherence could enhance the use of medications to help patients live well with their rheumatic conditions.

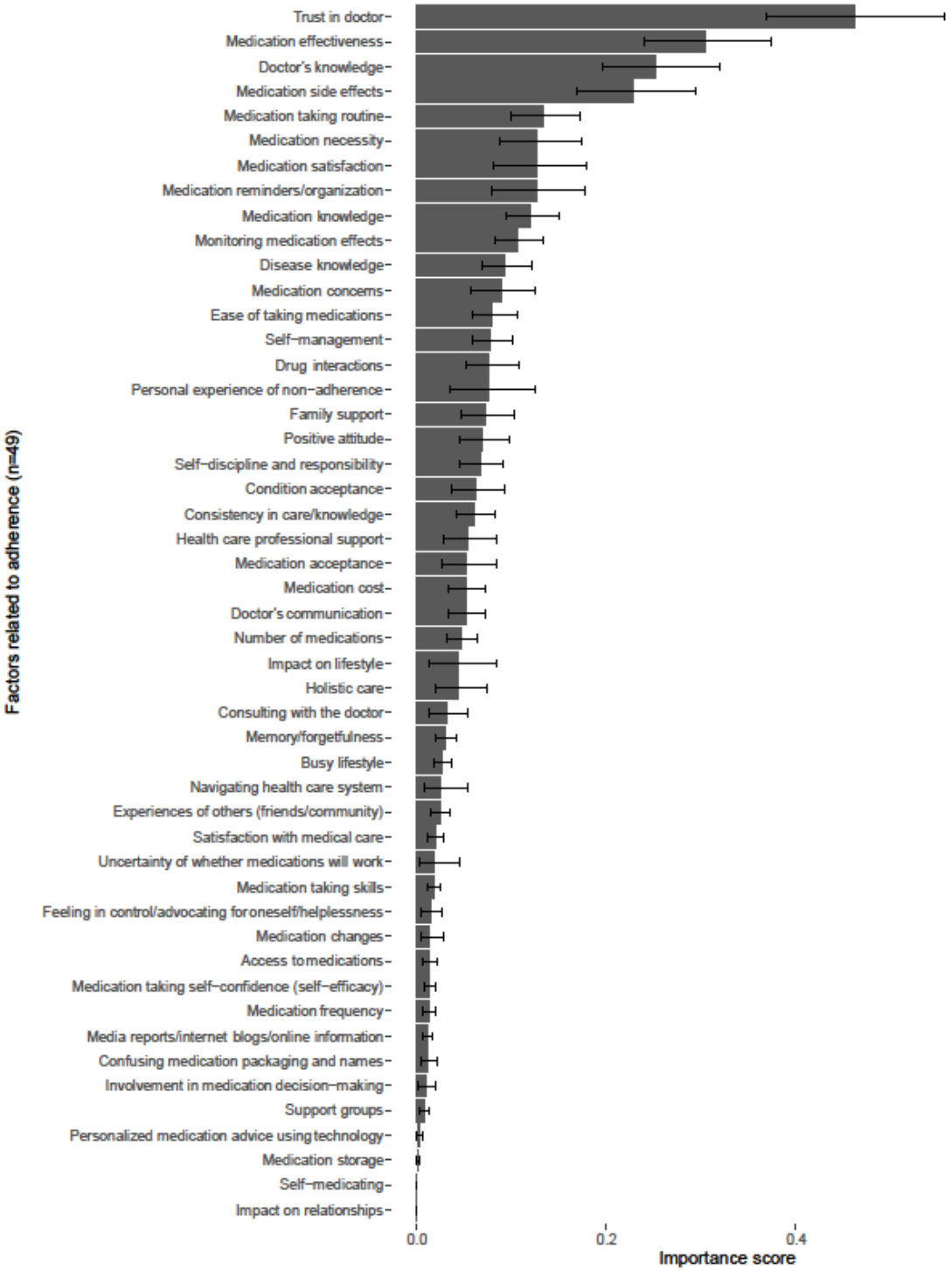

Figure 6.1. Ranking of all factors for all participants

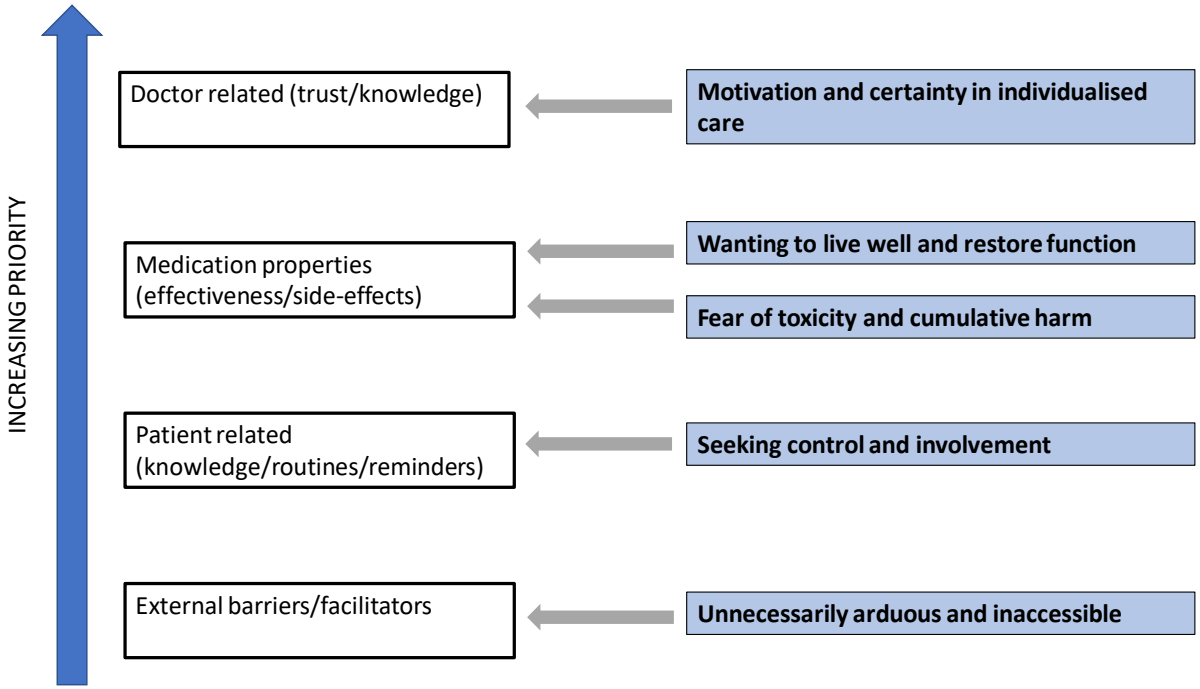

Figure 6.2. Thematic schema

Factors related to the doctor and medication properties were of highest priority in influencing medication adherence, with a focus on supportive individualised health care, and effectiveness outweighing harms for a patient to ultimately help a patient live well. Patients sought to be an empowered member of the team through greater knowledge and self-management skills. Despite supportive relationships, effective medications and self-sufficient patients, many other external barriers to acquiring and managing medications existed.

Table 6.1. Participant demographics

Patients				
	RA (n=29)	Gout (n= 21)	OP (n=17)	All (n=67)
Age (years) Mean (SD)	62 (13)	68 (13)	71 (8)	66 (12)
Gender (female) N (%)	23 (79%)	5 (23%)	14 (82%)	42 (62%)
Country of birth				
Australia	13 (45%)	15 (71%)	15 (88%)	43 (64%)
Other:	15 (52%)	5 (24%)	2 (12%)	22 (33%)
Asia-Pacific	6 (21%)	3 (14%)	1 (6%)	12 (18%)
Europe	5 (17%)	1 (5%)	1 (6%)	7 (10%)
Africa	2 (7%)	0 (0%)	0 (0%)	2 (3%)
South America	1 (3%)	0 (0%)	0 (0%)	1 (1%)
Not specified	1 (3%)	1 (5%)	0 (0%)	2 (3%)
Highest level of education	1 (3%)	0 (0%)	0 (0%)	1 (1%)
No school	3 (10%)	2 (10%)	0 (0%)	5 (7%)
Primary school	7 (24%)	12 (57%)	11 (65%)	30 (45%)
High school	8 (28%)	4 (19%)	2 (12%)	14 (21%)
Diploma/TAFE	8 (28%)	3 (14%)	3 (18%)	14 (21%)
University	1 (3%)	0 (0%)	1 (6%)	3 (4%)
Not specified				
Years since diagnosis Mean (SD)	20 (14)	14 (12)	8 (12)	15 (13)
Medication N (%)	Any csDMARD 22 (76%) Any bDMARD 12 (41%) Any tsDMARD 3 (10%) None specified 2 (7%)	Allopurinol 20 (95%) None specified 1 (5%)	Bisphosphonate 5 (29%) Denosumab 10 (59%) None specified 2 (12%)	
CQR5				
Low adherer	3 (10%)	5 (24%)	2 (3%)	10 (15%)
High adherer	25 (86%)	14 (67%)	15 (88%)	54 (81%)
Not specified	1 (3%)	2 (9%)	0 (0%)	3 (4%)
Caregivers				
	RA (n=8)	Gout (n=4)	OP (n=3)	All (n=15)
Age (years) Mean (SD)	55 (17)	51 (14)	63 (19)	56 (16)
Gender (female) N (%)	3 (37%)	3 (75%)	1 (33%)	7 (47%)
Country of birth				
Australia	2 (25%)	2 (50%)	3 (100%)	7 (47%)
Other:	6 (75%)	2 (50%)	0 (0%)	8 (53%)
Asia-Pacific	3 (37%)	2 (50%)	0 (0%)	5 (33%)
Europe	1 (12%)	0 (0%)	0 (0%)	1 (7%)
Africa	1 (12%)	0 (0%)	0 (0%)	1 (7%)
South America	1 (12%)	0 (0%)	0 (0%)	1 (7%)
Duration of being a caregiver (Years) Mean (SD)	9 (6)	6 (10)	3 (-)	8 (7)

RA, rheumatoid arthritis; OP, osteoporosis; SD, standard deviation; TAFE, Technical and Further Education (government run system providing education after high school in vocational areas); csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; bDMARD, biologic disease-modifying anti-rheumatic drug; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug; CQR5, 5 item version of the Compliance Questionnaire in Rheumatology

Table 6.2. Illustrative quotations

Motivation and certainty in supportive and individualised care
Where there is trust, you are bound to get on whatever the doctor says to you. If there is no trust, then there is no treatment effectively. (*M, Caregiver of patient with RA, 50s)*
It's a waste of time if you don't trust the prescriber. You might as well find one that you can trust. End of story. *(M, Patient with OP, 70s, Zoledronic acid)*
She genuinely cares and shows sympathy as well. If I show her there's pain in certain parts, she actually looks at it. Like sometimes I say, she's a professor, but she doesn't mind to touch my foot. It's sort of… it's different. *(F, Patient with RA, 60s, Methotrexate/Tofacitinib)*
If (the doctor) doesn't know what he's doing, you're buggered. *(M, Patient with gout, 70s, Allopurinol)*
I found that sometimes you see different doctors, and they're only looking at their own plate. They're not looking at the big picture. They don't talk to each other, and I reckon that that sort of complex situation, they should have a pharmacy to overlook all the medication, balance the complications, the dosage and all those physical problems. *(F, Patient with OP, 60s, Zoledronic acid)*
I sort of introduced my specialist and everybody to my chemist… It's good, the communication between chemist and my doctors and specialists and stuff. It makes it a lot easier. *(M, Patient with gout, 50s, Allopurinol)*
Wanting to live well and restore function
When I got diagnosed, I couldn't walk. I couldn't drive my kids to school. I felt like a 90-year-old in a 30-year-old body, and I was in so much pain… so it's kind of like well, if I can take something that's going to make this better, despite reading the side effects, any medication has got side effects. But I need to get myself better. *(F, Patient with RA, 30s, Methotrexate/Sulfasalazine/Hydroxychloroquine/Etanercept)*
When they tell me to drink 500 a day, so I drink, I think one week. When the gout starts getting better, I just change it to 400. Now I stick to 400. *(M, Patient with gout, 30s, Allopurinol)*
I think that's sort of the difference. You got better, so you continue. But I don't see any difference at all. There's absolutely no difference. I don't get any pain relief, I get nothing. *(F, Patient with OP, 70s, previously on Risedronate)*
Yeah, I tend to think holistic approach. Working with medication, exercise, diet. I feel that all of that helps, but it might just help me, I don't know. I just think it does work. *(F, Patient with OP, 60s, previously on Alendronate)*
I'm now on four medications and one injection but still having massive issues medically, for not a great result. *(F, Patient with RA, 50s, Sulfasalazine/Leflunomide/Adalimumab)*
Fear of toxicity and cumulative harm
But the Methotrexate and going through all the side effects, you want me to take this forever? I'm 26, and I'm supposed to just take this forever now, even though you've told me the effects it's going to have on my liver etcetera and that was their answer. *(F, Patient with RA, 20s, Methotrexate)*
How long has the drug been on the market? Because there are side effects that maybe you only see after 40 years, but he drug has been in the market for five, so you have to wait to see what happens. *(F, Caregiver of patient with RA, 30s, Methotrexate)*
Interviewer: You mentioned you were on methotrexate and it really made you feel very ill. For two and a half years you continued to take it…
Patient with RA: I had young children at the time, they were babies. I just felt like I had no life, or I was just spending my time in bed wanting to cry all the time because it just made me feel so ill. I was made to feel like it was all in my mind, that it was just my repulsion against the medication. *(F, Patient with RA, 40s, Leflunomide)*

It concerns me sometimes because I'm taking 14 pills in the morning. What's happening when they all go down, do they all agree with one another? … how effective are they when you're taking so many? *(F, Patient with gout, 80s, Allopurinol)*
What confuses me is the dentists and the doctors give me a totally different answer on the incidence of problems. The dentist, 0.4%.. the doctor far less likely. *(F, Patient with OP, 60s, previously on Alendronate)*
Seeking control and involvement
I wouldn't blindly take anything because the doctor said to take it. You've got to have the knowledge of the disease. There's a lot of information available, and you have to just do a bit of research *(F, Patient with OP, 70s, Denosumab)*
The only way to know whether it's effective or not is to monitor it, having the blood test. Not only effectiveness, it's actually monitoring the side effects as well. *(F, Patient with RA, 60s, Methotrexate/Tofacitinib)*
I've had arthritis for 50 years, so I'm really used to taking my tablets. I keep them on the kitchen table. I have to take them twice a day. I just take them because they're right in front of me. I don't forget. *(F, Patient with RA/OP, 70s, Sulfasalazine)*
If you're, as we've been, in bed a couple of days, you've got to change your routine totally. If the medication's in another room, you've got to change it. It's the discipline that I find helps. *(M, Patient with gout/OP, 80s, Allopurinol/Denosumab)*
Because she will at times forget to take, especially when she's got a morning shift starting at 6:30, so at times she forgets to take the tablet. By the time she finishes at 3:30 she's already tired, so she forgets to take the tablet *(M, Caregiver of patient with RA, 50s, Methotrexate)*
Unnecessarily difficult and inaccessible
Like I'm on all these medications, I've had to be put on them before I get put on the Enbrel so that I qualify. So it was like whoa, so I'll have to take all these medications, all the side effects, before I get on this. *(F, Patient with RA, 30s, Methotrexate/Sulfasalazine/Hydroxychloroquine/Etanercept)*
I take 22 a day, costs me 130 bucks a month and I'm on the pension, you know. $130 out of your pension. *(M, Patient with gout, 60s, Allopurinol)*
I don't like the taste. But I just take it because I know it's helping me. Sometimes as a patient I try things, I change the time. Sometimes I say because I don't' like it, I'll wait until the evening. When I'll take it in the evening, sometimes I end up forgetting. *(F, Patient with RA, 50s, Methotrexate)*
Wish they'd stop making generics. I don't know what I'm taking, because all the pills I take, every time I go to the chemist they seem to give me a different brand. I'm very confused with the number of medications that I take and the different names I'm presented with. *(F, Patient with gout, 80s, Allopurinol)*

Information in italics indicate the gender, patient/caregiver status, age (years) and current disease modifying anti-rheumatic drug, urate lowering therapy or anti-resorptive therapy of the participant. M, male; F, female; OP, osteoporosis; RA, rheumatoid arthritis

Chapter 7: Addressing challenges in developing a core domain set in adherence interventions in rheumatology: a report from the OMERACT-Adherence group

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405. I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Addressing challenges in developing a core domain set in adherence interventions in rheumatology: a report from the OMERACT-Adherence group.

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Endorsed

Kathleen Tymms	18/11/20	**Diana Perriman**	19/11/20
Primary supervisor	Date	Delegated authority	Date

7.1 Abstract

Objective: The OMERACT-Adherence meeting was convened to discuss the conceptual and methodological challenges in developing a Core Domain Set (Adherence-CDS) for trials of interventions for medication adherence in rheumatology.

Methods: Forty participants from nine countries participated.

Results: Four ideas emerged: An Adherence-CDS could add adherence to the inner circle of a condition-specific CDS; some adherence related factors are targets of interventions or explanatory variables for adherence; adherence is a critical factor in drug trials; and standardised adherence measures are needed.

Conclusion: Despite the challenges, the meeting clarified an approach to developing an Adherence-CDS which complements existing OMERACT work and methodology.

7.2 Introduction

Medication adherence is suboptimal in rheumatic diseases and has been reported to be as low as 10% in gout, 30% in rheumatoid arthritis (74, 87). Broadly, adherence is defined as “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”(34). The Outcome Measures in Rheumatology Adherence Special Interest Group (OMERACT-Adherence Group) is currently developing a Core Domain Set for trials of interventions to improve medication adherence in Rheumatology (Adherence-CDS). Our group includes patients, health professionals and other stakeholders in a project consisting of a systematic review, qualitative studies, a Delphi survey and a consensus workshop (102).

There are a number of trials of adherence interventions in Rheumatology (93). However, no group has examined what outcome domains should be measured in these trials, and those used currently are inconsistent and heterogenous (367). Historically, most CDS in OMERACT have been established for specific conditions. Developing a CDS that is focused on the intervention type rather than a specific condition requires careful thought. In addition, the work of this group is challenging due to the complexity of adherence. There are hundreds of determinants of non-adherence, and reviews of adherence interventions have shown that multifaceted, behavioral interventions are needed to address adherence and produce a substantial change (75, 86).

Developing a CDS for complex behavioural interventions that address adherence in rheumatic conditions does not easily fit with the existing OMERACT Filter. (76, 368) This report summarises discussions during the OMERACT-Adherence Group meeting at OMERACT 2018, Australia to:

1) understand how an Adherence-CDS can be developed alongside existing condition-specific CDS,

2) review the candidate adherence-related domains from the work to date, and

3) modify the existing working plan.

7.3 Methods

OMERACT-Adherence pre-meeting reading materials

Prior to the meeting, participants were provided with the OMERACT-Adherence protocol paper (102), the European society of patient adherence, compliance and persistence medication adherence reporting guidelines (EMERGE) (369) and the proposed meeting agenda.

Meeting presentations

The meeting commenced with presentations on the definition of medication adherence (including phases; initiation - when the patient takes the first dose of medication; implementation – extent to which a patient's actual dosing corresponds to the prescription; and persistence - length of time between initiation and last dose) (35), research plan (102), and preliminary results of the systematic review and focus group studies. These studies will be reported separately, however preliminary findings are provided below for background to the meeting discussion.

The systematic review examined adherence-related domains in existing randomised and non-randomised trials of interventions to improve medication adherence in rheumatic conditions. Extracted domains included adherence and adherence-related domains (any domain related to adherence behaviour). To date, the most common domains included medication adherence, concerns, knowledge, beliefs and necessity. Preliminary findings from a nominal group technique study of patients and caregivers with rheumatoid arthritis, gout and osteoporosis indicated that trust in doctor, medication effectiveness, medication side effects, doctor's knowledge and disease knowledge were important factors influencing medication adherence. Australian Capital Territory Health Human Research Ethics Committee (ETHLR.15.137) provided ethical approval and all participants provided written informed consent to publish the results of this study.

Meeting discussion

Attendees were provided with an exercise sheet (Figure 7.1) and a list of preliminary adherence-related domains. Smaller group discussions facilitated by OMERACT-Adherence co-chairs and group members (AK/SJB/MDW/TD/VE/MG/GH/MSV/KT) preceded a larger group discussion facilitated by AK, summarising participants' perspectives and suggestions on a flip chart. OMERACT-Adherence Group member attendees contributed to this report.

7.4 Results

Forty participants including patients, health professionals, researchers, industry and regulators from nine countries contributed to four main themes:

An Adherence-CDS could complement existing OMERACT work and methodology

Meeting attendees discussed the Adherence-CDS using the PICOC framework (Patient/Intervention/Comparator/Outcome/Context) (Figure 7.2). They suggested adding adherence as a domain to the condition-specific CDS. Although adherence was perceived as a domain itself, it was also considered an explanatory variable, process measure or biomarker for the condition-specific CDS. One participant suggested that subdomains of adherence could address the phases of initiation, implementation and persistence. Participants noted that there may be inadequate power or duration of follow-up to demonstrate changes in disease outcomes even if adherence is improved. For example, use of a comparator group also taking anti-rheumatic medications may reduce the magnitude of clinical benefit. There was considerable dissensus about whether adherence versus clinical outcomes should serve as the primary outcome. It was suggested that trials aiming to improve adherence in the real-world setting should only be conducted on medications with established efficacy, and should be specified in the "Context" of the PICOC framework for the Adherence-CDS.

Adherence is important in drug trials

Drug trials (e.g. placebo-controlled trial for an osteoporosis medication) are different to adherence trials (e.g. randomised trial of intensive pharmacist support to address non-adherence). The OMERACT-Adherence Group is currently developing a CDS for adherence trials. Attendees discussed that in drug trials, adherence is an important contextual factor affecting the interpretation of clinical benefit and safety, although this is currently out of the scope of the OMERACT-Adherence work. There was agreement that the reasons for non-adherence in drug trials may differ to adherence trials and therefore different studies would be required to explore this topic. Some attendees thought that non-adherence was not an issue in drug trials, although there is existing evidence to the contrary (370).

Standardised adherence measures are needed in all trials

Participants recognised the need to standardise adherence measures in both adherence and drug trials. There was agreement that in trials, objective measures of adherence are essential, given the well-recognised bias associated with self-reports. Several individuals noted the potential role for measuring serum drug levels and use of technology such as micro biosensors integrated into pills. The OMERACT-Adherence Group plans to develop a core outcome measurement set after the CDS is established. However, a few participants proposed moving directly to standardising adherence measures as they felt the OMERACT Filter was difficult to apply to an adherence trial.

Factors from the systematic review and focus groups should be classified as targets of interventions, explanatory variables or outcome domains

Participants noted that some adherence-related domains identified from the systematic review and focus groups were more accurately classified as targets of interventions or explanatory variables/contextual factors/process measures that influence adherence (e.g. medication knowledge). They provide insight into how adherence interventions can be conceptualised and designed, or could be used to develop a tool to predict adherence, and were suggested to be termed “adherence-related factors”.

7.5 Discussion

Forming consensus on what to measure in complex behavioural interventions that address medication adherence across rheumatic conditions is challenging and the direct application of OMERACT Filter 2.1 (76, 368) is not straight forward. The suggestion to add adherence to the inner circle of a condition-specific CDS (as being mandatory in an adherence trial) offers a potential solution. Adherence-related factors must be clearly classified as targets of interventions or explanatory variables for adherence, though some may be candidate outcome domains. Adherence as a contextual factor of drug trials, and consensus on standardised adherence measures are important and require further investigation.

Participants who found it difficult to apply the OMERACT Filter to an adherence trial did not see the value in reaching consensus on outcome domains and suggested proceeding immediately to standardisation of adherence measures. However, similar to condition-specific CDS, an Adherence-CDS can reduce inconsistent reporting, reporting bias, and promotes measurement of outcomes that matter to patients (10).

Clinical outcomes represented by the condition-specific CDS are infrequently reported domains of adherence trials, but are examples of outcomes that matter to patients and were highly valued in our focus groups. The importance of measuring medication side effects was demonstrated in a cohort study of kidney transplant recipients who had increased risk of malignancy with higher medication adherence (371). Including the condition-specific CDS as mandatory to measure in all adherence trials could provide valuable information and progress in adherence research. Although discussions highlighted the difficulties of using the condition-specific CDS in adherence trials, limitations in power and duration of follow up can also apply to drug trials for some clinical outcomes such as mortality.

Future steps need to address the interdependence of the condition-specific CDS with the Adherence-CDS and whether clinical outcomes are important and feasible to measure in all adherence trials. These activities have been prioritised to move forward. We will update the systematic review and assess whether existing adherence trials also include the condition-specific CDS, including reporting of medication side effects. Domains extracted from the systematic review and focus groups will be termed “adherence-related factors”, with further work to scrutinise what will be candidate

domains for the Adherence-CDS. We plan to reconcile the dissensus regarding the primary outcomes in adherence trials (improved adherence versus clinical benefit).

Adherence is important in the clinical setting not only to patients and clinicians, but also to regulators and payers to ensure that patients maximise the potential health benefits from medications. As an increasing number of interventions are conducted to improve adherence in Rheumatology, these need to measure relevant and consistent outcome domains.

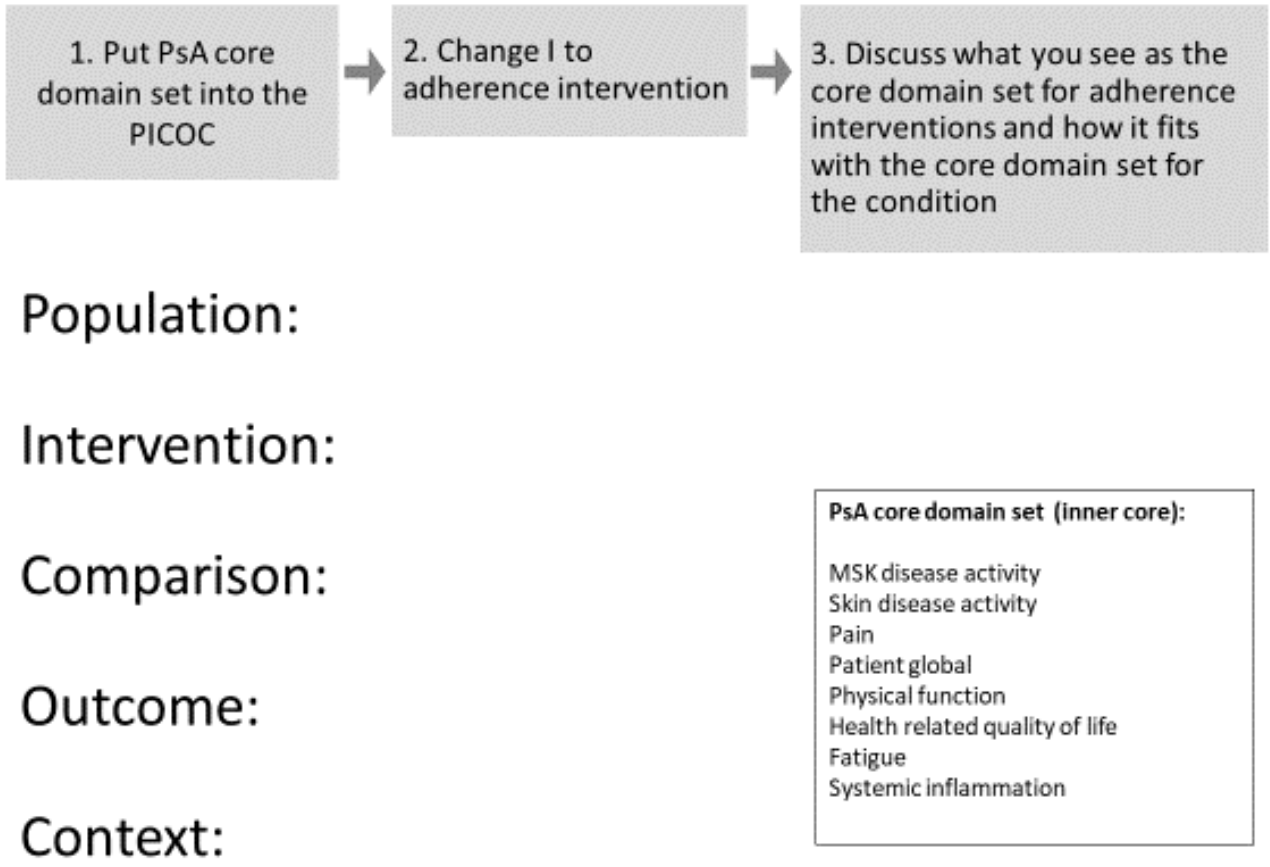

Figure 7.1. Exercise sheet for OMERACT-Adherence meeting discussion

PsA, Psoriatic arthritis; MSK, Musculoskeletal

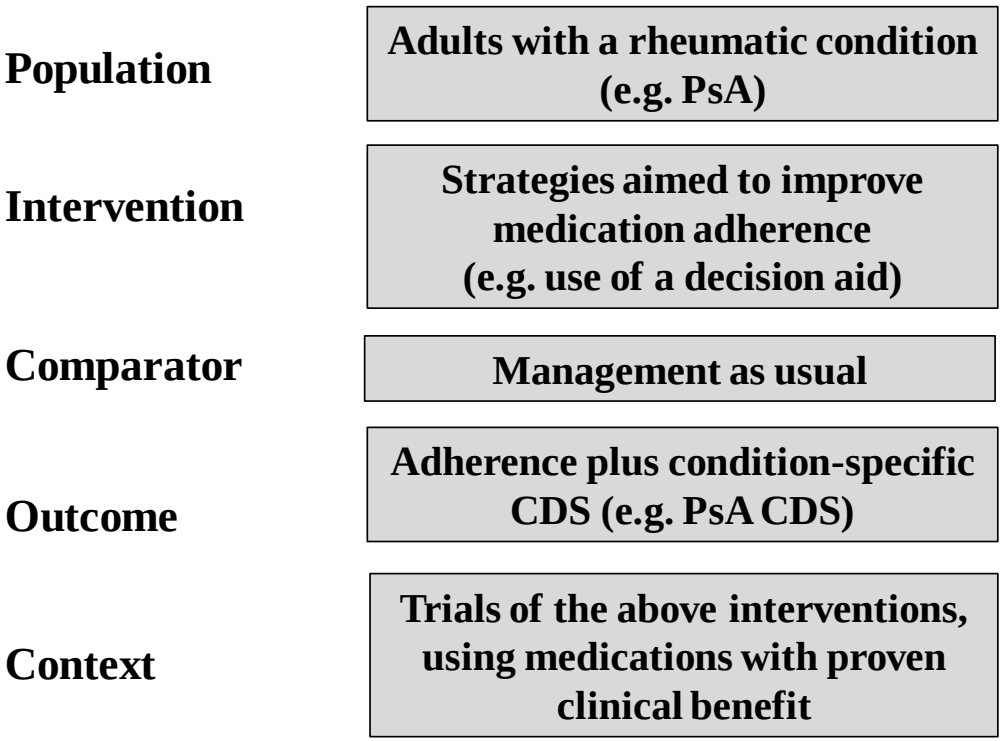

Figure 7.2. Proposed OMERACT-Adherence core domain set

PsA, Psoriatic arthritis; CDS, Core Domain Set

Table 7.1. Key recommendations from the OMERACT-Adherence workshop

Key recommendations
1. Adherence in the clinical setting is important to all stakeholders, and better ways to measure the efficacy of trials of adherence interventions are needed 2. There is value in determining the outcome domains to be measured in adherence trials prior to standardising adherence measures 3. The key outcome domains that may be in the core domain set for adherence trials are adherence in addition to the core domain set for the condition 4. Using the condition-specific core domain set for adherence trials is difficult due to lack of power, duration of follow up, participant burden and the comparator group used 5. Our systematic review will evaluate the use of condition-specific core domains including medication toxicity/side effects in adherence trials 6. We will determine which adherence-related factors are outcome domains versus targets of interventions or explanatory variables for improving adherence 7. Adherence in drug trials and adherence measures are important independent areas of study

Appendix A: Supporting data for Chapter 1

A.1 OMERACT-Adherence 5 phase study protocol

Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405. I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Outcome measures in rheumatology - interventions for medication adherence (OMERACT-Adherence) core domain set for trials of interventions for medication adherence in rheumatology: 5 phase study protocol.

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Senior author or collaborating author's endorsement: Kathleen Tymms

Ayano Kelly Candidate	18/11/20 Date

Endorsed

Kathleen Tymms Primary supervisor	18/11/20 Date	**Diana Perriman** Delegated authority	19/11/20 Date

Abstract

Background: Over the last 20 years, rheumatic conditions such as gout, osteoporosis and rheumatoid arthritis (RA) have seen marked improvement in the availability of effective medications, which have led to reduction in disease flares, risk of re-fracture in osteoporosis and slowing of disease progression in RA. However, medication adherence remains suboptimal as treatment regimens can be complex and difficult to continue long-term. Many trials have been conducted to improve adherence to medication; 'core domains', which are the outcomes of most relevance to patients and clinicians, are a pivotal component of any trial. These 'core domains' should be measured by consistent measurements so all relevant trials can be combined in systematic reviews and meta-analyses to reach more valid conclusions. Failure to do this severely limits the potential for trial-based evidence to inform decisions on how to support medication adherence. The Outcome Measures in Rheumatology (OMERACT) – Interventions for Medication Adherence study by the OMERACT-Adherence Group aims to develop a core domain set for interventions aimed to support medication adherence in rheumatology.\

Methods: This OMERACT-Adherence study involves five phases: 1) a systematic review to identify outcome domains that have been reported in interventions focused on supporting medication adherence in rheumatology; 2) semi-structured stakeholder interviews with patients and caregivers to determine their views on core domains; 3) focus groups using Nominal Group Technique (NGT) with patients and caregivers to identify and rank domains that are relevant to them, including the reasons for their choices; 4) an international three-round modified Delphi survey involving patients with diverse rheumatic conditions, caregivers, health professionals, researchers and other stakeholders to develop a preliminary core domain set; and 5) a stakeholder workshop with OMERACT members to review, vote and reach consensus on the core domain set for interventions to support medication adherence in rheumatology

Discussion: Establishing a core domain set to be reported in all intervention studies undertaken to support patients with medication adherence will enhance the relevance and the impact of these results to improve the lives of people with rheumatic conditions.

Background

Musculoskeletal conditions are a major cause of disability worldwide and a burden on individuals and health care systems. (386) Advances in drug development have led to a dramatic improvement in outcomes for patients with rheumatic conditions throughout the 21st century. (387, 388) Conditions such as gout, osteoporosis and rheumatoid arthritis (RA) are amongst the most common rheumatic conditions that require long-term use of medications to improve morbidity, mortality and other health outcomes. (351-353, 389) However, rates of medication adherence have been reported to be as low as 10% in gout, 30% in RA and 45% in osteoporosis. (74, 87, 88) Barriers to medication adherence include perceptual barriers (e.g. concerns of side effects, uncertainty regarding efficacy of medications) and practical barriers (e.g. forgetfulness, inconvenience, cost). (145, 373, 390, 391)

Researchers most commonly support the use of the word “adherence” in preference to “compliance” or “concordance”.(35, 36) “Adherence” highlights the outcomes of a shared decision making approach where the patient and physician agree upon a treatment plan that the patient will follow (34). “Compliance” may portray a negative paternalistic relationship between the healthcare provider and the patient. (35) “Concordance” emphasises a balanced therapeutic alliance between the patient and the healthcare provider, (37) however, even when “concordance” is successful, patients may alter or decide not to take their medicine. (37) Thus, adherence remains the preferred term. While non-pharmacological management is an important aspect of many rheumatic conditions, adherence to non-pharmacological management is currently beyond the scope of this study.

The ABC taxonomy of adherence (35, 38) defines adherence as “the process by which patients take their medications as prescribed” and comprises: a) initiation (when the patient takes the first dose of a prescribed medication); b) implementation (the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose); and c) persistence (the length of time between initiation and the last dose, which immediately precedes discontinuation , *i.e.,* when the patient stops taking the prescribed medication). (35) The behaviour change wheel will be used to categorise intervention approaches relevant to improving adherence behaviours (Appendix 1 available online). (38) In the OMERACT-Adherence study, interventions may focus on any adherence phase (initiation, implementation, or persistence), source of medication adherence behaviour (capability, opportunity or motivations) and method

(education, persuasion, incentivisation, coercion, training, restriction, environmental restructuring, modelling and enablement) (Fig 1, available online).

Adherence research plays an important role in bridging the chasm between recommended and best practice approaches to disease management to improve medication adherence. Clinical trials have been conducted in people with rheumatic conditions to resolve ambivalence and improve medication acceptance, adherence and thereby enhance health outcomes. (93) Yet few interventions have demonstrated meaningful improvements in either medication adherence or clinical outcomes across medical specialties. (75, 93) A limitation in collating results of these trials to better identify successful interventions is the lack of clarity of core outcomes and wide variability in adherence measures. There is need for a consensus-based core domain set for interventions to improve medication adherence.

Worldwide, there are many initiatives to develop core domain sets, (77, 78) defined as the minimum set of outcome domains that should be measured and reported in clinical trials for a specific condition. The Outcome Measures in Rheumatology (OMERACT) initiative commenced in 1992 and has expanded to develop core domain sets in multiple rheumatic conditions. (76). There are now over 20 groups developing core domain sets for specific conditions (77, 392) and several methodological groups examining core domains of interventions and measurements of outcomes that are relevant across rheumatic conditions, including health literacy, shared decision-making, and work productivity. (79-81)

The OMERACT-Adherence Group aims to establish a core domain set for clinical trials to support medication adherence in patients with rheumatic conditions of all ages (Fig 2, available online). The OMERACT-Adherence group was established in December 2016, and is comprised of over 40 members from 11 countries including Australia, Canada, Germany, Greece, the Netherlands, Singapore, the United Kingdom, Oman, Switzerland, Denmark and the United States. The members include patients, rheumatologists, nurses, pharmacists, behavioural scientists, occupational therapists, industry representatives, researchers in outcomes and medication adherence and clinical trialists. The patient perspective is highly valued and integrated into all OMERACT activities, as the ultimate aim is to improve clinical outcomes for patients. (393) Patient research partners (PRPs) are members of the steering committee of the OMERACT-Adherence Group and will help with the design, conduct, analysis, and dissemination of all studies.

The five specific objectives of this OMERACT-Adherence study are to: 1) conduct a systematic literature review to describe the scope and consistency of domains used in rheumatology interventions addressing medication adherence; 2) identify additional domains that are important to patients and their caregivers and elucidate the reasons for their choices; 3) ascertain the perspectives of other stake holders including health professionals, researchers, purchasers, payers, policy makers and industry representatives on core domains; 4) develop a preliminary core domain set for clinical trials with input from all stakeholder groups; and 5) seek consensus on the OMERACT-Adherence core domain set by a vote from OMERACT members.

Methods/Design

The OMERACT-Adherence study methodology is adapted from OMERACT framework which is recognised as a valid approach for establishing a core domain set. (77) The protocol includes a SPIRIT checklist for recommended items to address in clinical trial protocol and related documents (Appendix 2, available online). The proposed scope of work to achieve the five OMERACT-Adherence study objectives is outlined below (Fig 3, available online):

Phase 1: Systematic review of outcome domains and measures reported in trials of medication adherence

A systematic review will be conducted to identify and compare outcome domains and measures reported in interventions to improve medication adherence in rheumatology clinical trials. Outcome domains are the name of the broad concept that is measured (e.g. adherence, medication knowledge, medication skill). An outcome is the specific result in a domain arising from exposure to a causal factor or a health intervention (e.g. disease-modifying anti-rheumatic drug knowledge in RA, self-injection skill). An outcome measure includes the specific measurement instrument (the tool to measure a quality or quantity of a variable, e.g. pill count), specific metric (e.g. a change from baseline) and method of aggregation (e.g. mean or median for continuous, or proportion for categorical measures). (394, 395)

Search strategy

Electronic databases (MEDLINE, Embase, PsycINFO, CINAHL, and CENTRAL) will be searched to 31st October 2017 to identify all trials of interventions aiming to improve medication adherence involving patients with rheumatic conditions. The search will use Medical Subject Headings for concepts including 'patient compliance', 'medication adherence', 'intervention', 'inflammatory arthritis', 'rheumatoid arthritis', 'psoriatic arthritis', 'ankylosing spondylitis', 'juvenile idiopathic arthritis', 'connective tissue diseases', 'systemic lupus erythematosus', 'vasculitis', 'Sjogren's syndrome', 'osteoporosis' and 'gout' and keywords for concepts that do not match. The bibliographies of included articles will be hand-searched.

Types of studies and interventions

All publications studying interventions aiming to improve medication adherence in rheumatic conditions will be included. Given the limited number of randomised controlled trials (RCTs) for medication adherence in rheumatic conditions, (93) non-controlled and single arm interventions for medication adherence in rheumatic conditions will be included.

Types of participants

Studies involving participants of all ages with any rheumatic condition including inflammatory arthritis, connective tissue diseases and osteoporosis will be included.

Exclusion criteria

Conference reports and abstracts will be excluded given their space constraints. For feasibility, the search will be restricted to English language articles.

Eligibility of studies

Two reviewers will independently screen all abstract and full text of potentially relevant studies. Any uncertainties on the eligibility of studies to be included will be resolved through a third reviewer.

Data extraction

Data will be extracted and entered into Microsoft Excel using a pre-designed form, piloted before full data extraction with a sample of included studies. The primary reviewer will extract the following from all included interventions: First author, date of publication, countries in which the trial was conducted, sample size, participant characteristics (age/gender/condition/medication) and trial duration. In addition, the type of intervention and all adherence related outcomes reported in the trial will be extracted. Adherence related outcomes include adherence, and any other outcomes related to adherence behaviour (including capability, opportunity and motivation). (38) For each outcome, the definitions, outcome measures used, time points, metric and method of aggregation will be extracted. Clinical outcomes for specific conditions will not be extracted as this work is already being undertaken by other OMERACT groups. (76) Clinical outcomes are defined as any outcome that would fall under the four core areas in the OMERACT filter of death, life impact, resource use and pathophysiological manifestations for the specific condition and also includes adverse events. (76)

Data analysis and presentation

Two reviewers will group similar outcomes into outcome domains which will be reviewed and modified by the OMERACT-Adherence steering committee. The frequency of each domain and outcome measure reported across trials will be calculated. Domains and measures will be compared with those identified in the 2014 Cochrane Systematic Review of RCTs to enhance medication adherence which includes 182 RCTs across other specialties. (367)

Phase 2: Stakeholder interviews

Semi-structured interviews will be conducted with patients and caregivers to ascertain individual perspectives on outcome domains. The interview guide will incorporate findings from phase 1 and help gain greater understanding for the values and beliefs that underlie candidate domains. Additional outcome domains will also be identified in this phase. We will follow the consolidated criteria for reporting qualitative research (COREQ) to guide our methods and reporting. (100).

Participants and recruitment

Adults with gout, osteoporosis or RA and their caregivers (defined by the patient as a significant person or family member who is aware of the patient's illness and treatments) will be eligible to participate in an interview. Three conditions have been chosen for the phase 2 interviews and phase 3 focus groups for feasibility and represent common rheumatic conditions with known poor levels of adherence. (74, 87, 88) Patients with diverse rheumatic conditions will be included in phases 1, 4 and 5 to ensure the core domain set is applicable to all rheumatic conditions. Participants will be identified by treating rheumatologists at participating centres in Australia - Liverpool Hospital (NSW), Canberra Rheumatology (ACT/NSW), BJC Health (NSW), Royal North Shore Hospital (NSW). Although this phase includes participants from one country only, all other phases will include participants from different countries. A purposive sampling technique will be applied to include a broad range of demographic (age, gender, socioeconomic status, educational level, ethnicity) and clinical characteristics (type, duration and severity of condition). Although this phase includes participants from one country only, all other phases will include participants from other countries.

Based on our experience with previous qualitative interview studies, target recruitment will be approximately 30 participants. However, final numbers will be determined by data saturation, defined as the point at which no new concepts or outcome domains are being identified. To achieve adequate participant enrolment at each site, additional recruiting clinicians will be contacted if needed. Written informed consent will be obtained from all participants.

Data collection

The interviews will be conducted face-to-face as first preference or by Skype/Facetime or telephone interviews if preferred by the participant. Each interview will take approximately 40 minutes and will be audio-recorded and transcribed verbatim. A preliminary interview guide is provided (Appendix 3, available online).

Data analysis

Transcripts will be available for participants to review and revise. A summary of the interview findings will be sent to participants for member checking. The transcripts will be imported into HyperRESEARCH (ResearchWare Inc. www.researchware.com, version 3.7.5) software for qualitative data analysis. Two experienced qualitative investigators will supervise the coding and development of descriptive and analytical themes. Using inductive thematic analysis, the findings from the study will be grounded in the participant data. (396) The transcripts will be coded line by line to identify concepts. Similar concepts will be grouped into themes that reflect different outcome domains with the reasons for identifying them. The analysis will be iterative, repetitively moving between the transcripts, analysis and subsequent interviews. The preliminary results will be reviewed and modified by the OMERACT-Adherence steering committee. Conceptual links amongst themes and subthemes will be identified to develop an analytical thematic schema.

Phase 3: Focus groups with modified nominal group technique with patients and caregivers

Patients and their caregivers will be asked to identify outcome domains they regard as important and relevant to measure in trials to support medication adherence, and to discuss the reasons for their choices. A modified Nominal Group Technique (NGT) will be used to systematically generate a prioritised set of ideas in a group and encourages participation of each member. (101, 397) The outcome domains from phase 1 and 2 will be incorporated for discussion and ranking in nominal groups. Additional outcome domains will also be identified in this phase. This study uses both quantitative and

qualitative data and has been used successfully in the development of other OMERACT core domain sets. (398, 399).

Participants and recruitment

At least 12 focus groups (with a minimum of 5 participants per group) will be convened. Adults aged 18 years and over with gout, osteoporosis and RA and caregivers will be invited to participate. The recruitment sites, and purposive sampling technique are outlined in phase 2. In addition, focus groups will take place in the Netherlands (through Sint Maartenskliniek). Participants who participate in focus groups will be different to those in individual interviews. The groups will be convened until data saturation. The focus groups will be convened by condition at each site. To achieve adequate participant enrolment at each site, additional recruiting clinicians will be contacted if needed. Written informed consent will be obtained from all participants.

Data collection

The focus groups will be up to 2 hours in duration. An experienced facilitator with training in NGT who is not involved in the patient's care will moderate the groups to encourage open discussion. The questions will be described in an interview guide and discussed among the steering committee. (395) All focus groups will be audio taped and transcribed verbatim, de-identified transcripts will be available for participants to review and revise. A note-taker will record notes on the interaction among the participants. The preliminary content for the focus group run sheet is provided (Appendix 4, available online).

Data analysis

Quantitative analysis: An importance score will be calculated for each outcome domain, based on the rankings attributed in the focus groups to give an overall ranking of all outcome domains identified. The distribution of the ranking for each outcome domain is calculated from the probability of each rank for each outcome domain. The probability has two components: 1) the importance given to the outcome domain by the ranking and

2) the consistency of being nominated by the participants. Higher values of the score identify outcome domains that are more valued by the participants. These probabilities will be used to compute the weighted sum of the inverted ranking $1-i$ to obtain the importance score (IS)

$$IS = \sum_{i=1}^{nr\ of\ outcomes} P\ Oj\ in\ rank\ i \times 1-i$$

The importance scores will also be calculated separately for each condition, as well as for patients and caregivers and compared using a *t*-test with a statistical significance level of $p<0.05$. Participants who have not ranked at least 10 outcome domains will be excluded from this analysis. The analysis will be conducted using statistical software Stata/SE (StataCorp. College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria).

Qualitative analysis: Transcripts will be imported into HyperRESEARCH (ResearchWare Inc. www.researchware.com, software for qualitative data analysis. Using thematic analysis, the transcripts will be coded line by line by an investigator experienced in qualitative research to identify concepts. Similar concepts will be grouped into themes that reflect the reasons for identifying and ranking the outcome domains. These themes will be discussed amongst the OMERACT-Adherence steering committee.

Phase 4: Modified Delphi consensus survey

An international online OMERACT-Adherence survey will incorporate all domains identified in phases 1-3 and generate consensus on up to seven core domains, as well as other domains that may fit under “optional” or “research” domains. Delphi surveys have been used to gain consensus on core domain sets in a range of health conditions. (400-403) The online survey will involve three rounds completed by participants with knowledge, experience or expertise on the topic.

Participants and recruitment

Although Delphi surveys used to develop core domain sets for trials in OMERACT have involved up to 250 participants. (402-404), there is no agreement on the sample size required for a Delphi survey. (405, 406) To achieve a minimum sample size of 200 respondents at the end of the Delphi survey, by assuming 20% attrition for each round, the initial target sample size will be 390. Participant retention in Delphi rounds will be encouraged with at least 2 reminder emails. This will include patients and caregivers (minimum n=200), rheumatologists (minimum n=63), pharmacists/nurses/allied health professionals/general practitioners (minimum n=63), outcomes researchers/adherence researchers/clinical trialists, representatives from the pharmaceutical industry and policy makers (minimum n=63).

To achieve adequate participant enrolment, participants will be identified from the networks of the OMERACT-Adherence group. Following this, a snowball sampling technique will be utilised for recruitment, whereby key informants will be identified for recruitment by existing participants to ensure that a broad range of participant characteristics (including countries, health care systems) and experiences are captured.

Data collection

Generating the list of outcome domains: The modified Delphi survey will include outcome domains identified in phases 1 to 3. The survey will include a plain language definition of each listed outcome domain. The survey will be reviewed by the OMERACT-Adherence group, and piloted with at least 3 patients, 3 clinicians and 3 other relevant stakeholders.

Survey administration: The surveys will be completed online using the survey platform Qualtrics (Qualtrics Provo, UT). Each participant will be given a unique identifier so that their responses from each round of the survey can be linked anonymously. A minimum of 3 reminders will be sent to participants during the Delphi rounds, with an aim to achieve a response rate of at least 70% across all 3 rounds of those who have agreed to participate.

Delphi Round 1

Participants will rate each outcome domain using a 9-point Likert scale. Ratings 1 to 3 are “not important”; 4 to 6 “important, but not a priority”; and 7 to 9 “very important and a priority”. “Unsure” will also be an option. Responses will be mandatory and participants will be encouraged to use the full range of scores. The sequence of outcome domains will be randomised to minimise ordering bias. Participants can provide comments for each outcome domain in a free text box and suggest new outcome domains. All new outcome domains that are suggested will be reviewed by the steering committee and discussed for inclusion in Round 2.

Any outcome domain where ≥ 70% in either patient/caregiver and other stakeholders rating the outcome domain to be very important and a research priority (scores 7-9), will be retained in Round 2 and reported back to participants. All items where ≥ 70% of the participants voted the item as not important (1-3) are excluded from the Delphi list. All the remaining items and new items will be sent back for re-scoring in round 2.

Delphi Round 2

Participants will be presented with a graph showing the distribution of scores for all retained domains for: (1) patients/caregivers, (2) other stakeholders, and (3) all participants. Comments from Round 1 by all other participants will also be provided. The participant’s own response from Round 1 will be highlighted. Participants will use the same Likert scale for re-scoring. Participants can provide comments for each outcome domain in a free text box.

Any outcome domain where ≥ 70% in either patient/caregiver and other stakeholders rating the outcome domain to be very important and a research priority (scores 7-9), will be retained in Round 3 and reported back to participants. All items where ≥ 70% of the participants voted the item as not important (1-3) are excluded from the Delphi list. All the remaining items will be sent back for re-scoring in Round 3.

Delphi Round 3

Participants will view the distribution of scores and comments for each domain from Round 2. Participants will see their own scores from Round 2 highlighted and re-score outcome domains. After the rating questions, participants will be asked to complete a best-worst scale survey. (407) In the best-worse survey, the group will be presented with up to six lists that will contain a subset of six of the outcome domains remaining in Round 3. Participants will be asked to choose the most important and least important outcome domains from each list. The best-worst scaling survey will quantify the relative importance of each of the Round 2 outcome domains.

Data analysis

The mean, median, and proportion of the ratings for each outcome domain from all three rounds will be calculated. The scores will be calculated separately for patients/caregivers and other stakeholders. Wilcoxon sign rank test or t-test will be used to compare the mean difference in rating scores between both stakeholder groups, with a significance value of $p<0.05$. The best-worst scale survey will calculate the relative importance score for each of the Round 2 outcome domains. Multinomial logistic regression models will be used to calculate a relative importance score for each outcome domain normalised to the range 0 (least important) to 10 (most important). Importance scores will be calculated separately for patients, caregivers and other stakeholders. The influence of demographic factors, such as age, gender and condition will be investigated. Participants who have not completed all 3 Delphi rounds will be excluded from the analysis.

Based on previous Delphi surveys used in outcomes research, a preliminary core domain set will be based on ≥ 70% of both patients/caregivers and other stakeholders rating the outcome domain critically important (rating 7-9). (404) For feasibility, up to seven critically important outcome domains (based on the means, medians and proportions of ratings and importance score) will be identified as the preliminary core domain set.

Phase 5: Consensus workshop

A consensus workshop will review results from phases 1 to 4 and discuss the potential core domain set. Strategies to develop outcome measures will also be discussed. The target will be at least 60 participants, with a minimum of 20 patients and caregivers. To achieve adequate participant enrolment, the stakeholder workshop is anticipated to occur during the 2020 OMERACT meeting. The Invitations will be extended to health professionals (rheumatologists, pharmacists, nurses and other allied health professionals), researchers, policy makers and pharmaceutical industry representatives with expertise in medication adherence in rheumatology. To facilitate implementation invitees will include: health professionals who have key roles in specialty professional organisations, guidelines, registries, journals, regulatory agencies and funding organisations. All parts of the workshop will be audio-recorded and transcribed.

Participants will be sent a copy of the results from phases 1 to 4 prior to the workshop and asked to consider the results to date, so that they are prepared to give informed and considered feedback. The preliminary agenda for the consensus workshop is presented below:

Part 1: Introduction The aims, method and the results from the OMERACT-Adherence phases 1 to 4, including the preliminary core domain set, proposed consensus definition and strategies to develop outcome measurements will be presented by the Chair of the OMERACT-Adherence group.

Part 2: Breakout groups Participants will be assigned to breakout groups with approximately 12 participants per group (each with a facilitator and co-facilitator chosen from the OMERACT-Adherence group). The groups will contain a mixture of stakeholders, including a minimum of two patients/caregivers to promote the exchange of different perspectives. A briefing session including a detailed run sheet with the question guide will be provided to train facilitators. The facilitators will moderate the group discussion and take notes to report back to the larger group, focusing on the candidate core domains and strategies to develop outcome measures.

Part 3: Plenary discussion The group will reconvene after the breakout group session. Each group will report back the results of their discussion to the wider group. Participants will be encouraged to provide feedback on the issues raised by other groups. The workshop chair will moderate the forum and summarise key points.

Finalisation of the core domain set

Final consensus voting will include voting on each proposed domain. Changes to domains (e.g. wording, definition) will be permitted during phase 5. All domains voted by ≥ 70% of participants will be included in the core domain set. In addition, attendees will vote on whether appropriate steps outlined in phases 1-4 were followed to obtain the core domain set and agreement on a proposed research agenda for core outcome measurement development. Following the workshop, all transcripts will be entered into HyperRESEARCH software (ResearchWare Inc. www.researchware.com, version 3.7.5). The data will be coded and analysed to identify participant perspectives on the potential core domain set, and suggestions and challenges for implementation. The key findings will be reviewed by the OMERACT-Adherence steering committee prior to submitting a finalised workshop report. Phases 1 to 5 of the OMERACT-Adherence process, including the workshop report on the core domain set, will be published in peer-reviewed journals.

Discussion

OMERACT-Adherence will use a validated and systematic approach to develop a consensus-based core domain set that OMERACT recommends to be reported in all clinical trials of interventions aimed to improve medication adherence in paediatric and adult rheumatic conditions. The OMERACT adherence core domain set may be considered for other contexts including other specialties, and other types of studies such as observational studies in which medication adherence is a key requirement to ensure optimal uptake of new medications. Once the OMERACT-Adherence core domain set has been ratified by OMERACT attendees, core outcome measurements for each of the core domains will be identified or developed as needed using the OMERACT filter to ensure that measures are truthful, discriminative and feasible.(368) Guidelines for

selecting outcome measurements for core domains that have been developed by the Core Outcome Measures in Effectiveness Trials (COMET) and Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) initiatives will also be used to guide this process. (78, 408)

In addition to publications and research presentations, to facilitate the dissemination and uptake of the OMERACT Adherence core domains set into clinical trials, national and international stakeholders will be consulted throughout the study phases and at an implementation workshop at the completion of the study. Ultimately, standardised use of a consensus-based set of high priority outcome domains will enable all stakeholders to make decisions about strategies to improve medication adherence.

Table 1. Schedule of study phases

	Study Period												
	2017	2018				2019				2020			Aim completion
	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	
Phase													
1													9/2018
2	X	X											3/2019
3			X	X									9/2019
4						X	X						3/2020
5											X		9/2020

N.B. Time line includes enrolment (X), data collection, analysis and manuscript preparation