3 November 2019

ISQOLS Best PhD Dissertation Award Review Committee
The International Society of Quality-of-Life Studies (ISQOLS)
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Gilbert, AZ 85299

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Dear ISQOLS Best PhD Dissertation Award Review Committee

I would like to nominate my student, Dr Yu Heng KWAN, who recently defended his PhD thesis entitled "Quality of Life of Patients with Spondyloarthritis". I am his primary supervisor in the Program in Health Services and Systems Research, Duke-NUS Medical School. He completed his defense successfully on 17 October 2019 at Duke-NUS Medical School.

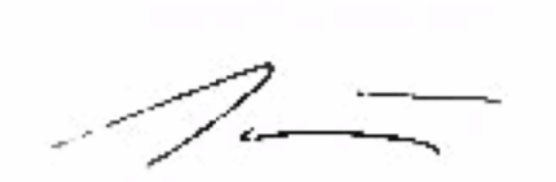
From his dissertation work, he published a total of 21 manuscripts, out of which 17 are first-authored. He also garnered grants totalling USD 1.7 million as co-investigator or principal investigator in this period. His PhD thesis aimed to understand and improve the quality of life of patients with spondyloarthritis, especially trying to understand the impact of the disease on the patients' life, validating patient-reported outcome measures to measure quality of life of patients with spondyloarthritis and developing a new model of care to treat patients with spondyloarthritis. His work has garnered international recognition and he was invited to be part of an international workgroup in the Assessment of Spondyloarthritis International Society to include quality of life as a core outcome measure in future research involving patients with spondyloarthritis.

A two-page summary of the significance of the dissertation research, an electronic copy of the full dissertation and a list of publications produced from this dissertation work are attached to this nomination letter.

I believe that Dr Kwan is well suited for this award and I give my full support in nominating him for the Best PhD Dissertation Award 2020. Please feel free to contact me if there are any questions at truls.ostbye@duke.edu.

Thank you very much.

Yours sincerely



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Nomination Information

Title and abstract of the dissertation:

Quality of Life of Patients with Spondyloarthritis

Maintaining and improving quality of life (QoL) is important in chronic disease management, especially in patients who are young as poor quality of life can inherently affect career trajectory and result in high disease burden on society. Patients with spondyloarthritis (SpA) experience pain and disability from their second decade of life and there are limited treatment options that can modify disease progression. The prevalence of SpA is around 1-2% and typically affect patients in the prime of their life. With this in mind, this thesis attempts to address the QoL of patients with SpA via four thematic approaches – exploring the impact of SpA on patients, validating QoL measures in SpA, exploring factors associated with QoL of patients with SpA, and proposing a novel collaborative care model with Traditional Chinese Medicine physicians to improve QoL of patients with SpA. Through this thesis, I hope that the QoL of patients with SpA can be improved and researchers will be able to utilize this approach as a foundation to improve QoL of patients with other chronic diseases.

Name of candidate: Yu Heng KWAN

Name of candidate's primary advisor: Professor Truls OSTBYE

Name of institution where the dissertation was defended: Duke-NUS Medical School, Singapore

Date of dissertation defence: 17 October 2019

Two pages summary of the significance of the dissertation work:

Dr Yu Heng KWAN is a MD-PhD candidate who recently successfully defended his thesis entitled, "Quality of Life of Patients with Spondyloarthritis", in the Program of Health Services and Systems Research in Duke-NUS Medical School. His defense was on 17 October 2019.

Throughout Dr Kwan had published 27 publications of direct relevance to his dissertation work. Out of the 27 publications, 21 of them are first-author publications and 4 of them are second-author publications. Dr Kwan also solicited grant of total 1.7million USD as principal and co-investigator. In particular to quality of life studies, he was awarded SGD26,800 as principal investigator to understand the quality of life domains and items relevant to patients with spondyloarthritis.

In terms of his thesis work, he first understands the impact of disease on quality of life through a systematic review and conducting focus group discussions to understand the impact of disease on quality of life in Singapore patients. Second, he proceeds to validate the Short-Form 36 and Health Assessment Questionnaire to assess the quality of life and function of patients with spondyloarthritis, Third, he assessed the association of having extra-spinal symptoms on quality of life in patients with spondyloarthritis. Last, he initiated and developed a proposal that create a new model of care by including traditional Chinese medicine as part of treatment in patients with spondyloarthritis in order to improve the quality of life. Currently, to manage patients with spondyloarthritis, it includes either pain killers or biologics. The treatment is largely symptomatic, and biologics cost around USD20,000, resulting in significant burden in our patients who are largely in their 20-30s whereby they do not earn much. Having an alternative choice like Traditional Chinese Medicine, will no doubt close the treatment gap and results in our patients having a direct improvement in their quality of life. Using this thematic approach of 4 parts (understanding the disease impact, validating patient-reported outcome measures, assessing factors associated with quality of life and developing interventions that improve quality of life), his work has resulted in direct impact in patients' quality of life and can be a potential model

for other interested researchers to adapt to understand and improve quality of life of patients with other chronic diseases.

His research work for quality of life in patients with spondyloarthritis had garnered international attention whereby he now participates on an international workgroup (Assessment of Spondyloarthritis International Society – Updating of the Core Set of Ankylosing Spondylitis) as an Asian representative. As of now, quality of life is a core outcome to be measured in all clinical trials involving patients with spondyloarthritis, therefore, directly translating to a direct impact on patients' life whereby quality of life is deemed important.

Other than that, during his PhD time, he had mentored at least 30 other like-minded students. This direct interaction with both undergraduate and postgraduate students resulted in publications and presentation opportunities and allow these students to further impact patients in their own way.

Therefore, I strongly support and nominate Dr Yu Heng KWAN for the Best PhD dissertation award on quality of life. His work had resulted in a better understanding of quality of life in patients with spondyloarthritis, and even better, resulted in a direct impact of the quality of life of patients with spondyloarthritis, which I believed is the main mission of the international society of quality- of-life studies.

A list of publications produced from the dissertation work:

1. **Kwan YH**, Uy EJ, Bautista DC, Xin X, Xiao Y, Lee GL, Subramaniam M, Vaingankar JA, Chan MF, Kumar N, Cheung YB, Chua TSJ, Thumboo J. Development and calibration of a novel positive mindset item bank to measure health-related quality of life (HRQoL) in Singapore. 2019. PLOS One. 14(7):e0220293
2. Xiang L, Teo EPS, Low AHL, Leung YY, Fong W, Xin X, Gandhi M, **Kwan YH**, Uy EJB, Hamilton L, Thumboo J. Cross-cultural adaptation of the Hamilton axial spondyloarthritis questionnaire and development of a Chinese version in a multi-ethnic Asian population. 2019. International Journal of Rheumatic Diseases. 22(9):1652-1660.
3. **Kwan YH*,** Aw FF*, Fong W*, Phang JK, Klitz U, Lim KK, Chew EH, Lui NL, Tan CS, Thumboo J, Ostbye T, Leung YY. Validity and reliability of the Assessment of Spondyloarthritis International Society Health Index in English-Speaking patients with axial spondyloarthritis in Singapore. 2019. International Journal of Rheumatic Diseases. 22(9):1644-1651. (*Co-first authors)
4. Lee YX*, **Kwan YH*,** Lim KK, Tan CS, Lui NL, Phang JK, Chew EH, Ostbye T, Thumboo J, Fong W. A systematic review of the association of obesity with the outcomes of inflammatory rheumatic diseases. 2019. Singapore Medical Journal. 60(6):270-280. (*Co-first authors)
5. Hong C, **Kwan YH**, Leung YY, Lui NL, Fong W. Comparison of ankylosing spondylitis and non-radiographic axial spondyloarthritis in a multi-ethnic Asian population in Singapore. 2019. International Journal of Rheumatic Diseases. 22(8):1506-1511.
6. **Kwan YH**, Uy EJ, Bautista DC, Xin X, Xiao Y, Lee GL, Subramaniam M, Vaingankar JA, Chan MF, Kumar N, Cheung YB, Chua TSJ, Thumboo J. Development and calibration of a novel social relationship item bank to measure health-related quality of life (HRQoL) in Singapore. 2019. Health and Quality of Life Outcomes. 17(1):82.
7. Xiang L, Teo EPS, Low AHL, Leung YY, Fong W, Xin X, Gandhi M, **Kwan YH**, Uy EJB, Sparks JA, Karlson EW, Thumboo J. Cross-cultural adaptation of the connective tissue disease screening questionnaire and development of a Chinese version in a multi-ethnic Asian population. 2019. Clinical Rheumatology. 38(9):2383-2397.
8. Wang CTM, **Kwan YH**, Fong W, Xiong SQ, Leung YY. Factors associated with patient-physician discordance in a prospective cohort of patients with psoriatic arthritis: An Asian perspective. 2019. International Journal of Rheumatic Disease. 22(7):1209-1215.
9. **Kwan YH**, Fong W, Leung YY, Lui NL, Tan CS, Malhotra R, Ostbye T, Thumboo J. Are extra-spinal symptoms associated with quality of life in patients with axial spondyloarthritis? A 1-year follow-up study. 2019. Clinical Rheumatology. 38(7):1881-1887.
10. **Kwan YH,** Fong W, Cheng GHL, Phang JK, Leung YY, Lui NL, Thumboo J, Ostbye T. The mediating role of pain and function in the association between stiffness and quality of life in patients with axial spondyloarthritis. 2019. Seminars in Arthritis and Rheumatism. (Epub ahead of print)
11. Choo HMC*, Cher WQ*, **Kwan YH**, Fong W. Risk factors for cytomegalovirus disease in systemic lupus erythematosus (SLE): a systematic review. 2019. Advances in Rheumatology. 59:12. (*Co-first authors)
12. **Kwan YH***, Fong W*, Ang XL*, Tan CS, Tai BC, Huang Y, Bilger M, Phang JK, Tan HC, Lee JV, Sun L, Tan CT, Dong BQ, Koh HL, Leung YY, Lui NL, Yeo SI, Ng SC, Fong KY, Thumboo J, Ostbye T. Traditional Chinese Medicine (TCM) colloborative model of care for patients with axial spondyloarthritis (AcuSpA): Protocol for a randomized controlled trial. 2019. Trials. 20(1):46. (*Co-first authors)
13. **Kwan YH*,** Ng A*, Lim KK*, Fong W, Phang JK, Chew EH, Lui NL, Tan CS, Thumboo J, Ostbye T, Leung YY. Validity and reliability of the ten-item Connor-Davidson Resilience Scale (CD-RISC10) instrument in patients with axial spondyloarthritis (axspa) in Singapore. 2018. Rheumatology International. 39(1):105-110. (*Co-first authors)

14. **Kwan YH**, Fong W, Leung YY, Tan VIC, Yap AF, Phang JK, Lui NL, Yoon SW, Malhotra R, Thumboo J, Ostbye T. A qualitative study of quality of life domains and subdomains relevant to patients with Spondyloarthritis. 2018. International Journal of Rheumatic Diseases. 22(2):242-251.
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19. Phang JK*, **Kwan YH*,** Goh H, Tan VIC., Thumboo J, Østbye T, Fong, W. Complementary and alternative medicine for rheumatic diseases: A systematic review of randomized controlled trials. Complementary Therapies in Medicine. 2018. 37: 143-157. (*Co-first authors)
20. Png K*, **Kwan YH*,** Leung YY, Phang JK, Lau JQ, Lim KK, Chew EH, Low LL, Tan CS, Thumboo J, Fong W, Ostbye T. Measurement properties of patient-reported outcomes for spondyloarthritis: A systematic review. 2018. Seminars in Arthritis and Rheumatism 48(2):274-282. (*Co-first authors)
21. Seng JJB*, **Kwan YH*,** Low LL, Thumboo J, Fong W. Role of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) in assessing disease control in Asian patients with axial spondyoarthritis. 2018. Biomarkers. 23(4):335-338. (* Co-first authors)
22. Goh H*, **Kwan YH***, Seah Y*, Low LL, Fong W, Thumboo, J. A systematic review of barriers affecting medication adherence in patients with rheumatic diseases. Rheumatology International. 2017. 37(10): 1619-1628. (*Co-first authors)
23. **Kwan YH**, Fong W, Tan VIC, Lui NL, R Malhotra, T Ostbye, J Thumboo. A systematic review of quality of life domains and items relevant to patients with Spondyloarthritis. Seminars in Arthritis and Rheumatism. 2017. 47(2):175-182.
24. **Kwan YH**, Chua CJ, JXL Kian, Fong W. The top 100 cited articles in the field of rheumatology. European Journal of Rheumatology. 2017. 4(4):294-304.
25. Lee XY*, **Kwan YH*,** Png WY, Lim KK, Tan CS, Lee NL, Chew EH, J Thumboo, T Ostbye, W Fong. Association of obesity with patient-reported outcomes in patients with axial spondyloarthritis: a cross-sectional study in an urban Asian population. Clinical Rheumatology. 2017. 36(10): 2365-2370. (*Co-first authors)
26. **Kwan YH**, Fong W, Yong ST, Lui NL, Cheung YB, R Malhotra, T J Thumboo, T Ostbye. Validity and reliability of the health assessment questionnaire among patients with spondyloarthritis. International Journal of Rheumatic Diseases. 2018. 21(3):699-704.
27. **Kwan YH**, Fong W, Yong ST, Lui NL, Cheung YB, R Malhotra, T Ostbye. J Thumboo. Validity and reliability of the Short Form 36 Health Surveys (SF-36) among patients with spondyloarthritis. Rheumatology International. 2016. 36(12):1759-1765.

QUALITY OF LIFE OF PATIENTS WITH SPONDYLOARTHRITIS

KWAN YU HENG
2019

ABSTRACT

Maintaining and improving quality of life (QoL) are important in chronic disease management, especially in patients who are young as poor quality of life can inherently affect career trajectory and result in high disease burden on society.(1, 2) Patients with spondyloarthritis (SpA) typically experience pain and disability from their second decade of life.(1)

This thesis addresses the QoL of patients with SpA via four thematic approaches – (1) Exploring the impact of SpA on patients, (2)Validating QoL measures in SpA, (3)Exploring factors associated with QoL of patients with SpA, and (4)Proposing a novel collaborative care model with Traditional Chinese Medicine physicians to improve QoL of patients with SpA. The publications around each theme are included in a table here.

No	Theme	Publications
1	Area of impact of QoL of disease	Kwan, Y. H et al (2017). A systematic review of quality-of-life domains and items relevant to patients with spondyloarthritis. *Semin Arthritis Rheum*, 47(2), 175-182 Kwan, Y. H., Fong, W., Leung, Y. Y., Tan, V. I. C., Yap, A. F., Lui, N. L., Phang, J.K., Yoon, S., Malhotra, R., Thumboo, J., & Ostbye, T. (2018). A qualitative study of Quality of Life domains and subdomains relevant to patients with Spondyloarthritis *International Journal of Rheumatic Diseases (Epub ahead of print)*.
2	Validation study of PROMs to measure QoL	Kwan, Y. H. et al (2016). Validity and reliability of the Short Form 36 Health Surveys (SF-36) among patients with spondyloarthritis in Singapore. *Rheumatol Int*, 36(12), 1759-1765. Kwan, Y. H. et al (2018). Validity and reliability of the Health Assessment Questionnaire among patients with spondyloarthritis in Singapore. *Int J Rheum Dis*, 21(3), 699-704.
3	Factors associated with QoL	*Kwan, Y. H. et al (2019). Are extra-spinal symptoms associated with poorer quality of life in patients with axial Spondyloarthritis? A 1-year follow up study. Clin Rheum. 38(7):1881-1887.*

4	Intervention to improve QoL	*Kwan, Y.H. et al (2018). Traditional Chinese Medicine (TCM) collaborative care in the management of patients with axial Spondyloarthritis (AcuSpA): Protocol for a pragmatic randomized controlled trial. Trials, 20:46*

First, I conducted a systematic review to summarize from the literature the QoL domains and items relevant to patients with SpA, and to determine if commonly used SpA patient-reported outcome measures (PROMs) include the identified QoL domains (Theme 1).(3) Results showed that SpA impacted a wide range of QoL domains. There were minimal differences in QoL domains between patients with axial and peripheral SpA. Clinicians may consider using peripheral SpA PROMs to measure QoL of patients with axial SpA.(3)

Second, from the systematic review, I found that there was a lack of evidence regarding QoL domains of patients with SpA from the Asian setting.(3) I therefore conducted a qualitative study to identify QoL domains and subdomains relevant to patients with different SpA subtypes in Singapore, and to assess how identified QoL domains and subdomains map onto currently used PROMs (Theme 1).(4) I found that patients with SpA in Singapore were more concerned about financial resources, work satisfaction and positive feelings, while being less concerned about freedom, physical safety and security than patients in western countries.(4) There were also minimal differences in QoL domains between SpA subtypes, giving further support to the development and validation of common QoL-specific PROMs for usage in SpA.(4)

Third, as there was support to create a common PROM to measure QoL or related constructs from our systematic review and qualitative study, I validated the Short Form-36 Health Surveys (SF-36) and Health Assessment Questionnaire (HAQ) to measure QoL and disability in patients with SpA in Singapore (Theme 2) .(5, 6) Results showed that both SF-36 and HAQ are valid and reliable PROMs to use in patients with SpA in Singapore.

Next, using the newly validated QoL PROMs from this thesis and the literature, I delved deeper to understand factors that were associated with QoL in a subgroup of patients

with SpA. I assessed whether presence of extra-spinal symptoms [i.e. a history of peripheral arthritis, enthesitis or dactylitis (HPED)] at baseline was associated with poorer QoL in patients with axial spondyloarthritis (axSpA) at baseline and one-year follow up (Theme 3). Results showed that HPED at baseline was associated with poorer QoL outcomes in patients with axSpA. After one year, HPED at baseline was associated with poorer QoL for domains of physical health and better QoL for domains of mental health.

Lastly, from the systematic review and qualitative study, pain was found to be an important QoL domain to patients with SpA. Back pain was the QoL item most relevant to patients with axSpA. I embarked on a trial aiming to incorporate a novel Traditional Chinese Medicine (TCM) care model (TCMCMC) in reducing pain for patients with axSpA (Theme 4). I am in the process of conducting a pragmatic trial to determine the clinical effectiveness, safety and cost-effectiveness of TCMCMC versus usual rheumatologic care for patients with AxSpA. Data is being collected currently and results are forthcoming on the efficacy of this potential treatment modality to improve QoL for patients with axSpA.

In conclusion, this thesis systematically addresses the improvement of QoL in SpA via four thematic approaches. This thesis shows the possibility to use a single set of PROMs to measure QoL in SpA and provides 2 validated PROMs to measure QoL and disability. This thesis also demonstrates the usage of validated PROMs to measure QoL in SpA and shows the impact of extra-spinal symptoms on QoL, which justifies early intervention by rheumatologists in order to reduce the disease impact on patients' lives. Last, this thesis details an interesting and relevant TCM care model to improve QoL of patients with axSpA.

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I would like to express my sincere gratitude to my wonderful mentors, Prof Truls Østbye, Prof Julian Thumboo and Dr Rahul Malhotra.

Thank you Prof Østbye for constantly teaching me the importance of writing clearly and concisely. The repetitive re-writing of manuscripts has improved my writing and made me confident in starting to write manuscripts on my own. Furthermore, despite being located in Durham, you are always the first to answer any questions I have. Thank you Prof Thumboo by instilling in me the passion to think of the patients in no matter what we do and constantly making our work meaningfully centered around them and lastly to always think of me with regards to any opportunities that can influence my career. Thank you, Dr Malhotra, for your constructive feedbacks and making me think more thoroughly with regards to methods and statistical analysis.

I would also like to thank my family, Hui Min, Mummy, Papa and Sis for constantly supporting me through this period. Thank you, Hui Min, for tolerating my constant working while at home. Thank you Mummy for always preparing food and making sure I am not hungry. Thank you, Papa, for fetching me to MRT and School when I need to and Thank you Sis for being there when I need it. I will also like to thank my two boys (Rui Yuan and Rui Zhi) for the constant fun and enjoyment of parenthood.

Also, I would like to thank the Graduate Office and my thesis advisory committee; A/Prof Silke Vogel, Prof David Matchar, Dr Marcel Bilger, Rosilah and Catherine for the constant support and advice with regards to the thesis.

Importantly, I would like to thank the Department of Rheumatology and Immunology in the Singapore General Hospital for their constant support for my work and confidence in my ideas, and allowing me to plan freely the resources and output for the Spondyloarthritis project. In particular, Dr Warren Fong, Dr Lui Nai Lee, Dr Andrea Low, Associate Professor Katy Leung, Phang Jie Kie, Lovynn Chan, ex coordinators of the Spondyloarthritis Team who have spent their effort and time in setting up the

database for my use in this thesis. Special mention to Associate Professor Ng Swee Cheng who personally tutored me on clinical skills in rheumatology.

Finally, I would like to thank my friends in the SingHealth RHS, HSSR, HSRC who have helped in one way and another to make this journey easier and more enjoyable. Lastly, I would like to thank Ka Keat, Ter Yong, Yihui, Geraldine, Shiyang and Yuheng for always being there for me to share my ideas, joys and tears during this PhD journey.

DEDICATION

Hui Min, Rui Yuan, Rui Zhi, Papa and Mummy

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Chapter 1: Introduction

Spondyloarthritis (SpA) is a chronic autoimmune disorder that predominately affects males in their productive years.(7) Till date, there are few, if any, disease modifying drugs for SpA; hence, maintaining and improving quality of life (QoL) is of paramount importance. This thesis will bring readers through important steps to improve QoL for patients with SpA – exploring the impact of SpA on areas of QoL, validating patient-reported outcome measures (PROMs) of SpA, quantitatively assessing factors that are associated with QoL of patients with SpA, and discussing a pragmatic trial of a novel care model which I have developed to improve QoL of patients with SpA.

1.1 Spondyloarthritis (SpA)

SpA is a chronic debilitating disease that has a prevalence of 0.9 to 1.4%.(7) The prevalence of SpA varies in the world with lower prevalence in countries around the equator. SpA affects predominately the young and the male gender.(8) SpA has a genetic association with HLA-B27; hence, researchers have hypothesized that SpA may likely have a genetic cause.(9) However, till date, the pathophysiology of SpA has yet to be clearly elucidated.(10)

SpA is a heterogeneous disease with various clinical manifestations.(11) SpA is divided into two main groups i.e. axial SpA (axSpA) and peripheral SpA (pSpA).(12) Patients with axial SpA have symptoms that largely manifest as inflammatory back pain while patients with peripheral SpA have symptoms that largely manifest as enthesitis (inflammation of the tendon that joins the bone), dactylitis (skin thickening of the finger) and peripheral arthritis.(12) Typical prototype diseases for axSpA and pSpA are ankylosing spondylitis (AS) and psoriatic arthritis (PsA) respectively.(12) AS is a disease described as the “bamboo spine disease” which is characterized by the stiffening of the spine, while PsA is a disease whereby the patient presents with both joint pain and psoriasis.(13) AxSpA and pSpA share common features such as HLA-B27 positivity, enthesitis, dactylitis, psoriasis, family history of SpA and inflammatory bowel disease.(12) Due to their complexity and heterogeneity, classification criteria were developed to guide clinicians and researchers in the field. Classification criteria were

developed by the Assessment of Spondyloarthritis International Society for axSpA and pSpA in 2009 and 2011 respectively.(12)

Management guidelines of SpA depend on whether clinicians classify patients as axSpA or pSpA.(12) As the classification criteria of SpA involved re-grouping of well established diseases such as AS and PsA under a wider umbrella, PROMs used to monitor disease activity, function and quality will also need to be streamlined to improve clinic logistics.(3) Currently, to monitor disease activity, clinician use PROMs pertaining to their prototype disease (i.e. AS or PsA); this may hence result in different PROMs being applied to patients with axSpA and pSpA and do not allow interpretation between subtypes.(14) Medications for axSpA are limited to non-steroidal anti-inflammatory drugs (NSAIDs) and biologics; for pSpA, disease modifying anti-rheumatic drugs (DMARDs) are available on top of NSAIDs and biologics.(15)

Therefore, as the classification criteria for SpA were only developed recently(16, 17), there remain significant research gaps, some of which I will address in this thesis.

1.2 QoL

QoL is defined by the World Health Organization as "the individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goal".(18) This means that, to improve patients' QoL, we need to define patients' treatment goals by having a thorough discussion of the patients' current ability and contextual needs. This abstract concept of QoL was further defined by a landmark paper by Cleary et al whereby QoL was represented by a model that includes the patient's symptoms, functions and environmental contextual factors.(19)

QoL is a latent construct which cannot be measured directly and needs to be measured indirectly using PROMs.(4) There are two types of PROMs being used currently – generic and disease specific.(14) Generic PROMs allow comparison of the same latent construct across different diseases, hence giving clinicians, administrators and researchers an opportunity to understand the disease better in the larger context

of other conditions, while disease-specific PROMs have greater sensitivity and are therefore the preferred option when planning intervention trials as they allow for reduced sample size, hence reducing overall cost.(20) One example of a generic PROM for QoL is the Short Form-36 Health Survey (SF-36) while one example of a specific PROM for QoL is the Ankylosing Spondylitis Quality of Life (ASQoL).(3, 14)

PROMs need to have good content validity and the cultural validity is greatly influenced by cultural context.(21) For example, previous studies by Thumboo et al have found that being able to kneel is very important in the Singapore context for patients with osteoarthritis as these patients need to perform various religious rituals.(22) These contextual situations can only be elicited through a qualitative study.(23) Qualitative studies complement quantitative studies as the former attempt to address exploratory questions while the latter is usually used to confirm relationships between factors.(24) Therefore, to understand QoL of patients, a qualitative study will be essential. This will allow us to understand the impacts of disease on patients and how PROMs are measuring them, therefore allowing suitable interventions to be started and patients' QoL to be improved.

1.3 Importance of Quality of Life in managing patients with Spondyloarthritis

There are a few reasons why improving QoL should be of paramount importance in managing patients with SpA.

First, there is currently no cure in patients with SpA. For axSpA, NSAIDs or biologics are used to relieve pain, restore functions, and hopefully, retard disease progression.(15) For pSpA, prescribing DMARDs is another option before patients are started on biologics.(15) Hence, ensuring that patients maintain their QoL and are able to continue their usual activities as far as possible is important.

Second, patients with SpA tend to be very young and of male predominance.(7) This means that the cumulative impact of SpA on the young patient over time compared to a chronic disease on the elderly patient will likely be greater.(25) Also, SpA strikes

very early in a patient's life, therefore leaving them likely to alter their career trajectory as their health may not be able to withstand the career that they had at the point of disease onset (i.e. military service).(2) The impact on the productive years of one's working life means that the impact to the society and economy is large as well.(25) Therefore, ensuring that patients maintain their QoL and ability to perform up to their potential will greatly impact the lives of patients with SpA and the society they belong to.(25)

Third, patients with SpA have comparable QoL to patients that are known to have significant QoL impairment.(26) A previous study done by Kwan et al showed that patients with axSpA generally have poorer SF-36 bodily pain (BP) scores and better general health (GH) scores when compared to patients with chronic kidney disease (CKD). Generally, as shown in Figure 1A and 1B, patients with axSpA have poorer QoL scores than patients with CKD pre-dialysis and similar QoL scores when compared to patients on dialysis.(26) CKD is a well-characterised disease and decision makers such as clinicians and policy makers understand the disease impact on patients' QoL.(27) Patients with AS and PsA have similar QoL.(28) Hence, by inference, the impact of disease on patients with SpA will be similar to that of axSpA. Due to the significant impairment of QoL of SpA on patients, there is an urgent need to study QoL in patients with SpA.(26)

Despite the importance of QoL in patients with axSpA, QoL is currently not included in the Assessment of Spondyloarthritis International Society (ASAS)-Outcomes in Rheumatology (OMERACT) as a core outcome for patients with axSpA.(12) This is because the research into QoL in patients with SpA was still in its infancy 20 years ago as there were limited PROMs to measure QoL in SpA.(14) However, QoL is included in the ASAS research agenda to be considered for addition in the next update of the ASAS-OMERACT core set.(18) Therefore, with improvement in the understanding of the disease and outcomes research, the QoL of patients with SpA can be better addressed and more evidence can be generated to support the inclusion of QoL as a core outcome in a future update of the ASAS-OMERACT core set.(29)

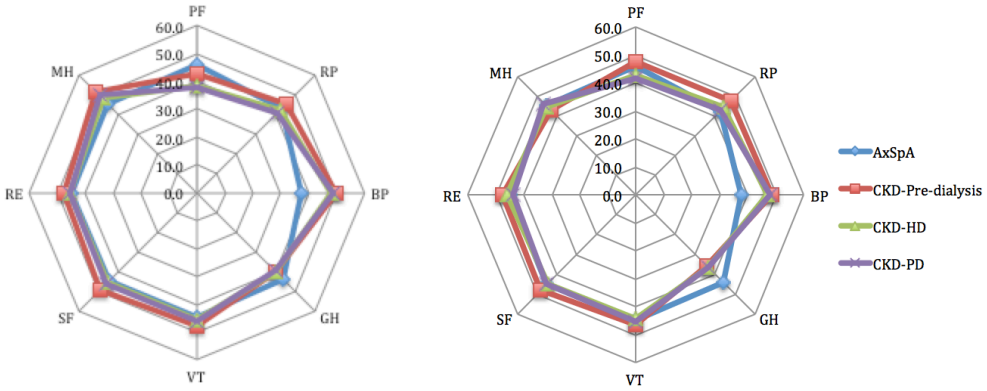

Figure 1A (Left). Spider chart of quality of life of patients with Axial Spondyloarthritis and Chronic Kidney Disease

Figure 1B (Right). Spider chart of quality of life of patients with Axial Spondyloarthritis and Chronic Kidney Disease adjusted for age, gender, ethnicity, education level, and marital status (plotted with the estimated marginal means)

Abbreviations: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), mental health (MH), chronic kidney disease (CKD), hemodialysis (HD), peritoneal dialysis (PD), axial spondyloarthritis (axSpA)

1.4 Gaps and research objectives

There is an urgent need to study QoL in patients with SpA.(26) As SpA remains a newly minted classification criterion, there are gaps to be answered in order to improve the QoL of patients with SpA.(16, 30) I summarized my research objectives in my thesis conceptual model in Figure 2.

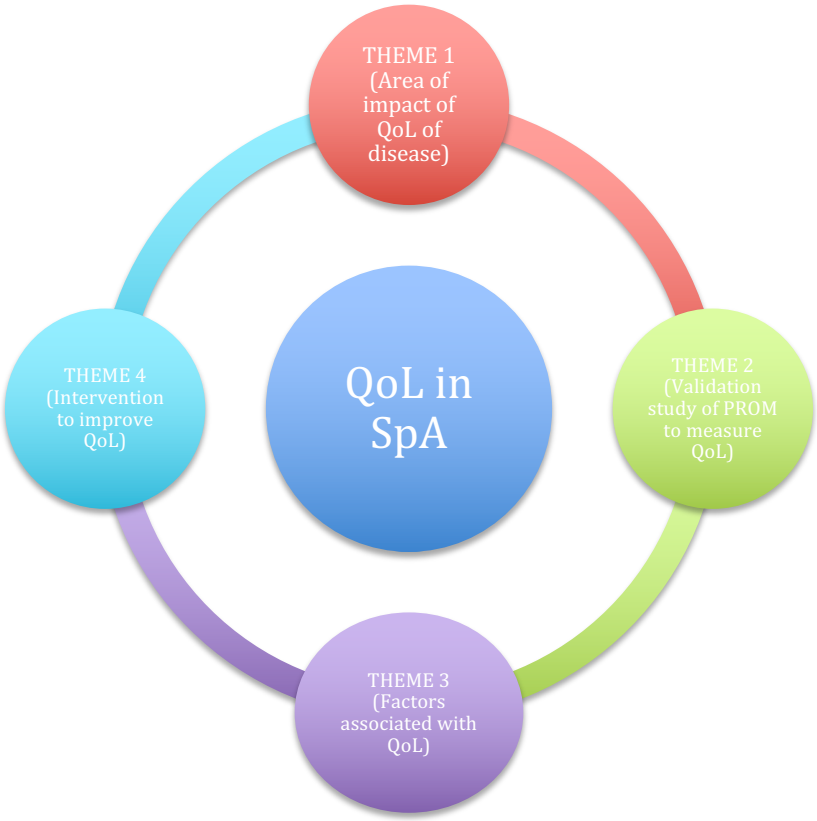

Figure 2. Thesis conceptual model of quality of life and spondyloarthritis

First, there are no studies that attempt to identify, group and present QoL domains and items of relevance to patients with SpA. The influence of different sociocultural contexts and the effectiveness of currently used PROMs in measuring domains and items of QoL related to patients with SpA have not been investigated. Therefore, under theme 1, I aimed to identify, group and present QoL domains and items of relevance to patients with SpA using a systematic review methodology. I further categorized these domains and items by type of SpA (axial vs peripheral) and the continent where the study was performed. I also assessed PROMs used in SpA to determine if they measured the domains and items identified. Furthermore, there is no data on domains and items of QoL related to SpA in the Singapore setting. Therefore, to improve the understanding of QoL of patients in SpA locally, a qualitative study to understand the impact of SpA on the QoL of patients is needed. I therefore conducted a series of focus group discussions (FGDs) among patients with SpA to identify (1) the QoL domains and subdomains that are relevant to SpA in Singapore,

(2) relevant QoL domains and subdomains that may differ between SpA subtypes, and (3) how identified QoL domains and subdomains map onto currently used PROMs.

Third, given the importance of QoL in patients with SpA, the ASAS-OMERACT classified QoL as a research priority in 2008 during the development of its core set because of the lack of suitable PROMs to measure QoL worldwide.(12, 31) In Singapore, there are currently no PROMs that have been validated for use in SpA. Hence, under theme 2, I assessed the validity and reliability of two PROMs (SF-36 and Health Assessment Questionnaire (HAQ)) in Singapore.

Fourth, as there are limited validated PROMs to assess QoL of patients with SpA, there are also few studies that seek to understand factors that are associated with QoL of patients with SpA. As there is a significant group of patients with both axial SpA and extra-spinal symptoms (i.e. peripheral arthritis, enthesitis and dactylitis), the impact of having a history of peripheral arthritis, enthesitis and dactylitis (HPED) on QoL and whether this impact persisted after a year have not yet been characterized. Therefore, under theme 3, I aimed to assess if HPED at baseline is associated with poorer QoL in patients with axSpA at baseline and 1-year.

Last, as pharmacological treatment in axSpA is limited to NSAIDs or biologics, more can be done to improve the treatment outcomes for these patients. NSAIDs cost about SGD 700 a year while biologics costs about SGD 24,000 a year. Although patients on biologics may have good symptomatic relief, the price of biologics may be too costly to a large group of patients. Therefore, there is a need to seek alternative treatment to alleviate the pain symptoms and QoL of patients with axSpA. Although acupuncture has been proven to be effective in relieving pain for patients with lower back pain and Traditional Chinese Medicine (TCM) is popular in Singapore, the uptake of TCM in mainstream healthcare is limited. Hence, under theme 4, my team developed a TCM physician involved collaborative model of care (TCMCMC) and aimed to assess the clinical effectiveness, safety and cost-effectiveness of this TCMCMC in patients with axSpA using a pragmatic trial approach.

1.5 How the thesis is organized to address the gaps in the field

This thesis attempts to address the above gaps presented in Section 1.4. The second chapter of this thesis will bring the reader through a systematic review of QoL domains and items relevant to patients with SpA. I presented how the QoL domains relevant to patients differ in items between different continents and also whether currently used PROMs are capturing QoL domains and items appropriately. The third chapter was based on the lack of Asian and in particular Singaporean data found in the systematic review, limiting understanding of the impact of the disease on patients in Singapore. I presented a qualitative study of QoL domains and items relevant to patients with SpA in Singapore. I adopted a similar presentation approach as per Chapter 2 to allow for cross comparison.

The fourth and fifth chapters were based on the need to have validated PROMs to assess QoL or its related constructs. Therefore, I assessed the validity and reliability of the SF-36 and HAQ in patients with SpA in Singapore in Chapter 4 and 5 respectively.

Having validated relevant PROMs to assess the QoL of patients with SpA, we explored how having a history of extra-spinal symptoms is associated with QoL in patients with axSpA at baseline and at one-year. In the sixth chapter, I present a longitudinal cohort analysis answering the question, “Are extra-spinal symptoms associated with QoL in patients with axSpA?”

Lastly, I presented a novel approach to address an unmet need to improve the QoL of patients with axSpA. In Chapter 7 I presented the protocol paper we developed for the TCMCMC.

Through this systematic approach of understanding the impact of disease on the QoL on patients with SpA, to developing an innovative approach to improve their QoL, we hope that the patients with SpA can improve their QoL and function, achieving their potential in life. I also hope that clinicians and researchers specializing in other rheumatic or chronic diseases can use this approach as a model to study QoL so that

these patients will be able to live their life with lesser physical pain and mental stress. To quote the Father of Modern Medicine, Sir William Osler: when practicing medicine, *“cure sometimes, treat often, comfort always”.*

Chapter 2. A systematic review of quality of life domains and items relevant to patients with Spondyloarthritis

This chapter was published in *Seminars in Arthritis and Rheumatism*.

Kwan, Y. H., Fong, W., Tan, V. I. C., Lui, N. L., Malhotra, R., Ostbye, T., & Thumboo, J. (2017). A systematic review of quality-of-life domains and items relevant to patients with spondyloarthritis. *Semin Arthritis Rheum*, 47(2), 175-182

2.1 Abstract

Objectives: To summarize, from the literature, QoL domains and items relevant to patients with SpA, and to determine if commonly used SpA PROMs include the identified domains.

Methods: The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) were adhered to. Medline® Embase® and PsycInfo® using relevant keywords were searched. In addition, hand searches of references of the included articles were conducted. All articles were reviewed for inclusion by 2 independent reviewers. QoL domains and items relevant to patients with axial or peripheral SpA were extracted and presented using the adapted World Health Organization Quality of Life (WHOQOL) domain framework. SpA PROMs were assessed to determine if they included the domains identified.

Results: 14,343 articles were retrieved, of which 34 articles fulfilled inclusion criteria for review. 25 articles were conducted in the European population. Domains such as negative feelings and activities of daily living were found to be present in 28 and 27 articles respectively. SpA impacted QoL in all domains of the adapted WHOQOL framework. Domains that differed between types of SpA were financial resources, general levels of independence and medication side effects. Embarrassment, self-image and premature ageing were items that differed by geographical setting. PROMs to capture domains for peripheral SpA were similar for axial SpA.

Conclusions: A wide range of domains and items of QoL, with minimal differences between patients with axial and peripheral SpA, were found to be relevant to patients with SpA. Clinicians may consider using peripheral SpA PROMs to measure QoL of patients with axial SpA.

2.2 Introduction

SpA is a heterogeneous group of chronic inflammatory diseases with inter-related clinical features and genetic linkages.(32) SpA includes diseases such as ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related arthritis and Reiter's arthritis.(33) SpA can result in severe disability in patients and causes impairment in the QoL of patients if left untreated.(1, 34)

PROMs to measure QoL can be categorized as generic or specific instruments, for example the SF-36 and ASQoL respectively.(35) Disease-specific instruments such as AsQoL have been established for use in SpA subsets such as AS.(36) SpA as a broader disease category has had to date few studies assessing QoL and thus the assessment of QoL is largely dependent on validation of a QoL PROM used in its subgroup of diseases.(36, 37) The QoL domains of relevance to patients with SpA may be broader than those of individual disease subsets, hence the PROMs used for a subset condition might not be useful for patients with SpA.(38) Currently, PROMs to measure QoL in SpA are not well established because the QoL domains and items of relevance to patients with SpA across various sociocultural contexts have not been well investigated. This study defined domains as a natural category of items whereby they fall under and items as the exact functioning or area of life that are impacted.(39) The QoL domains and items of relevance to patients with SpA will allow us to appropriately assess the areas of life that are affected in patients with SpA, therefore allowing us to have an accurate understanding of their overall QoL.(40, 41) As sociocultural issues affect QoL, an understanding of the domains and items of QoL will allow researchers and clinicians to use appropriate domains and items to assess the QoL of their research participants and patients respectively.(42) This is especially relevant to SpA because the sub-diseases classified under it are sometimes diverse and may result in different impact on QoL.(33)

To the best of our knowledge, there are no studies that attempt to identify, group and present the QoL domains and items of relevance to patients with SpA. Therefore, this chapter aimed to identify, group and present QoL domains and items of relevance to

patients with SpA. This chapter further categorized these domains and items by type of SpA (axSpA vs pSpA) and the continent where a study was performed. This chapter also assessed PROMs used in SpA to determine if they measured the domains and items identified.

2.3 Methods

Search Strategy

Relevant articles were identified using PubMed®, Scopus® and PsycINFO® searches with a search strategy as defined below. References were identified from 2 popular Rheumatology textbooks, Kelley's Textbook of Rheumatology 9th Edition and Rheumatology 5th Edition, and from hand searches of relevant articles. This three-pronged approach has been shown to be effective in improving the search comprehensiveness.(41) Literature review start date was unrestricted and was current as of July 2016. The keywords used were Spondyloar*, ankylosing spondy*, psoriatic arthritis, reactive arthritis, inflammatory bowel disease related arthritis AND quality of life, health-related quality of life, outcome measure, outcome assessment, clinical outcome, pain, function*, disability, symptom, functional disability, disable, disability evaluation, self-perception, preference, priority, psychosocial, social support, item, domain, qualitative, focus group, open-ended, interview, rating, tools, and patient-reported outcome.

Inclusion and exclusion criteria

Two authors (YH Kwan and VLC Tan) independently reviewed the articles for inclusion and exclusion. Only articles that studied subjects with SpA or its subset diseases (AS, PsA reactive arthritis and IBD-related arthritis) were included. Articles were included if they contained information on QoL domains and/or items of relevance to patients with SpA derived from patients' own perceptions or reports. Patients' own perceptions or reports were defined as information solicited from patients using methods such as focus groups, patient interviews with open-ended questions, or

patients' rating of importance. Articles that investigated patients above 18 years of age were included.

Articles that examined diseases other than SpA or subjects that were not diagnosed with SpA, articles on QoL of patients with SpA that did not involve patients' preference through ratings or qualitative approaches were excluded. Also, articles that examined juvenile SpA were excluded.

Collection of PROMs used in clinical practice

To gather PROMs that are used in clinical practice, the Patient-Reported Outcomes and Quality of Life Database (PROQOLID) on all instruments related to SpA and its subset diseases was searched. The Rheumatology 5th Edition and Kelley's Textbook of Rheumatology 9th Edition were referred to supplement the collection. This method was used in order to gather PROMs that were the most relevant to what clinicians are using currently in their practice instead of PROMs that were validated in the literature.

Data presentation

The QoL domains or items of relevance to patients with SpA were presented by type of SpA and continent of the world whereby the patients were included. (43)

The domains and items of PROMs that measure QoL domains and items of relevance to patients with both axial and peripheral SpA were presented to allow readers to understand the coverage of these PROMs on the domains and items relevant to patients with SpA. Patients with AS and non-radiographic axSpA were considered as axSpA, while patients with PsA, reactive arthritis and inflammatory bowel disease-related arthritis were considered as pSpA.(44, 45) This was used because the ASAS criteria for axSpA and pSpA were only developed in 2009 and 2011 respectively while some of the studies in this review were conducted prior to these dates.(12, 17) For this chapter, we adapted our classification of domains of QoL based on the domains proposed by the WHOQOL.(18) There were 7 broad domains included in WHOQOL: physical, psychological, level of independence, social relationship, environment, spirituality and general health perception. This was chosen as it focuses on the

patient's own views of their own well-being, providing new perspective for their disease, and it is a framework conducted through fifteen centers in different cultural setting.(46) Two authors (YH Kwan and VLC Tan) independently linked the items to domains from the WHOQOL framework and reached a consensus where there was disagreement. An item might be assigned to more than 1 domain if the item contained concepts from more than 1 domain.

2.4 Results

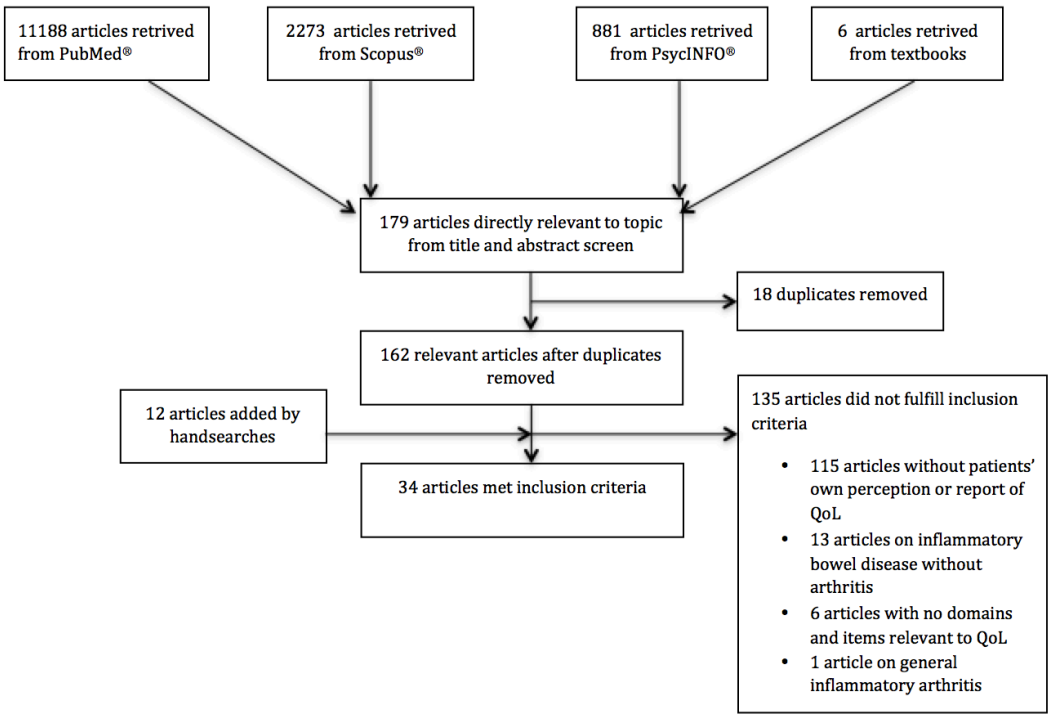

Figure 3. Flow chart on selection of articles for systematic review

Literature search results

As shown in Figure 3, 14343 articles were retrieved by our searches. A total of 11188, 2273 and 881 articles were gathered from PubMed®, Scopus® and PsycINFO® respectively. Six more articles were retrieved from our textbook searches. A total of 179 articles were deemed relevant after title and abstract screening. After hand searches, full text review and removal of duplicates, a total of 34 articles being included for data extraction.

As shown in Table 1, studies involved patients with axSpA (n=22), pSpA (n=9) or both (n=3). Studies were cross continental (n=4) and studies involved patients in Europe (n=25), North America (n=7), Oceania (n=3), Asia (n=2), Africa (n=2) and South America (n=1).

Domains of relative relevance in SpA

Table 1 outlines the top ranked QoL domains relevant to patients with SpA found in each article. The top domains were negative feelings (n=28), activities of daily living (n=27), energy and fatigue (n=26), personal relationship (n=23), pain and discomfort (n=22), work capacity (n=22) and mobility (n=20).

Differences of domains and items between the types of SpA

As shown in Table 2, the QoL domains of relevance to patients with axSpA and pSpA were largely similar except for financial resources, general level of independence and treatment burden, which were identified for axSpA and not for pSpA.

In general, the QoL items of relevance to patients with axSpA and pSpA were largely similar. QoL items of relevance to patients with axSpA but not pSpA were weight and tone, tender to touch, weakness, need for rest, optimism, problem solving, learning, guilt, turning head, balancing, caring for pets, emotional support, sex drive, work culture, financial losses, turning head while reversing, looking into rear view mirror, getting in and out of car and medication side effect. QoL items of relevance to patients with pSpA but not axSpA were skin pain, time to recover, hopelessness, injustice, withdrawn, kneeling, family culture and being prepared by healthcare professional. Details of QoL items relevant to patients with SpA can be viewed on Supplementary Table 1.

Differences between domains and items of subjects in different continents of the world

The domain bodily image and appearance, as shown in Table 2, and the items embarrassment, self-image and premature ageing, as shown in Supplementary Table

1, were found to be relevant to patients in Europe and North America but not relevant in other parts of the world.

Coverage of PROMs for axSpA

As shown in Table 3, PROMs for axSpA covered 14 out of 30 domains. PROMs such as ASQoL and Health Assessment Questionnaire – Spondyloarthritis (HAQ-S) covered 7 and 6 domains respectively. Usage of all 4 Bath Ankylosing Spondylitis Functional Index (BASFI), ASQoL, HAQ-S, Bath Ankylosing Spondylitis Global Score (BASG) or patient global assessment (PGA) will allow full coverage of the 14 domains with minimal overlaps. The domain coverage for PROMs for patients with axSpA did not cover all the QoL domains relevant to patients with pSpA.

Coverage of PROMs for pSpA

As shown in Table 3, PROMs for pSpA covered 21 out of 30 domains. PROMs such as Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and SF-36 covered 15 and 11 domains respectively. Usage of all 4, SF-36, HAQ, Dermatology Life Quality Index (DLQI) and FACIT-F will allow coverage of all 21 domains with minimal overlaps. The QoL domain coverage of PROMs for patients with pSpA also covered the QoL domains of relevance to patients with axSpA.

Table 1. Summary of articles fulfilling inclusion criteria for systematic review

Author	Disease/ Country/Continent/Language	Primary aim	Methods	Top ranked domains of relevance (taxonomy adopted from WHOQOL)						
				Negative feelings	Activities of daily living	Energy and fatigue	Personal relationships	Pain and discomfort	Work capacity	Mobility
Kiltz et al[28]	axSpA/Belgium, Croatia, France, Germany, Hungary, Italy, Netherlands, Portugal, Russia, Spain, Turkey, Australia, Canada, Colombia, Egypt, Korea, Mexico, Thailand, USA/North America, Europe, Asia, Oceania, Africa/English	To investigate the importance of aspects of health for patients with axSpA	Best-worst scaling	1	1	1	1	1		1
Boonen et al[30]	AS/Netherlands/Europe/English	To investigate the concepts important to patients with AS are covered by disease-specific self-report health status instruments	FGD	1	1	1	1	1	1	1
Wink et al[31]	PsA/Netherlands/Europe/Dutch	To translate PsAQoL into Dutch and determine its psychometric properties	IDI	1	1	1	1		1	
Doward et al[32]	AS/USA, Canada, Germany, France, Italy, Spain, Sweden/Europe/As per the countries' native languages	To translate and adapt the ASQoL	IDI	1	1	1	1	1		
Cieza et al[33]	AS/Netherlands and Germany/Europe/ Dutch and German	To explore the possibility of constructing clinical measures for patients with AS by integrating information from the ICF	IDI	1	1	1	1	1		1
Naegeli et al[34]	AS/USA/North America/English	To perform qualitative research to support the development and content validity of the WF-NRS	IDI	1	1	1		1		1
Jenks et al[35]	SpA/New Zealand/Oceania/English	To examine the validity of the ASQoL in New Zealand	IDI	1	1	1	1	1		
Eilertsen et al[36]	AS/Norway/Europe/Norwegian	To elucidate the experience of fatigue across several long-term illnesses	IDI	1		1				
Cooksey et al[37]	AS /UK/Europe/English	To explore severe flare and constant disease pattern in AS	Free text analysis	1		1		1	1	
Stenstrom et al[38]	AS/Sweden/Europe/Swedish	To investigate the reliability and validity of a Swedish version of the Revised Leeds Disability Questionnaire	IDI		1					1
Guillemin et al[39]	AS/ France/Europe/France	To develop a questionnaire measuring quality of life in AS	FGD	1	1		1	1	1	1
Miedany et al[40]	AS/ Egypt and England/Africa, Europe/ English	To assess validity, reliability and sensitivity of the CASQ	Rating	1	1		1		1	1
Davis et al[41]	SpA/Canada/North America/English	To evaluate the measurement properties of the social role participation questionnaire	IDI				1		1	
Bagcivan et al[42]	AS/Turkey/Asia/Turkish	To explore AS patients' experience with pain and its effect on their lives	IDI	1	1		1		1	
Hamilton-West et al[43]	AS/USA/North America/English	To understand the psychosocial consequences of AS	IDI	1		1	1	1	1	1
Mengshoel et al[44]	AS/Norway/Europe/Norwegian	To examine the nature of fatigue and how it is managed in daily life situations by AS patients	IDI	1	1	1		1		1

Moverley et al[45]	PsA/UK/Europe/English	To explore patients' perspective of flares	IDI	1	1	1					
Van Echteld et al[46]	AS/ Netherlands, Germany/Europe/Dutch and German	To identify common health problems based on the ICF from patients' perspective	IDI	1	1	1	1	1	1	1	
Berenbaum et al[47]	SpA/France/Europe/English	To explore beliefs and apprehensions about disease and its treatment in patients	IDI	1	1	1	1	1	1	1	
Haywood et al[48]	AS/UK/Europe/English	To develop and evaluate a patient-reported outcome measure of quality of life	IDI	1	1	1	1	1	1	1	
Taylor et al[49]	PsA/New Zealand/Oceania/English	To determine the categories of the ICF checklist and core sets in RA and AS that frequently occur in PsA patients	IDI	1	1	1	1	1	1	1	
Chisholm et al[50]	PsA/UK/Europe/English	To explore patients' illness beliefs, emotions and behavior relate to living with PsA	IDI	1			1		1		
McKenna et al[51]	PsA/UK/Europe/English	To assess the validity and reliability of PsAQoL in UK	IDI	1	1	1	1		1		
Doward et al[52]	AS/UK and Netherlands/Europe/ English and Dutch	To assess the validity and reliability of ASQoL in UK and the Netherlands	IDI	1	1	1	1	1			
Torre-Alonso et al[53]	PsA/Spain/Europe/Spanish	To develop and validate an instrument to measure QoL in patients with PsA	FGD	1	1	1	1	1	1	1	
Brophy et al[54]	AS/UK/Europe/English	To examine the patients' perception of the factors important in defining flares in AS	FGD	1		1		1		1	
Stamm et al[55]	PsA/Austria/Europe/Austrian	To explore whether the concepts important to patients with PsA are covered by self-report instruments assessing function	FGD	1	1	1	1	1	1	1	
Shinjo et al[56]	AS/Brazil/South America/Brazilian-Portuguese	To cross-culturally adapt the HAQ-S Brazilian-Portuguese to AS	IDI		1				1	1	
Van Tubergen et al[57]	Axial SpA/USA/North America/English	To evaluate psychometric properties of AS patient reported outcome tools in axSpA	IDI	1	1	1	1	1	1	1	
Billing et al[58]	PsA/Sweden/Europe/Swedish	To cross-culturally adapt the PsAQoL for use in Sweden	IDI	1	1	1	1		1		
Pedersen et al[59]	AS/Denmark/Europe/Danish	To adapt the BASDAI, BASFI, BASG for use in Denmark	IDI		1	1		1	1	1	
Gossec et al[60]	PsA/USA/North America/English	To develop the PsA Impact of Disease questionnaire	FGD	1	1	1	1	1	1		
Calin et al[61]	AS/UK/Europe/English	To develop a tool to measure function in AS	IDI		1				1	1	
Garrett et al[62]	AS/UK/Europe/English	To develop a tool to measure disease activity in AS	IDI			1		1			
		Number of articles		28	27	26	23	22	22	20	

Abbreviations: Axial SpA (axSpA), World Health Organization Quality of Life (WHOQOL), United States of America (USA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), spondyloarthritis (SpA), United Kingdom (UK), International Classification of Functioning (ICF), focus group discussion (FGD), in-depth interview (IDI), Worst Fatigue – Numeric Rating Scale (WF-NRS), Combined AS Questionnaire (CASQ), Quality of Life (QoL), Health Assessment Questionnaire – Spondyloarthritis (HAQ-S), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global (BASG).

Table 2: Domains relevant to QoL in patients with SpA categorized by SpA types and continent

Domains	Axial SpA							Peripheral SpA						
	Europe	North America	South America	Africa	Oceania	Asia	Total	Europe	North America	South America	Africa	Oceania	Asia	Total
Physical														
General	2	0	0	0	0	0	2	1	0	0	0	1	0	2
Pain and discomfort	14	4	0	1	1	1	18	3	1	0	0	2	0	6
Energy and fatigue	14	4	0	1	1	1	18	7	1	0	0	2	0	10
Sleep and rest	12	3	0	2	1	1	16	2	1	0	0	2	0	5
Other symptoms	11	2	0	1	0	0	14	3	0	0	0	1	0	4
Psychological														
Positive feelings	4	2	0	1	0	0	5	0	0	0	0	1	0	1
Thinking, learning, memory and concentration	6	2	0	1	1	1	7	0	1	0	0	1	0	2
Self-esteem	3	2	0	1	0	0	5	3	1	0	0	0	0	4
Bodily image and appearance	0	1	0	0	0	0	1	2	0	0	0	0	0	2
Negative feelings	14	4	0	2	1	1	16	8	1	0	0	2	0	11
Level of independence														
General	1	1	0	0	0	0	2	0	0	0	0	0	0	0
Mobility	13	3	1	2	1	1	18	3	0	0	0	1	0	4
Activities of daily living	14	3	1	2	1	1	20	7	1	0	0	1	0	9
Dependence on medicinal substances and medicinal aid	3	0	0	0	0	0	3	1	0	0	0	1	0	2
Work capacity	9	3	1	1	0	1	14	7	2	0	0	1	0	10
Social relationship														
Personal relationship	10	5	0	2	1	1	15	7	2	0	0	2	0	11
Social support	4	0	0	0	0	0	4	2	0	0	0	0	0	2
Sexual activity	5	3	0	1	1	1	9	2	2	0	0	1	0	5
Environment														
Freedom, physical safety and security	3	0	0	0	0	1	4	3	0	0	0	1	0	4
Home environment	1	0	0	0	0	0	1	1	0	0	0	1	0	2
Work satisfaction	0	0	0	0	0	1	1	1	0	0	0	0	0	1
Financial resources	2	1	0	1	1	2	3	0	0	0	0	0	0	0
Health and social care	2	0	0	0	0	0	2	1	0	0	0	1	0	2
Opportunities for learning	1	1	0	0	0	0	2	0	1	0	0	0	0	1
Participation in leisure activities	9	3	0	1	1	1	14	5	2	0	0	1	0	8
Physical environment	3	0	0	0	0	0	5	4	0	0	0	0	0	4
Transport	8	2	1	2	1	1	12	1	0	0	0	1	0	2
Spirituality/religious/personal beliefs														
Spirituality/religious/personal beliefs	1	1	0	0	0	0	2	0	1	0	0	0	0	1
Overall QoL and general health perception														
General	4	3	0	0	0	0	7	1	2	0	0	0	0	3
Treatment burden	0	1	0	0	0	0	1	0	0	0	0	0	0	0

The number in the cells refers to the number of studies reporting the affected domains.
Abbreviations: Spondyloarthritis (SpA), Quality of Life (QoL)

Table 3: Domains relevant to QoL in patients with SpA and compared with their commonly used PROs

Types of SpA	Commonly used PROs in axial SpA					Commonly used PROs in peripheral SpA						
Domains	**ASQoL**	**HAQS**	**DFI**	**BASFI**	**BASG**	**PGA**	**Pain**	**SF36**	**DLQI**	**PsAQoL**	**HAQ**	**FACITF**
Physical												
General												
Pain and discomfort	1						1	1	1			1
Energy and fatigue	1							1		1		1
Sleep and rest	1		1									1
Other symptoms												1
Psychological												
Positive feelings								1				1
Thinking, learning, memory and concentration												
Self-esteem									1			
Bodily image and appearance												
Negative feelings	1							1		1		1
Level of independence												
General		1								1	1	
Mobility		1	1	1				1			1	
Activities of daily living	1	1	1	1				1	1	1	1	1
Dependence on medicinal substances and medicinal aid		1									1	
Work capacity		1		1				1	1			1
Social relationship												
Personal relationship	1							1	1	1		1
Social support												1
Sexual activity									1			1
Environment												
Freedom, physical safety and security	1							1		1		
Home environment												
Work satisfaction												1
Financial resources												
Health and social care												
Opportunities for learning												
Participation in leisure activities				1				1	1	1		1
Physical environment												
Transport		1	1								1	
Spirituality/religious/personal beliefs												
Spirituality/religious/personal beliefs												
Overall QoL and general health perception												
General					1	1		1				1
Treatment burden									1			1

Abbreviations: Spondyloarthritis (SpA), Quality of Life (QoL), Health Assessment Questionnaire – Spondyloarthritis (HAQS), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global (BASG), Patient Global Assessment (PGA), Pain Visual Analogue Score (Pain), Ankylosing Spondylitis Quality of Life (ASQoL), Patient-Reported Outcomes (PRO), Dougados Functional Index (DFI), Short-Form 36 (SF36), Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQoL), Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy – Fatigue (FACITF)

2.5 Discussion

A systematic literature review to identify, group and present the QoL domains and items of relevance to patients with SpA was conducted using the PRISMA checklist, and domains and items were mapped to the WHOQOL framework to improve the rigor of this study.(47) The goal in performing this systematic review was to allow other researchers that are working in this field to use our results and improve on the measurement of these domains in patients with SpA.(18) This is the first review that tried to comprehensively identify, group and present the QoL domains and items of relevance to patients with SpA. The difference of the QoL domains and items relevant to patients with different types of SpA as well as different socio-cultural contexts was presented. Last, the coverage of the PROMs was explored to allow recommendations to be made for a suitable set of PROMs to measure the QoL domains and items of relevance to patients with SpA.

The impact of SpA on QoL of the patients differed in axial and peripheral SpA for some domains of the WHOQOL framework. The domains of financial resources and treatment burden were affected in patients with axSpA but not patients with pSpA. This may be due to patients with axSpA having fewer treatment options, compared to pSpA patients, before needing to have biologics for disease remission. Biologics are generally more costly compared to oral DMARDs and NSAIDs, and have a higher risk of infections and melanotic skin cancers.(48) The greater relevance of skin pain, injustice, withdrawn and kneeling for patients with pSpA were likely due to the natural pathophysiology of their illness whereby peripheral joint and skin involvement such as psoriasis present as greater problems to them than patients with axSpA.(49) Patients with axSpA expressed greater relevance to certain items when compared to pSpA items such as guilt, financial losses, turning head while reversing, looking into rear view mirror, getting in and out of car and medication side effect, and these were probably due to the disease progression such as stiffening of spine, greater medication cost and also possibly genetic transmission due to HLA-B27.(50-52)

The impact of SpA on QoL differed by geographic location. The results showed that self-image, embarrassment and premature ageing were of greater relevance to the Europeans and North Americans, who in general prioritize individualism. (53) The lack of domains of relevance may also be due to the seemingly lack of research in areas such as Asia particularly South-East Asia and Africa.

The results allow some suggestions to be made for selection of PROMs for assessing QoL in SpA. The coverage of the PROMs was only sufficient for 21 out of 30 domains. Domains such as sexual activity, thinking, learning, memory and concentration and financial resources and bodily image and appearance should be measured by using a specific sexual function questionnaire or sexual domain incorporated into a general QoL questionnaire.(54) This chapter may provide support for the use of the ASAS Health Index as a potential PROM when studying SpA since it includes items addressing sexual function and financial resources.(55) The coverage of pSpA overlaps with general SpA and this result may prompt us to consider using PROMs that were validated for disease such as PsA to be used for general SpA including AS. This may reduce significant logistics burden of differing monitoring PROMs and may allow further comparison across different diseases if they can be monitored the same way.(56)

The findings from this chapter will allow clinicians to understand the area of impact of SpA to the patients' QoL, therefore allowing a comprehensive understanding of the disease impact beyond the medical aspect. For the researchers, this provides a foundation to future development and implementation of PROMs to measure QoL, in particular facilitating the development of item banks and computer-adaptive tests (CATs) that allow more precise measurement of QoL with lower cognitive burden. For the students conducting systematic review in the field of QoL, this chapter provides a model to starting their first systematic review especially through the usage of keywords and database suggestions.

This chapter has several limitations. First, psychometric studies that did not contain any patients' input were not included, and this may result in loss of items and domains

important to patients with SpA. However, as patients' opinions were of particular interest, only studies with patients' direct input such as qualitative or rating of importance studies were included. Second, although studies of other languages were not included, there was no article that was non-English and met our inclusion criteria during our search. Third, there was a paucity of articles from other continents than Europe. Hence, the lack of relevance of QoL domains or items in patients with SpA from these areas may rather be interpreted as a lack of research rather than a lack of relevance of these domains. Lastly, although there was no comparison between non-radiographic axSpA and AS as this was not part of the aim a priori, we did not notice any significant differences between the QoL domains of radiographic axSpA and AS.

In conclusion, a wide range of QoL domains and items relevant to patients with SpA with minimal differences between patients with axSpA and pSpA was found. Clinicians may consider using pSpA PROMs to measure QoL of patients with axSpA. Also, more studies are needed in geographical areas other than Europe to determine the QoL domains and items of relevance to patients across different sociocultural contexts. The findings from this chapter gave the impetus to continue with a local qualitative study to understand the impact of SpA on Singapore patients as presented in Chapter 3. Furthermore, this chapter gave us the confidence that PROMs such as SF-36 and HAQ are reasonable PROMs to be selected for assessment of their psychometric properties in Chapter 4 and 5 respectively.

Chapter 3. A qualitative study of Quality of Life domains and subdomains relevant to patients with Spondyloarthritis in Singapore

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3.1 Abstract

Objectives: To identify QoL domains and subdomains relevant to patients with different SpA subtypes in Singapore, and to assess how identified QoL domains and subdomains map onto currently used PROMs.

Methods: Nine focus group discussions (FGDs) including two previously conducted FGDs from the Updating the Psoriatic Arthritis Core Domain Set Study were conducted with patients with SpA in Singapore. The FGDs were organized by SpA subtype and language spoken. All FGDs were audio-taped and transcribed verbatim. After thematic analysis through open and axial coding, the domains were organized using the WHOQOL framework. Identified QoL domains and subdomains were mapped to currently used PROMs.

Results: The 9 FGDs included 51 patients. In total, 27 domains and 92 subdomains were identified and then organized within the 7 broad categories of the WHOQOL framework. Patients in Singapore were more concerned about “financial resources”, “work satisfaction” and “positive feelings” while less concerned about “freedom, physical safety and security” than patients in western countries. “Home environment” and “work satisfaction” emerged as unique QoL domains relevant to patients with axSpA. PROMs for PsA can capture both identified domains of PsA and axSpA.

Conclusions: A wide range of QoL domains and subdomains are relevant to SpA patients in Singapore, and there appears to be minimal differences in their relative importance between SpA subtypes. This chapter supports the development and validation of common QoL-specific PROMs for usage in SpA.

3.2 Introduction

SpA is a chronic disease that causes significant pain, fatigue and impairment in mobility.(1, 57) Managing and improving QoL for patients with SpA is central to achieving good outcomes.(58)

SpA refers to a clinically heterogeneous group of diseases including AS, PsA, inflammatory bowel disease (IBD) with joint involvement, and reactive arthritis.(8) Recent classification criteria have helped to refine the categorization of SpA. AxSpA is defined as having more than 3 months of back pain with age of onset less than 45 years old with supporting SpA features, laboratory tests and imaging tests, while peripheral SpA is defined as either peripheral arthritis, enthesitis or dactylitis with other supporting SpA features, laboratory and imaging tests.(12, 30)

Patient-reported outcomes (PROs) are defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a health care professional or other individual.(59) PROMs are instruments used for measuring PROs. PROMs can be categorized as generic or disease-specific instruments; examples are the SF-36 and ASQoL respectively.(35) Disease-specific instruments such as the AsQoL and ASAS Health Index have been developed for use in AS while the Psoriatic Arthritis Quality of Life (PsAQoL) and the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire for use in PsA.(36, 60-62) There have been few studies validating disease-specific QoL PROMs used in AS or PsA to assess QoL in patients with SpA as a broader disease category.(36, 37) The QoL domains of relevance to patients with SpA may be broader than those relevant to individual disease subtypes, hence the PROMs used for a subtype might not be useful for patients with SpA overall.(38) Hence, using QoL PROMs that have not been adapted to SpA may result in an inaccurate or imprecise understanding of QoL among patients with SpA.

In the validation of QoL PROMs in SpA, quantitative methods including psychometric analyses have been used to assess the reliability and validity of these PROMs.(36) These studies, though necessary, are not sufficient because they do not determine how important or relevant the domains of a given QoL PROMs are in a specific socio-cultural context.(36) Qualitative methods (such as interviewing, observing and interpreting) can address these issues by capturing the views of individuals regarding the impact of SpA, which may not be adequately addressed by quantitative methods.(63) Qualitative methods are useful in understanding the impact of socio-cultural factors on health and thus the suitability of QoL PROMs in different socio-cultural contexts.(64) Qualitative studies are also superior in elucidating new aspects or dimensions of a problem unique to local populations and in elucidating the perspective of patients.(65) From our systematic review of QoL domains and subdomains relevant to patients with SpA in Chapter 2, 34 qualitative studies involving patients with SpA, PsA or AS have investigated the impact of SpA on QoL.(3) Very few studies have attempted to elicit the relevant QoL domains and subdomains from patients with different SpA subtypes especially in the Asian setting. There have been limited studies to assess whether currently used PROMs are capturing the QoL domains and subdomains relevant to patients with SpA in Singapore. Chapter 2 revealed that out of the 34 studies, only 2 studies had been conducted in Asia.(3) Singapore, being a multi-ethnic country, is a unique setting to conduct such a qualitative study. Previous research in systemic lupus erythematosus and osteoarthritis from Singapore revealed unique socio-cultural impacts of these diseases on the patients' QoL.(22, 66, 67)

Therefore, a series of focus group discussions (FGDs) among patients with SpA was conducted to identify (1) the QoL domains and subdomains that are relevant to SpA in Singapore, (2) relevant QoL domains and subdomains that may differ by SpA subtypes, and (3) how identified QoL domains and subdomains map onto currently used PROMs.

3.3 **Methods**

Study Design

Seven FGDs in the period August 2016 to November 2016 were conducted. To supplement the data relating to peripheral SpA from these seven FGDs, transcript data from two FGDs of 6 and 7 patients with PsA conducted in Singapore in September 2015 was used. These latter FGDs were part of the International Updating the Psoriatic Arthritis Core Domain Set study of patients with PsA (a form of pSpA) to better understand the impact of psoriatic arthritis on their lives.(68) FGD methodology was selected because it incorporates elements of participant observation and individual interviews while allowing for dynamic group interactions, enhancing the richness of the data obtained.(69) Out of the nine FGDs, six were conducted in English, including individuals from the three ethnic groups in Singapore (Chinese, Malay and Indian) and three were conducted in Mandarin, including ethnic Chinese only. Malay- or Tamil-speaking groups were not conducted because 71% of Singaporeans from these ethnic groups speak both English and their mother tongue, and often prefer to speak in English.(70) Three FGDs were conducted separately for the following two SpA subtypes: 1) axSpA and 2) PsA subtypes; while conducting the groups by language using a ratio of two English-speaking to one Mandarin-speaking FGDs for each SpA subtype. Patients with axSpA fulfilled the 2009 ASAS criteria for axSpA.(16) Patients with PsA fulfilled the 2006 classification criteria for psoriatic arthritis (CASPAR) (71). To ensure comparison of the two distinct SpA subtypes, we confirmed that patients with axSpA either fulfilled the 1984 Modified New York Criteria for AS or had magnetic resonance imaging evidence of sacroiliitis while patients with PsA only had inflammatory back pain symptoms after the age of 45. Separate FGDs were conducted for group with axSpA and PsA.

For each FGD, four to ten patients were invited and three to eight patients attended. Each FGD consisted of a mixture of patients recruited through purposive sampling with different genders, age, languages spoken, disease subtypes and varying disease severity to achieve a diversity and range of opinions. Patients were identified from a registry maintained by the Department of Rheumatology and Immunology in the Singapore General Hospital, a tertiary referral hospital. All were patients of the study rheumatologists (W Fong, NL Lui, YY Leung).

An experienced facilitator fluent in the respective language led each FGD with two note-takers in a private meeting room.(72) The facilitator was not involved in the data analysis. A topic guide was developed and piloted (Supplementary Table 2). The topic guide was designed to be open and was supplemented with probes anchored by the WHOQOL framework as described in our systematic review.(3) There were 7 broad domains included in WHOQOL: physical, psychological, level of independence, social relationship, environment, spirituality/religious/personal beliefs and overall QoL and general health perception. This framework was chosen as it focuses on the patient's own views of their well-being, providing new perspectives for their disease. It has been used in fifteen centres in different cultural setting.(46) As one of the cons of FGD was that patients may not be willing to share on sensitive topics, patients were allowed to write down their thoughts relating to these topics, for example how SpA may affect their sexual life and finances. Each FGD lasted 1 to 1.5 hours.

All FGDs were audiotaped and transcribed verbatim, with subsequent translation into English for the groups conducted in Mandarin. Accuracy of key domains and subdomains was repeatedly and iteratively checked with translators so that the meanings were correctly conveyed in the English translations.

Data analysis

The qualitative analytical software Nvivo 11 for Macintosh was used for analysis of the transcribed discussions. Each FGD was coded inductively immediately after it had been completed, and this further directed and refined the conduct of subsequent FGDs.(73) First, the main areas of impact of SpA (i.e. subdomains) were determined by open coding by naming or defining the impact of SpA through close examination of the data. Axial coding was employed with the aim of grouping the open codes. Axial codes (i.e. domains) refer to the categories under which open codes (i.e. subdomains) were classified. As shown in Figure 4, the axial codes and open codes were organized according to the domains and subdomains of the WHOQOL framework as described in the systematic review in the previous chapter.(3) During the process, both existing and emerging axial and open codes were verified and/or

modified by re-reading the transcripts. The axial codes were then further grouped under their respective 7 broad domains (i.e. physical, psychological, level of independence, social relationship, environment, spirituality/religious/personal beliefs and overall QoL and general health perception) based on the WHOQOL framework. The axial codes and open codes were reapplied into the transcripts to check for accuracy. New emerging axial codes and open codes were noted and presented separately. Two coders, experienced in qualitative research (YH Kwan and AF Yap), conducted the coding analysis, and consensus was reached through discussion should differences arise. The axial codes and open codes were stratified and presented by SpA subtypes. The relevant QoL domains and subdomains unique to Singapore were compared to other studies as per the systematic review in the previous chapter.(3)

Example quotation:
"That was during younger time la. And then when you pain you very frustrated because you have to go out and you have to cancel appointment, family can understand, friends don't understand, affected our lifestyle because we need social friends … so that does affect also ... then people will start to ask you how come when you walk you start to limp then you have to explain all over again yea that kind of thing so you affected also"

Example of an ***open code (i.e. Subdomain)*** extracted from this quotation:
"Frustrated"

Example of an ***axial code (i.e. Domain)*** to which "Frustrated" related to: "Negative feelings"

Linking to the "Psychological" broad domain of the ***WHO Quality of Life (WHOQOL) Framework***

Figure 4. An example of the qualitative analysis: Quotation, open codes, axial codes and the corresponding broad domain in the WHO Quality of Life Framework

Mapping of QoL domains and subdomains relevant to patients with SpA to currently used PROMs

The themes from the items of currently used PROMS for SpA were mapped to the domains and subdomains that were identified. The currently used PROMs were adapted from the systematic review in the previous chapter by comparing axial and open codes identified in this study against those in these adapted PROMs.(3) A content gap was identified when the QoL domains and subdomains relevant to

patients with SpA elicited from these FGDs were not addressed by any questions from these currently used PROMs.

Ethical approval

This study was conducted with the approval of the SingHealth Centralized Institutional Review Board (Ref: 2016/2463) and written informed consent was obtained from all patients before commencement of the study.

3.4 Results

Patients participating in the FGDs

As shown in Table 4, 51 patients participated in this study. 34 (66.7%) of the patients had axSpA and 17 (33.3%) had PsA. The median age was 43 years (range: 21 to 77). The majority was Chinese (n=44, 86.2%). Patients with axSpA were younger and had a higher proportion of men than patients with PsA. Six and 3 FGDs were conducted and analysed with patients with axSpA and PsA respectively. Thematic saturation was reached after these 9 FGDs for SpA in general and for each subtype of SpA.

Table 4. Characteristics of participants in qualitative study

Characteristics	Total (N=51)	Axial SpA[1] (N=34)	PsA[2] (N=17)
Number of Focus Groups	9	**6**	**3**
Current age, median (range), years	43 (21-77)	41 (21-73)	51 (21-77)
Gender, male, N (%)	28 (54.9%)	20 (58.8%)	8 (47.0%)
Race			
Chinese, N (%)	44 (86.2%)	31 (91.1%)	13 (76.4%)
Malay, N (%)	1 (2.0%)	0 (0%)	1 (5.8%)
Indian, N (%)	5 (9.8%)	2 (5.8%)	3 (17.6%)
Others, N (%)	1 (2.0%)	1 (2.9%)	0 (0%)
Highest education level (Age started)			
No formal education, N (%)	1(2.0%)	0 (0%)	1 (5.8%)
Primary (6 years), N (%)	5 (9.8%)	4 (11.7%)	1 (5.8%)
Secondary (12 years), N (%)	14 (27.4%)	7 (20.5%)	7 (41.1%)
Tertiary (16 years), N (%)	28 (54.7%)	22 (64.7%)	6 (35.2%)
Others, N (%)	3 (5.9%)	1 (2.9%)	2 (11.7%)
Marital status			
Single, N (%)	20 (39.2%)	14 (41.1%)	6 (35.2%)
Married, N (%)	29 (56.9%)	19 (55.8%)	10 (58.8%)
Divorced, N (%)	2 (3.9%)	1 (2.9%)	1 (5.8%)
Occupation			
Employed or self-employed, N (%)	38 (74.5%)	28 (82.3%)	10 (58.8%)
Full time student, N (%)	3 (5.9%)	2 (5.8%)	1 (5.8%)
Home-maker, N (%)	5 (9.8%)	2 (5.8%)	3 (17.6%)
Retiree, N (%)	4 (7.8%)	2 (5.8%)	2 (11.7%)
Unemployed, N (%)	1 (2.0%)	0 (0%)	1 (5.8%)
Time since diagnosis (median (range), years	9 (2-34)	11 (3-34)	5 (2-24)
HAQ(median (range: 0-3)	0.125 (0-1.625)	0.187 (0-1.571)	0.125 (0-1.625)
Disease manifestations, ever (%)			
Inflammatory back pain, N (%)	37 (72.5%)	34 (100.0%)	3 (17.6%)
Peripheral joint arthritis, N (%)	40 (78.4%)	23 (67.6%)	17 (100.0%)
Uveitis, N (%)	13 (25.5%)	11 (32.3%)	2 (11.7%)
Enthesitis, N (%)	16 (31.3%)	12 (35.2%)	4 (23.5%)
Dactylitis, N (%)	15 (29.4%)	3 (8.8%)	12 (70.5%)
Psoriasis, N (%)	18 (35.3%)	1 (2.9%)	17 (100.0%)
Inflammatory bowel disease, N (%)	1 (2.0%)	1 (2.9%)	1 (5.8%)

[1]Patients were classified using the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria for axial Spondyloarthritis

[2]Patients were diagnosed with psoriatic arthritis using the 2006 Classification criteria for psoriatic arthritis (CASPAR)

Numbers are presented as median (range) or number (percentage).

Abbreviation: Health Assessment Questionnaire (HAQ), Spondyloarthritis (SpA)

Relevant QoL domains and subdomains *of patients with SpA*

A total of 92 open codes (i.e. subdomains) were identified. As shown in Table 5, using the adapted WHOQOL framework, 27 axial codes (i.e. domains) were created. These axial codes were subsumed under the 7 broad domains of WHOQOL mentioned. The relevant QoL subdomains were presented in Supplementary Table 3.

Relevant QoL domains and subdomains of patients with SpA unique to Singapore

As shown in Table 5, domains of environment, which included concept of "freedom, physical safety and security" and "opportunities for learning" were not thought to be relevant QoL domains for patients with SpA in Singapore, even with deliberate prompting from the interviewers.

Table 5: QoL domains relevant to patients with SpA, by SpA subtype in Singapore

Subtypes of SpA	Axial SpA[1] (N=34, FGD=6)	Peripheral SpA[2] (N=17, FGD=3)
Domains		
Physical		
General	3 (50.0%)	2 (66.7%)
Pain and discomfort	6 (100.0%)	3 (100.0%)
Energy and fatigue	5 (83.3%)	3 (100.0%)
Sleep and rest	6 (100.0%)	3 (100.0%)
Other symptoms	6 (100.0%)	3 (100.0%)
Psychological		
Positive feelings	6 (100.0%)	3 (100.0%)
Thinking, learning, memory and concentration	3 (50.0%)	2 (66.7%)
Self-esteem	4 (66.7%)	3 (100.0%)
Bodily image and appearance	1 (33.3%)	3 (100.0%)
Negative feelings	6 (100.0%)	3 (100.0%)
Level of independence		
General	0 (0%)	0 (0%)
Mobility	6 (100.0%)	3 (100.0%)
Activities of daily living	6 (100.0%)	3 (100.0%)
Dependence on medicinal substances and medicinal aid	6 (100.0%)	3 (100.0%)
Work capacity	6 (100.0%)	3 (100.0%)
Social relationship		
Personal relationship	1 (16.7%)	1 (33.3%)
Social support	6 (100.0%)	3 (100.0%)
Sexual activity	6 (100.0%)	2 (66.7%)
Environment		
Freedom, physical safety and security	0 (0%)	0 (0%)
Home environment	5 (83.3%)	0 (0%)
Work satisfaction	5 (83.3%)	0 (0%)
Financial resources	6 (100.0%)	3 (100.0%)
Health and social care	2 (33.3%)	2 (66.7%)
Opportunities for learning	0 (0%)	0 (0%)
Participation in leisure activities	5 (83.3%)	3 (100.0%)
Physical environment	2 (33.3%)	2 (66.7%)
Transport	4 (66.7%)	1 (33.3%)
Spirituality/religious/personal beliefs		
Spirituality/religious/personal beliefs	5 (83.3%)	2 (66.7%)
General QoL and general health perception		
General	4 (66.7%)	3 (100.0%)
Treatment burden	5 (83.3%)	3 (100.0%)

N refers to number of patients.
The numbers of tick marks represent the number of focus group discussions where the relevant QoL domains in each SpA subtypes were discussed.
The domains were adapted from a combination of focus group responses and World Health Organsiation QoL domains

[1] Patients were classified using the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria for axial Spondyloarthritis. [2]Patients were diagnosed with psoriatic arthritis using the 2006 Classification criteria for psoriatic arthritis (CASPAR)
Abbreviations: Spondyloarthritis (SpA), Quality of Life (QoL), focus group discussion (FGD)

The domains “work satisfaction”, “financial resources” and “positive feelings” were relevant to patients with SpA in Singapore but not so in Western patients.

The following quotes illustrate how “work satisfaction”, “financial resources” and “positive feelings” are relevant to QoL to patients with SpA in Singapore:

Work satisfaction

"Basically its actually 6 weeks I have to go back but this is actually under my company claim so my company has been treating me quite well I have been staying in this company for 9 years" English speaking patient with axSpA

"There was once when I had to go for consultation every 2 weeks later, because I still don't know what is the problem, I have to keep going for doctor's appointment. So you will keep taking medical leave, keep going for consultation. Then the boss cannot decide to give you more work or not. Sometimes, I look well but they don't understand it's because of the painkillers. When the boss stress me, my condition worsen." Chinese speaking patient with axSpA

Financial resources

"Cause it's very expensive that one one year at least 20k. Now the new drug, the medicine itself is already 5k which is more expensive than infliximab so after deduct medisave I still have to pay cash" English speaking patient with axSpA

"So then medicine the jab one is very expensive, which I can't afford, it will drain up my savings, so thanks God that time was they, there's a clinical trial, so I was put on the clinical trial, and thanks God again" English speaking patient with PsA

Positive feelings

"Positive attitude because you are already in this situation I mean you only can help yourself" English speaking patient with axSpA

"Yes, because I always feel that, I always think positive that we have now, other people might be more worse than me" English speaking patient with PsA

Relevant QoL domains and subdomains of *different SpA subtypes*

As shown in Table 5, 27 QoL domains were relevant to patients with axSpA and 25 QoL domains were relevant to patients with PsA.

The QoL domains relevant to patients with axSpA and PsA were largely similar. However, there were more environmental concerns, such as “home environment” and “work satisfaction”, brought up by patients with axSpA compared to patients with PsA.

The following quotes illustrate how “home environment” are relevant to QoL to patients with axSpA:

“The mattress is extremely important for me. It has to be very hard, a lot support not the support” English speaking patient with axSpA

“I have to choose the chair for me to sit. Because if it is not suitable, the pain will come. The back here will ache” English speaking patient with axSpA

All QoL subdomains of different subtypes of SpA and quotes for the corresponding QoL subdomains were presented in Supplementary Table 3 and 4 respectively.

Mapping of relevant QoL domains for patients with SpA to currently used PROMs
As shown in Table 6, PROMs for axSpA covered 12 out of the identified 27 domains. PROMs such as SF-36, ASQoL and HAQ-S covered 10, 6 and 6 domains respectively. Using all 3 of these PROMs, SF-36, Dougados Functional Index (DFI), HAQ-S, allowed full coverage of all 12 domains with minimal overlap. HAQ-S, DFI are disease specific PROMs for axSpA while SF-36 is generic PROM.

PROMs for PsA covered 19 out of 25 domains. PROMs such as FACIT-F and SF-36 covered 15 and 10 domains respectively. Usage of all four, SF-36, HAQ, DLQI and FACIT-F will allow coverage of all 19 domains with minimal overlaps. DLQI is a disease specific PROM while FACIT-F, SF-36 and HAQ are non-disease specific PROMs. The PROMs for patients with PsA also covered the QoL domains of relevance to patients with axSpA.

Table 6: QoL domains relevant to patients with SpA in Singapore mapped onto PROMs commonly used in SpA

Subtypes of SpA	Commonly used PROMs in axial SpA[1]					Commonly used PROMs in PsA[2]						
General or disease specific PROMs	**S**	**S**	**S**	**S**	**S**	**G**	**G**	**G**	**S**	**S**	**S**	**G**
Domains	**ASQoL**	**HAQS**	**DFI**	**BASFI**	**BASG**	**PGA**	**Pain**	**SF36**	**DLQI**	**PsAQoL**	**HAQ**	**FACITF**
Physical												
General												
Pain and discomfort	1	1					1	1	1		1	1
Energy and fatigue	1							1		1		1
Sleep and rest	1		1									1
Other symptoms												1
Psychological												
Positive feelings								1				1
Thinking, learning, memory and concentration												
Self-esteem									1			
Bodily image and appearance												
Negative feelings	1							1		1		1
Level of independence												
General	*Not found to be relevant to patients*											
Mobility		1	1	1				1			1	
Activities of daily living	1	1	1	1				1	1	1	1	1
Dependence on medicinal substances and medicinal aid		1									1	
Work capacity		1		1				1	1			1
Social relationship												
Personal relationship	1							1	1	1		1
Social support												1
Sexual activity									1			1
Environment												
Freedom, physical safety and security	*Not found to be relevant to patients*											
Home environment												
Work satisfaction												1
Financial resources												
Health and social care												
Opportunities for learning	*Not found to be relevant to patients*											
Participation in leisure activities				1				1	1	1		1
Physical environment												
Transport		1	1								1	
Spirituality/religious/personal beliefs												
Spirituality/religious/personal beliefs												
Overall QoL and general health perception												
General					1	1		1				1
Treatment burden									1			1

[1] Patients were classified using the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria for axial Spondyloarthritis.
[2] Patients were diagnosed with psoriatic arthritis using the 2006 Classification criteria for psoriatic arthritis (CASPAR).

Not found to be relevant to our population meant that the respective domain was not being elicited from the respective focus group discussions. Abbreviations: Spondyloarthritis (SpA), Psoriatic Arthritis (PsA), Quality of Life (QoL), Health Assessment Questionnaire – Spondyloarthritis (HAQS), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global (BASG), Patient Global Assessment (PGA), Pain Visual Analogue Score (Pain), Ankylosing Spondylitis Quality of Life (ASQoL), Patient-Reported outcome measures (PROMs), Dougados Functional Index (DFI), Short-Form 36 (SF36), Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQoL), Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy – Fatigue (FACITF), Disease-specific PROMs (S), General PROMs (G)

3.5 Discussion

This qualitative study identified QoL domains and subdomains relevant to patients with SpA using focus group methodology in Singapore, an urban Asian setting. This is the first study comparing domains of QoL in different SpA subtypes. Furthermore, the COREQ criteria, which outlines a rigorous approach to qualitative research, was used explicitly.

Relevant QoL domains and subdomains among patients with SpA were similar to those identified in the systematic review conducted in our previous chapter, and the WHOQOL framework can be used to explore the impact of SpA on QoL.(3) This chapter showed that the QoL domains "general level of independence", "freedom, physical safety and security" and "opportunities for learning" are not relevant to patients in Singapore. This may be due to the fact that Singapore is a small country with high connectivity, and therefore accessibility appeared to be of lesser concern to the patients in this study.(74) Also, domains including "positive feelings", "financial resources" and "work satisfaction" are relevant to patients of different SpA subtypes in Singapore but not to their western counterparts (3) because Singapore has a healthcare system that places significant emphasis on individual responsibility on own's health care needs and the need for co-payment.(75) Therefore, support from the employers of patients with SpA through insurance coverage or medical leave may result in better care satisfaction and experience.(76) Hence, this will impact work satisfaction and positive feelings such as optimism, affecting QoL more than for patients in Western settings.

The QoL domains relating to the home environment were relevant to patients with axSpA but not to patients with PsA. This may be due to the impact of spinal stiffness which results in the need for modification of home environment to adapt to the disease.(77)

The findings from this chapter will allow clinicians from Singapore to understand the area of impact of SpA to the patients' QoL, allowing suitable interventions to be

prescribed to treat the disease beyond the medical aspect. For researchers of SpA in Singapore, this provides a foundation for selection of suitable PROMs as well as development and testing of new interventions to improve QoL. For students conducting qualitative study in the field of QoL for the first time, this chapter provides the approach as well as describes the thought processes behind the methodology that students can reference before they start on their first qualitative study.

As shown in this chapter, there are limitations in currently used PROMs in measuring the relevant QoL domains in patients with SpA. However, this chapter showed that patients with different SpA subtypes largely share common domains/subdomains, hence it may be possible to measure QoL in SpA subtypes using a single common platform.(3) One promising PROM, the ASAS Health index, addresses relevant QoL domains such as sexual function, financial resources, and home environment. The ASAS Health Index is a patient derived and unidimensional instrument built upon the International Classification of Functioning, Disability and Health model for measurement of health status in axSpA(60); and it has been culturally adapted in multiple languages and socio-cultural contexts.(78) The ASAS Health Index could potentially be used as a PROM in different SpA subtypes.(55) As the ASAS health index has not been extensively evaluated in PsA, more work is needed to adapt the ASAS HI for PsA. Corroborated with the data presented in this chapter, home environment may not be so relevant to patients with PsA. This chapter supports a common set of domains that applies to both axial and pSpA; however, more work is needed to further evaluate the usage of a similar set of PROMS in both axSpA and pSpA.(79)

This chapter has several limitations. First, there were few patients of Malay and Indian ethnicity in our FGDs and the concerns expressed regarding QoL may not be generalizable to these groups. However, the lower representation of minorities in this chapter is comparable to the ethnic composition of the axSpA cohort in this center and in Singapore.(5, 80, 81) Second, the results may not capture QoL domains affected by SpA in patients from other cultural backgrounds. However, the multi-

ethnic nature of Singapore may allow some applicability of findings to other Southeast Asian countries. Third, there were a relatively small number of patients in each subgroup. However, saturation was reached for each subgroups and the number of FGDs per subgroup was within what is recommended in the literature.(82) Last, use of FGDs may have limited discussions of sensitive issues (e.g. sexual functioning), hence limiting what was expressed. However, the patients were separately requested to list the impact of SpA on their sexual life to reduce this problem.

In conclusion, a wide range of QoL domains and subdomains were relevant to patients with SpA in Singapore, and there were minimal differences between the SpA subtypes. Patients with PsA were less concerned with the home environment and work satisfaction than patients with axSpA. Patients in Singapore were more concerned about financial resources, work satisfaction and positive feelings while less concerned about freedom, physical safety and security. This chapter supports a common set of QoL domains for different SpA subtypes, and it provides evidence for further development and validation of common QoL-specific PROMs for use among patient with SpA. The findings from this chapter gave us the confidence to continue with the validation work of SF-36 and HAQ in Chapter 4 and 5 respectively. Furthermore, during the FGDs, usage of TCM by the patients was a theme derived, therefore giving us strong confidence to start a trial to study a TCM collaborative model in patients with axSpA in Chapter 7.

Chapter 4. Validity and reliability of the Short Form 36 Health Surveys (SF-36) among patients with Spondyloarthritis in Singapore

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4.1 Abstract

Objectives: The SF-36 is a popular QoL PROM. However, few studies have assessed its psychometric properties in patients with SpA. The aim of this chapter is to assess the validity and reliability of the SF-36 in patients with SpA in Singapore.

Methods: Cross-sectional data from a registry of 196 patients with SpA recruited from a dedicated tertiary referral clinic in Singapore from 2011-2014 was used. Analyses were guided by the **CO**nsensus-based **S**tandards for the selection of health **M**easurement **IN**struments (COSMIN) framework. Internal consistency reliability was assessed using Cronbach's alpha. Construct validity was assessed through 33 a priori hypotheses by correlations of the 8 subscales and 2 summary scores of SF-36 with other health outcomes. Known-group construct validity was assessed by comparison of the means of the subscales and summary scores of the SF-36 of patients with SpA and the general population of Singapore using student's t-tests.

Results: Among 196 patients (155 males (79.0%), median (range) age: 36 (17-70), 166 Chinese (84.6%)), SF-36 scales showed high internal consistency ranging from 0.88 to 0.90. Convergent construct validity was supported as shown by fulfillment of all hypotheses. Divergent construct validity was supported, as SF-36 MCS was not associated with PGA, pain and HAQ. Known-group construct validity showed patients with SpA had lower scores of 3.8 to 12.5 when compared to the general population at $p<0.001$.

Conclusions: This chapter supports the SF-36 as a valid and reliable measure of QoL for use in patients with SpA.

4.2 Introduction

SpA is a chronic debilitating disease that affects QoL. SpA is a group of rheumatic diseases with similar features but distinct from other inflammatory arthritis. Features that link this group of rheumatic diseases are an association with HLA-B27, a characteristic pattern of peripheral arthritis that is oligoarticular, asymmetric and predominates in the lower extremities, and possible uveitis, spondylitis, sacroiliitis, dactylitis and enthesitis.(7) Patients with SpA experience significant pain and fatigue.(83, 84) As there are no disease-modifying drugs for SpA, management of patients with SpA tends to focus on improving function and reducing pain so that their QoL can improve.(58)

There is widespread use of PROMs in the management of patients with SpA.(36) Depending only on clinical parameters such as erythrocyte sediment rate has been shown to be a poor reflection of the disease progression of patients with SpA.(84) Hence, instruments such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and BASFI are used in clinical practice to gain a better understanding of patients with SpA.(84)

Other PROMs such as QoL are also gaining importance in the management of patients with SpA as they allow clinicians to understand the overall health state of the patient.(85) There are general and disease specific PROMs to measure QoL of patients with SpA.(86) Both types of PROMs have their advantages and disadvantages. General QoL PROMs allow measurement of all persons irrespective of their type or number of illnesses but they may not be as sensitive to some problems unique to particular diseases.(87) On the other hand, specific PROMs are more targeted and sensitive but make comparison between different patient groups difficult and may be hard to interpret if the person has multiple comorbidities.(87) A specific PROM used in patients with SpA is the ASQoL which allows for more sensitive measurement of the overall health state of patients with SpA.(88) An example of a popular generic QoL PROM is the SF-36, which allows for comparison of health state among other diseases.(89)

While SF-36 is one of the most widely used QoL PROMs in the world, its psychometric properties in patients with SpA are not well studied.(90) Most PROMs used for patients with SpA are PROMs for patients with AS.(91) A study that compared if QoL PROMs used for patients with AS are appropriate for patients with SpA showed good validity and reliability. However, this study was done only in patients with active disease, which does not represent the true situation of most patients.(36) Another study done by Leung et al, however, was done only on the PsA population but not the patients with AS that made up a significant proportion of patients with SpA.(92)

Although there have been psychometric studies of the SF-36 in the subpopulations of SpA such as AS or PsA, till date, few validate and assess its reliability in the SpA population.(36) Therefore, the aim of this chapter is to assess the validity and reliability of English language SF-36 in patients with. In this chapter, the COSMIN framework was followed closely.(93)

4.3 Methods

Study design and data collection

A cross-sectional, Institutional Board Review approved study was conducted using a questionnaire administered in English at the first visit of all consenting patients seen at a dedicated SpA clinic in a tertiary referral hospital in Singapore from 2011-2014. All patients who were diagnosed with SpA using 2009 ASAS Classification Criteria were recruited into a registry.(30, 94)

Demographic characteristics and PROMs including pain scores, global health assessment, BASDAI, BASFI, BASG, HAQ and SF-36 were collected.

Instruments and definitions

SF-36 version 2 is a self-administered generic questionnaire used to measure QoL in eight areas of perceived health. The 36 individual questions make up 8 subscales with

lower scores reflecting poorer health (range 0-100). Norm-based scores were used. The eight subscales are: physical functioning (PF), role limitation due to physical problem (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation due to emotional problem (RE) and mental health (MH). These eight scales were summed with different weights to give two summary scores – physical summary scores (PCS) and mental summary scores (MCS).(95)

HAQ is a self-administered measurement of disability validated for use in Singapore and it ranges from 0-3 with a higher score reflecting worse disability.(96) The 8 domains in HAQ are: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. BASDAI (ranges from 0 - 10) is a self-administered disease specific questionnaire used to measure disease activity with higher values indicating more active disease.(97) There are 6 questions in BASDAI and encompassed domains from fatigue, spinal and peripheral joint pain, tenderness and inflammation. BASFI (ranges from 0 -10) is a self-administered disease specific questionnaire used to measure function with higher values indicating worse functioning.(97) BASG, pain and PGA scores were also collected (ranges from 0-100). BASG, pain and PGA reflect poorer functioning and pain with higher score. Both BASG and PGA reflected the global assessment of the disease over a certain time point.

Statistical analysis

Data analysis was planned a priori and analyzed with STATA SE14.0 for Macintosh. Imputations for missing data were conducted as recommended.(98) The Shapiro-Wilk test was used to investigate the normality of the distribution of the continuous variables. Descriptive statistics were tabulated as median (range) or n (%).

Due to the non-normal nature of the continuous variables, the median and range of the 8 subscales and summary scores of SF-36 were tabulated. Floor and ceiling were reported. Floor is defined as the percentage of observations at the lowest possible value of the scale while ceiling is defined as the percentage of observations at the highest possible value of the scale. Floor or ceiling above 15% is considered to be a matter of concern.(99)

Reliability was defined by the overall consistency of a measure and was measured using internal consistency. A reliable instrument is one where the observed values are true with acceptable errors of measurement.(100) Reliability was studied using internal consistency assuming all items were similar and measure a single construct. Internal consistency is supported if Cronbach's alpha exceeded 0.70.(101)

Validity is the degree to which the instrument is able to measure what it proposes to measure.(100, 102) A valid SF-36 instrument should differentiate the QoL of the patient with different disease characteristics. Inter-scale correlation was conducted to assess the convergent construct validities between the subscales. P values of less than 0.001 were considered as statistically significant after adjusting for multiple testing using Bonferroni's correction.

Construct validities of SF-36 were supported if there were differences between SF-36 with measures of disease activity. Convergent construct validities were tested with 33 a priori hypotheses based on a literature search. The following: a) All 8 subscales of SF-36 were negatively correlated with BASDAI, BASFI and BASG.(103) b) SF-36 PCS was negatively correlated with BASDAI, BASFI, HAQ, BASG, PGA and pain.(104) c) SF-36 MCS was negatively correlated with BASDAI, BASFI and BASG were hypothesized.(105) Divergent construct validity of SF-36 was tested with correlation of SF-36 MCS with HAQ, PGA and pain.(106) Spearman's rank correlation was used to assess the associations. To reduce the likelihood of Type I errors, the p values were adjusted using Bonferroni's correction and p values less than 0.0015 were considered significant.

Also, patients with SpA have poorer SF-36 scores than the general population in Singapore were hypothesized. Values reported by Thumboo et al were used in a psychometric study of SF-36 in the general population of Singapore. The subjects included in that study were reflective of the general population of Singapore and had a balanced gender ratio and a higher proportion of elderly subjects.(107) The construct validity was further supported if the SF-36 scores of patients with SpA were

lower than that of the general population (known groups construct validation). Student's t test was used to understand the differences between SF-36 scores of the general population and patients with SpA.

4.4 Results

Sociodemographic and clinical characteristics

In total, 216 patients were recruited into the registry. There were 9 (4.2%) patients with missing SF-36 data and 11 (5.0%) of the SF-36 questionnaires used were administered in Mandarin. In total, 196 patients remained for analysis as shown in Table 7.

There were 155 (79.1%) male patients and 174 patients had 10 or more years of education (88.8%). The median scores of BASDAI, BASFI, BASG, PGA, Pain and HAQ scores were 3.1 (range: 0-7.9), 1.3 (range: 0-8.4), 35 (range: 0-94), 36 (range: 0-99), 35 (range: 0-99), 0.1 (range: 0-1.5) respectively.

Descriptive statistics of the 8 subscales and summary scores of SF-36

Table 8 shows the median and range of the 8 subscales and 2 summary scores of the SF-36. Significant ceiling effects were seen for PF, RP, SF and RE while no significant floor effects were seen across all scales.

Table 7. Sociodemographic and clinical characteristics of patients with SpA (Validation of SF-36)

Characteristics	Median (range), n (%) (N=196)
Age	36 (17-70)
Gender	
Male	155 (79.1%)
Race	
Chinese	166 (84.7%)
Malay	5 (2.6%)
Indian	11 (5.6%)
Others	14 (7.1%)
Highest education level (Years of education)	
PSLE (6)	15(7.6%)
GCE O and N Level, ITE (10)	36 (18.4%)
GCE A Level (12)	14 (7.1%)
Diploma (13)	50 (25.5%)
Degree (16)	74 (37.8%)
Others	7 (3.6%)
Marital status	
Single	86 (43.9%)
Married	105 (53.6%)
Divorced	4 (2.0%)
Widowed	1 (0.5%)
Living arrangement	
Staying alone	9 (4.6%)
Staying with spouse only	26 (13.3%)
Staying with children and spouse	78 (39.8%)
Staying with my children only	2 (1.0%)
Staying with others	81 (41.3%)
Occupation	
Employer or self-employed	29 (14.8%)
Employee	100 (51.0%)
Full time student	22 (11.2%)
Home-maker	6 (3.1%)
Under compulsory military training	14 (7.1%)
Retiree	7 (3.6%)
Unemployed	18 (9.2%)
Disease duration (years)	3.1 (0-41.2)
Type of SpA[1]	
Axial	190 (96.9)
Non-axial	6 (3.1)
BASDAI (range 0-10)	3.1 (0-7.9)
BASFI (range 0-10)	1.3 (0-8.4)
BASG (range 0-100)	35 (0-94)
PGA (range 0-100)	36 (0-99)
Pain (range 0-100)	35 (0-99)
HAQ (range 0-3)	0.1 (0-1.5)

[1] As diagnosed with 2011 Assessment of Spondyloarthritis International Society (ASAS) criteria. Abbreviation: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BASG), Patient global assessment (PGA), Health Assessment Questionnaire (HAQ), Primary School Leaving Examination (PSLE), Institute of Technical Education (ITE), Spondyloarthritis (SpA)

Reliability

As shown in Table 9, good internal consistency was seen across all 8 subscales of SF-36 with Cronbach's alpha ranging from 0.88 to 0.90.

Table 8. Descriptive statistics for the SF-36

Scales	Median (range)[a]	Median (range)[b]	Skewness	Floor (%)	Ceiling (%)
PF	85.0 (15-100)	50.2 (14.1-57.9)	-0.83	0.0	16.3
RP	81(0-100)	45.6 (1.7-55.8)	-0.66	0.5	31.6
BP	62 (0-100)	39.0 (7.8-58.2)	-0.33	1.5	4.0
GH	57 (5-100)	43.9 (14.4-68.4)	-0.06	0.0	1.0
VT	63 (12-100)	46.4 (14.9-70.0)	0.03	0.0	2.0
SF	75 (0-100)	42.9 (2.4-56.5)	-0.69	0.5	35.7
RE	92 (0-100)	50.4 (-1.8-55.2)	-0.98	0.5	45.9
MH	75 (0-100)	47.0 (-4.3-64.2)	-0.59	0.5	8.1
PCS	NA	45.4 (6.3-62.2)	-0.63	0	0
MCS	NA	46.2 (16.3-71.4)	-0.04	0	0

[a]0-100 scoring was used. [b]Norm-based score was used. Abbreviations: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH), physical component summary (PCS) and mental component summary (MCS).

Construct validity

As shown in Table 9, good construct validity was shown in the inter-scale correlation of the 8 subscales of SF-36. Most of the scales were generally distinct as they showed inter-scale correlations that were low to moderate (0.33 to 0.70). Subscales of similar construct such as PF and RP showed higher inter-scale correlations of 0.75 while those with competing constructs such as RP and MH showed lower inter-scale correlation of 0.37.

Table 9. Inter-scale correlations and internal consistency reliability of the 8 subscales on SF-36

		Inter-scale correlation							
	α	PF	RP	BP	GH	VT	SF	RE	MH
PF	0.89	1.00							
RP	0.89	0.70*	1.00						
BP	0.89	0.63*	0.62*	1.00					
GH	0.89	0.38*	0.45*	0.41*	1.00				
VT	0.89	0.43*	0.47*	0.54*	0.58*	1.00			
SF	0.88	0.60*	0.62*	0.59*	0.46*	0.56*	1.00		
RE	0.88	0.50*	0.64*	0.45*	0.42*	0.44*	0.63*	1.00	
MH	0.89	0.38*	0.33*	0.41*	0.55*	0.68*	0.58*	0.56*	1.00

*p<0.001. Abbreviations: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH), physical component summary (PCS) and mental component summary (MCS), Cronbach's alpha (α)

In terms of convergent construct validity, there were significant associations between the 8 subscales and summary scores with BASDAI, BASFI, BASG, pain, PGA and HAQ. As shown in Table 10, all of the 33 associations assessed were statistically significant with p values less than 0.0015. Divergent construct validity was supported, as MCS was not associated with pain, PGA and HAQ.

Table 10. Construct validities of SF-36: Spearman's rank correlation when compared with BASDAI, BASFI, BASG, pain, PGA and HAQ

	Spearman's correlation coefficient					
	BASDAI	BASFI	BASG	Pain	PGA	HAQ
PF	-0.52*	-0.71*	-0.50*	-0.50*	-0.51*	-0.72*
RP	-0.48*	-0.53*	-0.50*	-0.45*	-0.44*	-0.57*
BP	-0.70*	-0.62*	-0.66*	-0.70*	-0.63*	-0.59*
GH	-0.34*	-0.31*	-0.39*	-0.27*	-0.25*	-0.33*
VT	-0.50*	-0.40*	-0.40*	-0.35*	-0.32*	-0.35*
SF	-0.42*	-0.48*	-0.41*	-0.38*	-0.35*	-0.50*
RE	-0.38*	-0.34*	-0.32*	-0.31*	-0.28*	-0.35*
MH	-0.35*	-0.29*	-0.34*	-0.26*	-0.24*	-0.27*
PCS	-0.51*	-0.58*	-0.49*	-0.51*	-0.49*	-0.61*
MCS	-0.34*	-0.25*	-0.32*	-0.22	-0.20	-0.22

*p<0.0015. Corrected using Bonferroni's correction as 33 a priori hypotheses were tested. Abbreviations: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH), physical component summary (PCS), mental component summary (MCS), Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis fatigue index (BASFI), Bath ankylosing spondylitis global score (BASG), patient's global assessment (PGA) and health assessment questionnaire (HAQ).

In terms of known groups validation in Table 11, construct validity was further strengthened as norm-based subscales and scores of SF-36 showed significantly poorer scores compared to the general population.

Table 11. SF-36 scores of patients with SpA compared with general population in Singapore

Scale	Mean ± SD	P-value
PF[a]		
SpA, n =196	46.3±10.6	<0.001
SG, n= 6151	50.0±10.0	
RP[a]		
SpA, n =196	42.6±13.1	<0.001
SG, n= 6151	50.0±10.0	
BP[a]		
SpA, n =196	37.5±11.1	<0.001
SG, n= 6151	50.0±10.0	
GH[a]		
SpA, n =196	43.5±12.1	<0.001
SG, n= 6151	50.0±10.0	
VT[a]		
SpA, n =196	44.3±11.8	<0.001
SG, n= 6151	50.0±10.0	
SF[a]		
SpA, n =196	44.7±11.5	<0.001
SG, n= 6151	50.0±10.0	
RE[a]		
SpA, n =196	44.5±12.7	<0.001
SG, n= 6151	50.0±10.0	
MH[a]		
SpA, n =196	44.8±13.1	<0.001
SG, n= 6151	50.0±10.0	
PCS[a]		
SpA, n =196	42.7±11.8	<0.001
SG, n= 6151	50.0±10.0	
MCS[a]		
SpA, n =196	44.9±11.9	<0.001
SG, n= 6151	50.0±10.0	

[a]All scales were converted to norm base as compared with normal population of Singapore with mean±SD of 50.0±10.0. Abbreviations: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH), physical component summary (PCS), mental component summary (MCS), spondyloarthritis patients (SpA) and Singapore (SG)

4.5 Discussion

Validation is required before a QoL PROM can be used. The results from this chapter showed that SF-36 is a valid and reliable measure to be used in patients with SpA in Singapore. This result coincides with what is recommended by Van et al i.e. that SF-36 is a suitable PROM to be used in the SpA population.(108) This is the first study done on a dedicated SpA population that has both active and inactive disease activity. Following the COSMIN guidelines, controlling for multiple testing and formulating hypotheses a priori were key strengths of the study.

Psychometric properties of the SF-36 in this paper showed that SF-36 is both valid and reliable. The results were comparable to a study done by Thumboo et al in terms of internal consistency, construct validity, flooring effect and ceiling effect. (107) There was good internal consistency of at least 0.88. Construct validity was well supported when the SF-36 scores of the SpA population were lower when compared to the general population. The differences of all scales when compared were more than 3 points, which was suggested by the minimal important clinical difference of SF-36.(91, 95) Although age was not adjusted for, the results should show a smaller reduction in the SF-36 compared to the general population if the scores were adjusted for age.(109) The moderate interscale correlation showed that the SF-36 was measuring a unique concept and the discriminant construct validity shown in this study was similar to that done by Revicki et al.(95) The lack of association between the MCS and pain, HAQ and PGA supported the divergent construct validity of SF-36 and the confirmation of all 33 hypothesized associations supported its convergent construct validity.(106) The ceiling and floor effect (RP 31.6 and 0.5%, RE 45.9 and 0.5%) is an improvement compared to a study done by Leung et al on patients with PsA (RP 42.9 and 26.8%, RE 39.4 and 36.9%). This may be due to the expanded Likert scale in version 2 as compared to the previous version of SF-36. However, caution has to be exercised in interpretation of the results as Leung et al conducted her study in Hong Kong on patients with PsA.(92)

This successful psychometric assessment of the SF-36 will give confidence to rheumatologists in Singapore in using this scale to measure QoL of patients with SpA. It also allows researchers to understand the issues regarding validation and how to design a better study in future. The usage of COSMIN as a guide will allow new students attempting to validate a PROM to have greater support while understanding the technical language of psychometric assessment.

A limitation of this chapter is that the results may not be able to generalize to other populations, even to other multi-racial and multi-cultural contexts like Malaysia; ideally, SF-36 should be further validated in these populations. Although COSMIN's framework was followed as closely as possible, test-retest reliability, inter- and intra-rater reliability, measurement errors and responsiveness were not assessed as this was a cross-sectional design. Cross-cultural and criterion validity were not assessed as there is currently no gold standard and the questionnaires were administered in English. Furthermore, results from factor analysis were not presented: latent factors are likely not meaningful unless sample sizes exceed a few hundred, as recommended by Jung et al.(110) Nevertheless, this chapter serves as a foundation for future psychometric work in patients with SpA.

In conclusion, this chapter supports the construct validity and reliability of SF-36 version 2 as an outcome measure in patients with SpA. This chapter provides evidence for researchers and clinicians to use SF-36 as a PROM for comparison across patients with different diseases and conditions. Together with findings from Chapter 2 and 3, this chapter gave me the confidence to use the SF-36 as an outcome measure in both Chapter 6 and 7.

Chapter 5. Validity and reliability of the Health Assessment Questionnaire (HAQ) among patients with Spondyloarthritis in Singapore

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Kwan, Y. H., Fong, W., Lui, N. L., Yong, S. T., Cheung, Y. B., Malhotra, R., Thumboo, J., & Ostbye, T. (2018). Validity and reliability of the Health Assessment Questionnaire among patients with spondyloarthritis in Singapore. *Int J Rheum Dis*, 21(3), 699-704.

5.1 Abstract

Objectives: The HAQ is a popular tool used to measure function. Few studies have assessed its psychometric properties in patients with Spondyloarthritis (SpA). This chapter aimed to assess the validity and reliability of the HAQ in patients with SpA in Singapore.

Methods: Cross-sectional data from a registry of 196 patients with SpA recruited from a dedicated tertiary referral clinic in Singapore from 2011-2014 was used. Analyses were guided by the COSMIN framework. Internal consistency reliability was assessed using Cronbach's alpha. Convergent construct validity was assessed by 30 a priori hypotheses through correlation of the summary score and the 8 domain scores of the HAQ with other PROMs - BASDAI, BASFI, BASG, pain, PGA and SF-36. Divergent construct validity was assessed by poor correlation of HAQ with SF-36 MCS.

Results: Among 196 patients (155 males (79.0%) Median (Range) Age: 36 (17-70); 166 Chinese (84.6%)), the HAQ showed a high internal consistency of 0.78 to 0.84. Convergent validity was supported by achieving 26 out of the 30 a priori hypotheses. Divergent validity was also established- correlation of SF-36 MCS with 7 domains and summary scores of the HAQ were not statistically significant.

Conclusions: This chapter supports the HAQ as a valid and reliable measure of function for use in patients with SpA.

5.2 Introduction

SpA is a multi-faceted chronic disease that can cause severe limitations in function.(57) Patients with SpA experience fatigue, pain, (83, 84) and in some patients limited mobility of the spine. As there are no disease-modifying drugs for SpA, management of patients with SpA currently focuses on improving function and reducing pain so that their health-related quality of life can improve.(58)

The OMERACT has defined the HAQ as one of the core domain outcomes set used in patients with SpA.(111) The HAQ is a popular instrument used to measure function in rheumatology(112) and is highly correlated with function as shown in many studies.(85, 113)

Although HAQ is one of the core domain PROMs in SpA recommended by OMERACT, it is surprising that so few studies have been done in Asia. Earlier studies have focused mostly on disease specific PROMs like HAQ-S, and the PsAQoL tool or on rheumatologic diseases like rheumatoid arthritis and systematic sclerosis. (114-117) Outcome measures are heavily influenced by socio-cultural context, hence ideally the psychometric properties of HAQ need to be assessed in every new context that it is intended to be used.(19)

Therefore, the aim of this chapter is to assess the validity and reliability of the English language HAQ in Singapore. The COSMIN framework was followed closely.(93)

5.3 Methods

Study design and data collection

A cross-sectional, institutional board review approved study was conducted using the questionnaire that were administered in English at the first visit of all consenting patients seen at a dedicated SpA clinic in a tertiary referral hospital in Singapore from

2011-2014. All patients who fulfilled the ASAS Classification Criteria 2009 were recruited into a registry.(30, 94)

Demographic characteristics and patient reported outcomes including pain scores, global health assessment, BASDAI, BASFI, BASG, HAQ and SF36 were collected through questionnaire. Radiographic progression was captured using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).

Instruments and definitions

HAQ is a self-administered questionnaire to measure disability and ranges from 0-3 with a higher score reflecting worse function.(96) It includes 8 domains namely dressing, arising, eating, walking, hygiene, reach, grip and daily activities.

SF36 version 2 is a self-administered generic questionnaire used to measure QoL in eight areas of perceived health. The 36 individual questions make up 8 subscales with lower scores reflecting poorer health. Norm-based scores were used whereby 50 represent the mean and 10 represent the standard deviation. Norm-based scores are simpler to interpret and easier to compare across subscales. The eight subscales are: physical functioning, role limitation due to physical problem, bodily pain, general health, vitality, social functioning, and role limitation due to emotional problem and mental health. These eight scales were summed with different weights to give two summary scores – PCS and MCS. (95) The SF36 has been widely validated in many countries including Singapore.(107)

BASDAI (ranges from 0 - 10) is a self-administered disease specific questionnaire used to measure disease activity with higher values indicating more active disease.(97) There are 6 questions in BASDAI and encompass domains from fatigue, spinal and peripheral joint pain, tenderness and inflammation. BASFI (ranges from 0 -10) is a self-administered disease specific questionnaire used to measure function with higher values indicating worse functioning.(97) BASG, pain and PGA scores were also

collected (ranges from 0-100). BASG, pain and PGA reflect poorer functioning and pain with higher score. Both BASG and PGA reflected the global assessment of the disease over a certain time point. The mSASSS (range: 0 to 72) is a clinician-scored radiographic score used to measure radiographic progression. It scores every corner of the anterior site of the lumbar and cervical vertebrae. Higher scores reflect poorer radiographic progression.

Statistical analysis

Data was analyzed with STATA SE14.0 for Macintosh. Imputations for missing data were conducted as recommended.(98) Descriptive statistics were tabulated as median (range) or n (%).

The median (range) of the 8 domains and summary score of HAQ were tabulated. Reliability was defined by the overall consistency of a measure and was measured using internal consistency. A reliable instrument is one where the observed values are true with acceptable errors of measurement.(100) Reliability was studied using internal consistency, assuming all items were similar and measured a single construct. Internal consistency is supported if Cronbach's alpha exceeded 0.70. (101)

Validity is the degree to which the instrument is able to measure what it proposes to measure.(100, 102) A valid HAQ should differentiate the disability of the patient with different disease characteristics. Construct validity was studied. Convergent construct validity of HAQ was tested using 30 a priori hypotheses based on a literature search.(91) The following hypotheses were generated: a) The 8 domains of HAQ were positively correlated with BASDAI, pain and PGA (except eating domain);(118) b) the summary score of HAQ was positively correlated with BASDAI, BASFI, BASG, PGA and pain and negatively correlated with SF-36 PCS;(104, 118) c) the Spearman's correlation coefficient of summary score of HAQ with BASFI was higher than BASDAI.(105) Spearman's rank correlation was used to assess the associations. Divergent construct validity of HAQ was tested with correlation of SF-36 MCS and mSASSS with the domains and summary scores of HAQ.(106, 119) To reduce the likelihood of type I

errors due to multiple comparisons, the p values using Bonferroni's correction were adjusted so that only p values less than 0.0016 were considered significant.

5.4 Results

Table 12. Sociodemographic and clinical characteristics of patients with SpA (Validation of HAQ)

Characteristics	Median (range), n (%) (N=196)
Age	36 (17-70)
Gender	
Male	155 (79.1%)
Race	
Chinese	166 (84.7%)
Malay	5 (2.6%)
Indian	11 (5.6%)
Others	14 (7.1%)
Highest education level (Years of education)	
PSLE (6)	15(7.6%)
GCE O and N Level, ITE (10)	36 (18.4%)
GCE A Level (12)	14 (7.1%)
Diploma (13)	50 (25.5%)
Degree (16)	74 (37.8%)
Others	7 (3.6%)
Marital status	
Single	86 (43.9%)
Married	105 (53.6%)
Divorced	4 (2.0%)
Widowed	1 (0.5%)
Living arrangement	
Staying alone	9 (4.6%)
Staying with spouse only	26 (13.3%)
Staying with children and spouse	78 (39.8%)
Staying with my children only	2 (1.0%)
Staying with others	81 (41.3%)
Occupation	
Employer or self-employed	29 (14.8%)
Employee	100 (51.0%)
Full time student	22 (11.2%)
Home-maker	6 (3.1%)
Under compulsory military training	14 (7.1%)
Retiree	7 (3.6%)
Unemployed	18 (9.2%)
Disease duration (years)	3.1 (0-41.2)
Type of SpA[1]	
Axial	190 (96.9)
Non-axial	6 (3.1)
Peripheral manifestations	
Uveitis	37 (18.8%)
Tenosynovitis	8 (4.0%)
Enthesitis	24 (12.2%)
Dactylitis	6 (3.0%)
Skin problems	19 (9.6%)
BASDAI (range 0-10)	3.1 (0-7.9)
BASFI (range 0-10)	1.3 (0-8.4)
BASG (range 0-100)	35 (0-94)
PGA (range 0-100)	36 (0-99)
Pain (range 0-100)	35 (0-99)
mSASSS (range 0-72)	1.5 (0-72)
SF-36 PCS (range 0-100)	45.4 (6.3-62.2)
SF-36 MCS (range 0-100)	46.2 (16.3-71.4)

[1] As diagnoses with 2011 Assessment of Spondyloarthritis International Society (ASAS) criteria. Abbreviation: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BASG), Patient global assessment (PGA), modified Stokes Ankylosing Spondylitis Spine Score (mSASSS), Short Form-36 Health Survey (SF-36), physical component summary (PCS), mental component summary (MCS), Primary School Leaving Examination (PSLE), Institute of Technical Education (ITE) and Spondyloarthritis (SpA)

Sociodemographic and clinical characteristics

In total, 216 patients were recruited into the registry. A total of 20 patients, comprising 9 (4.2%) patients with missing HAQ data and 11 (5.0%) patients administered the questionnaire in Mandarin, were excluded from the analysis. Characteristics of the 196 patients in the analysis sample are shown in Table 12. There were 155 (79.1%) male patients and 174 patients had 10 or more years of education (88.8%).

Descriptive statistics of the 8 domains and summary score of HAQ

Table 13 shows the median and range of the 8 domains and summary score of the HAQ.

Table 13. Descriptive statistics and internal consistency for the HAQ

Domains	Median (range)	α
Dressing	0 (0-2)	0.79
Arising	0 (0-3)	0.79
Eating	0 (0-1.1)	0.83
Walking	0 (0-2)	0.80
Hygiene	0 (0-2)	0.80
Reach	0 (0-3)	0.78
Grip	0 (0-2)	0.84
Daily activities	0 (0-3)	0.78
HAQ	0.1 (0-1.5)	-

Abbreviations: Health Assessment Questionnaire (HAQ), Cronbach's alpha (α)

Reliability

As shown in Table 13, good internal consistency was seen for all 8 domains of the HAQ, with Cronbach's alpha ranging from 0.78-0.84.

Construct validity

In terms of convergent validity, there were significant associations between the 8 domains and summary score of the HAQ with BASDAI, BASFI, BASG, pain, PGA and SF36 PCS and MCS. As shown in Table 14, 26 out of 30 associations assessed were statistically significant with p values less than 0.0016. In terms of divergent construct validity, the correlations of the 7 domains and summary scores of the HAQ and SF-36 MCS were not statistically significant. The correlations between the domains and summary scores of HAQ and mSASSS were also not statistically significant.

Table 14. Construct validity of HAQ: Spearman's rank correlation when compared with BASDAI, BASFI, BASG, pain, PGA and SF-36 PCS and MCS.

	Spearman's correlation coefficient						
	BASDAI	BASFI	BASG	Pain	PGA	PCS	MCS
Dressing	0.41*[A]	0.58*	0.33*	0.38*[A]	0.35* [A]	-0.46*	-0.25*
Arising	0.52*[A]	0.71*	0.43*	0.46*[A]	0.41* [A]	-0.49*	-0.17
Eating	0.14	0.15	0.10	0.11	0.07[A]	-0.25*	-0.01
Walking	0.37*[A]	0.47*	0.37*	0.30*[A]	0.34*[A]	-0.48*	-0.11
Hygiene	0.30*[A]	0.45*	0.22	0.29*[A]	0.25*[A]	-0.33*	-0.15
Reach	0.46*[A]	0.65*	0.34*	0.44*[A]	0.42*[A]	-0.52*	-0.15
Grip	0.21	0.25*	0.22	0.14	0.23*[A]	-0.28*	-0.03
Daily activities	0.41*[A]	0.63*	0.29*	0.40*[A]	0.34*[A]	-0.50*	-0.22
HAQ	0.56*[A]	0.79*[AA]	0.47*[A]	0.52*[A]	0.50*[A]	-0.64*[A]	-0.22

*p<0.0016. [A]Confirmed hypothesis. Corrected using Bonferroni's correction as 30 a priori hypotheses were tested. Abbreviations: Physical component summary (PCS), mental component summary (MCS), Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis fatigue index (BASFI), Bath ankylosing spondylitis global score (BASG), patient's global assessment (PGA) and health assessment questionnaire (HAQ).

5.5 Discussion

This chapter provides support for the validity and reliability of the HAQ questionnaire in patients with SpA in a multi-ethnic population in Singapore. HAQ is a PROM that is well validated in many other countries and disease conditions.(96) This chapter provides good evidence for usage of HAQ in patients with SpA in Singapore. Key strengths of the study were following the COSMIN guidelines and controlling for multiple testing and formulating hypotheses a priori in context of convergent and divergent validity.

There was good internal consistency of at least 0.78. Construct validity was supported with the confirmation of 26 out of the 30 hypothesized associations between HAQ and BASDAI, BASFI, BASG, pain, PGA and SF-36. One possible reason for lack of association of the grip domain of HAQ with BASDAI is that grip is more closely associated with disease of the hand joints.(120) Furthermore, in diseases involving limited function, HAQ domains correlate more strongly to PCS than MCS.(106, 121)

HAQ has been adapted and modified for patients with SpA with the disease specific HAQ-S.(116) The difference between HAQ-S and HAQ is the added domains of driving and other activities primarily involving the neck and spinal motion.(116) However, HAQ can be used as a generic PROM that measures function across different diseases.(87, 122) Being able to use a general HAQ rather than a specific HAQ will allow rheumatologists to implement standardized PROMs routinely in a busy clinical

practice and compare function status across patients with various rheumatologic conditions, saving time and manpower needs.(56) This chapter provides further support for this approach, boosting confidence to researchers and clinicians using HAQ and further extends the socio-cultural context where HAQ can be used. Budding researchers can follow my approach and use COSMIN as a guide to their validation work.

A limitation of this chapter is that the results may not be able to be generalized to other Asian populations – though the data do provide a basis for conducting such studies and for comparisons with such studies in the future. Although the COSMIN framework was followed, some aspects of this framework such as test-retest reliability, inter and intra rater reliability, measurement errors and responsiveness could not be tested as this was a cross-sectional design. Cross-cultural and criterion validity were not assessed as there is currently no gold standard and the questionnaires were administered in English. Results from factor analysis were not presented: latent factors are likely not meaningful unless sample sizes exceed a few hundred, as recommended by Jung et al.(110) Furthermore, qualitative work around HAQ was not performed, however, a qualitative study will be conducted in the near future. Nevertheless, this chapter serves as a foundation for future psychometric studies in patients with SpA.

In conclusion, this chapter supports the construct validity and reliability of HAQ as a PROM to measure function in patients with SpA. This chapter gives greater confidence for researchers and clinicians using this PROM in their practice, in Singapore. Together with findings from Chapter 2 and 3, this chapter gave me the confidence to use the HAQ as an outcome measure in both Chapter 7.

Chapter 6 – Are extra-spinal symptoms associated with quality of life in patients with axial spondyloarthritis? A 1-year follow-up study

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Kwan, Y. H., Fong, W., Leung, Y. Y. Lui, N. L., Tan, C.S., Malhotra, R., Ostbye, T., & Thumboo, J. (2019). Are extra-spinal symptoms associated with poorer quality of life in patients with axial Spondyloarthritis? A 1-year follow up study. Clin Rheum. 38(7): 1881-1887.

6.1 Abstract

Objectives: To assess the extent to which a history of extra-spinal symptoms (including peripheral arthritis, enthesitis or dactylitis) (HPED) is associated with QoL in patients with axSpA at baseline and 1-year follow-up.

Methods: Data from 138 patients with axSpA from a tertiary referral center in Singapore, seen between 2011 and 2015, was analysed. Demographic, clinical variables and patient-reported outcomes (ASQoL and SF-36) at baseline and 1-year follow up were collected. Linear mixed models to assess the association of HPED with QoL at baseline and 1-year post-baseline were used.

Results: Among 138 patients (mean age: 39.3 years, 74.6% males, 87.6% Chinese, disease duration: 7.4 years), HPED was associated with poorer QoL for 3 of 8 SF-36 domains [RP scores β − 8.38, $p < 0.05$; SF scores β − 6.74, $p < 0.05$; RE scores β − 9.37, $p < 0.01$] and SF-36 PCS (β − 4.52, $p < 0.01$) scores, but not ASQoL scores. At 1-year post-baseline, HPED was associated with poorer ASQoL (β 1.61, $p < 0.05$) scores, SF-36 PCS (β − 5.61, $p < 0.01$) scores, and three out of eight SF-36 domains (PF scores β − 9.60, $p < 0.01$; RP scores β − 12.17, $p < 0.01$; RE scores β − 7.87, $p < 0.05$). HPED was associated with QoL in patients with axSpA.

Conclusions: HPED was associated with QoL in patients with axSpA. After one year, patients with HPED has poorer QoL especially for physical health domains than patients without HPED.

6.2 Introduction

SpA is a heterogeneous inflammatory chronic disease that can cause severe limitations in function.(57) Patients with SpA experience fatigue, pain(83, 84) and in some patients limited spinal mobility. SpA is classified into axSpA or pSpA. Patients with AS and non-radiographic axSpA are classified as having axSpA, while patients with PsA, IBD-related arthritis and reactive arthritis are predominantly classified as pSpA.(123) It is of note that patients with axSpA or pSpA can have peripheral arthritis, enthesitis or dactylitis. It is debatable whether axSpA or pSpA should be separated or grouped in assessing outcomes, and the influence of peripheral arthritis, enthesitis or dactylitis in both axSpA and pSpA remains unclear.(3, 79)

As there are few if any disease-modifying drugs for axSpA, management of patients with axSpA currently focuses on improving function and reducing pain to improve QoL.(124) QoL refers to a patient's subjective perception of well-being,(19) and can be measured using generic or disease-specific PROMs.(3) Generic PROMs allow for comparison across diseases while disease-specific PROMs usually are generally more sensitive to changes than generic PROMs.(14, 125) Of the possible domains encompassed by QoL, physical function, fatigue, pain and patient global assessment have been identified as the core domains for ASAS outcome measures for AS.(12) These core domains have also been found to be relevant to QoL among patients with SpA.(3, 126, 127)

Patients with peripheral arthritis in AS have poorer QoL and more aggressive disease than patients without peripheral arthritis.(128) Furthermore, 40 to 60% of patients with axSpA have peripheral arthritis, enthesitis or dactylitis.(129) The qualitative study in chapter 3 showed that patients with axSpA who have HPED have greater number of affected QoL domains (i.e.. body image and appearance, personal relationship and thinking, learning, memory and concentration) than patients without HPED.(4) HPED was found to be associated with HLA-B15.(130)

There have been no studies investigating the association of HPED at baseline with QoL in patients with axSpA, and whether this association differs over time. Therefore, this chapter aimed to assess if HPED are associated with poorer QoL in patients axSpA at baseline and 1-year post-baseline. In all analyses, the ASQoL was used as the primary outcome and the eight domains of the SF-36 and its relevant summary scales were used as secondary outcomes.

6.3 Methods

Study Design

Data from the PREcision medicine in SPondyloarthritis for better Outcomes aNd Disease remission (PRESPOND) registry was used. Data from PRESPOND was collected from a tertiary referral center in Singapore, from January 2011 to July 2015.

Subjects

All patients recruited into the PRESPOND registry were over 18 years old and fulfilled the 2009 ASAS criteria for axSpA. For our analysis, the analysis was limited to patients who had complete QoL data at both baseline and 1-year.

Data collection

Demographic characteristics and clinical data PROMs at point of recruitment (baseline) and 1 year later were prospectively collected using a standardized, pre-tested data collection form.

Demographic data included age, gender, ethnicity, marital status and education status. Disease duration, erythrocyte sedimentation rate, comorbidities, HLA-B27, extra-articular and extra-spinal features of SpA, family history of SpA, current treatment and Bath Ankylosing Spondylitis Metrology Index (BASMI) (range 0-10, higher scores reflect poorer metrological measurement) were collected as part of the clinical assessment. BASDAI (range 0-10, higher scores reflect higher disease activity), BASFI (range 0-10, higher scores reflect poorer functioning), BASG (range 0-

100, higher scores reflect poorer patient's opinion of disease), pain visual analog scale (VAS) (range 0-100, higher scores reflect more pain), HAQ (range 0-3, higher scores reflect poorer function) were also collected. The ASQoL and SF-36 were self-administered in English as PROMs. If a patient had difficulties reading, the interviewer administered the questionnaire.

Independent variable: HPED

HPED was the independent variable in this study. HPED was present if peripheral arthritis, enthesitis or dactylitis (or some combinations of these three) was reported by the attending rheumatologist in the past using a standardized pre-tested data collection form. HPED was selected because the qualitative study in chapter 3 revealed that patients with HPED have greater impact on QoL than patients without HPED.(4)

Outcome: QoL

The primary outcome was ASQoL scores, while the 8 domains of the SF-36 and the physical and mental component summary scores of the SF-36 were the secondary outcomes. Both ASQoL and SF-36 were validated PROMs to measure QoL in Singapore.(5, 131)

ASQoL

ASQoL is a patient-derived and disease specific measure of QoL for axSpA. It consists of 18 items with a yes (scored as 1) or no (scored as 0) response to each item. All item scores are summed to a total 0-18 score(132), with *higher* scores indicating *worse* QoL. It comprised questions involving mobility, dressing, activities of daily living, emotions, sleep, social activities, fatigue, energy, pain and stiffness. In terms of measurement properties, the ASQoL was found to have the highest level of evidence among other PROMs for use in patients with axSpA.(14)

SF-36

The SF-36 version 2 is a self-reported generic Health Related Quality of life (QoL) questionnaire. It comprises of 8 health domains: physical functioning (PF), physical role functioning (RP), emotional role functioning (RE), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF) and mental health (MH). The eight domains are further summarized into physical component summary (PCS) and mental component summary (MCS) scores. PCS and MCS are norm-based scores with a mean of 50 and a standard deviation of 10, with *higher* scores indicating *better* QoL.(133)

Statistical analysis

Descriptive statistics are presented as frequencies and percentages or means and standard deviations. Shapiro-Wilk test was used to determine normality. Continuous data were analyzed using Student's t-test or Wilcoxon rank sum test as appropriate while categorical data were analyzed using either chi-square test or Fisher's exact test as appropriate.

To assess the association of HPED with QoL in patients with axSpA at baseline (i.e. cross-sectionally), Student's t-test or Wilcoxon rank sum test was used as appropriate to assess the difference of QoL scores between the patients with or without HPED at baseline.

To assess the association of HPED with QoL in patients with axSpA, a linear mixed model with random subject effect was developed in stages. Linear mixed model was selected as we have repeated measures in our dependent variable and linear mixed model allows us to adjust for autocorrelations. (134) Linear mixed model is also superior to generalized estimating equation when using data with significant missingness and of smaller sample size.(135) The initial model has HPED included as the sole independent variable (Model 1) and QoL (ASQoL or SF-36) as the outcome variable separately. The model was then adjusted with age, gender, comorbidities, disease activity, treatment and disease duration as confounders (Model 2).(136) These confounders were chosen because they had been shown to be associated with QoL in the literature and were tested to be associated with HPED and QoL in our

univariate analyses. Collinearity was checked for and all variables have variance inflation factor of less than 5 before being included in the model.

To assess the association of HPED with QoL at baseline and 1-year post-baseline, the time of assessment (baseline or 1-year) and an interaction term between HPED at baseline and time of assessment were added as independent variables (Model 3). The mathematical equation representing Model 3 can be found in the Supplementary Figure 5.

STATA SE15.0 was used for all analyses and p values less than 0.05 were considered statistically significant.

Ethical approval

This study was conducted with the approval of the SingHealth Centralized Institutional Review (CIRB Ref 2012/498/E) and written informed consent was obtained from all patients before commencement of the study.

6.4 Results

Study sample

This study included 138 patients with axSpA, of whom 85 (61.5%) had HPED (or some combination of these three). As shown in Table 15, there were fewer males (67.0% vs 86.7%; p=0.01), more patients were on sulphasalazine (27.0% vs 7.5%; p<0.01) and more patients with higher BASDAI scores (3.7±1.8 vs 2.6±1.6; p<0.01) when comparing patients with and without HPED respectively.

Table 15. Characteristics of axSpA patients with and without extra-spinal features (HPED)

Characteristics	Total (n=138)	With HPED (n=85)	Without HPED (n=53)	P value
Age	39.3±17.1	39.3±9.3	39.4±25.2	0.22
Male	103 (74.6)	57 (67.0)	46 (86.7)	0.01
Chinese ethnicity	121 (87.6)	75 (88.2)	46 (86.7)	0.80
Marital status				

Single	58 (42.0)	33 (38.8)	25 (47.1)	0.51
Married	75 (54.3)	48 (56.4)	27 (50.9)	
Others	5 (3.6)	4 (4.7)	1 (1.8)	
Education (years of education)				
No formal education	1 (0.7)	1 (1.1)	0 (0)	0.12
Primary School (6)	3 (2.1)	3 (3.5)	0 (0)	
GCE O or N Level (10)	37 (26.8)	28 (32.9)	9 (16.9)	
GCE A Level or Diploma (13)	47 (34.0)	24 (28.2)	23 (43.4)	
Degree (16)	45 (32.6)	26 (57.7)	19 (35.8)	
Others	5 (3.6)	3 (3.5)	2 (3.7)	
Disease duration (years)	7,4±8.7	8.3±9.2	5.8±7.6	0.09
Disease subtypes				
Ankylosing Spondylitis	121 (87.6)	74 (87.0)	47 (88.6)	0.77
Non-radiographic axSpA	17 (12.4)	11 (13.0)	6 (11.4)	
BASMI (0-10)	2.8±2.2	2.9±2.3	2.6±2.0	0.49
Presence of HLA-B27 allele	116 (84.6)	76 (89.4)	40 (76.9)	0.05
Peripheral arthritis[a]	64 (46.3)	64 (75.2)	0 (0)	<0.01
Dactylitis[a]	10 (7.2)	10 (11.7)	0 (0)	<0.01
Heel enthesitis[a]	46 (33.3)	46 (54.1)	0(0)	<0.01
Uveitis[a]	43 (31.1)	30 (35.2)	13 (24.5)	0.18
Psoriasis[a]	4 (2.9)	2 (2.3)	2 (3.7)	0.63
Inflammatory bowel disease[a]	7 (5.0)	5 (5.8)	2 (3.7)	0.70
Family history of SpA	21 (15.2)	13 (15.2)	8 (15.0)	0.97
On biologics currently	10 (7.2)	8 (9.4)	2 (3.8)	0.21
On sulphasalazine currently	29 (21.0)	23 (27.0)	4 (7.5)	<0.01
PROMs				
BASDAI (0-10)	3.3±1.8	3.7±1.8	2.6±1.6	<0.01
BASFI (0-10)	2.0±2.0	2.4±2.2	1.4±1.5	0.01
BASG (0-100)	36.4±21.1	39.5±21.3	31.3±19.8	0.03
Pain (0-100)	32.4±23.8	38.1±23.6	22.7±20.9	<0.01
HAQ Score (0-3)	0.2±0.3	0.3±0.4	0.1±0.2	0.02

Date presented as frequency (%) or mean ± standard deviation.

[a]Ever presence of symptoms

Abbreviation: Presence of peripheral arthritis, enthesitis or dactylitis at baseline, ever (HPED), axial spondyloarthritis (axSpA), spondyloarthritis (SpA), erythrocyte sedimentation rate (ESR), Patient-reported outcomes measures (PROMs), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functioning Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Global Score (BASG), Patient Global Assessment (PGA), Health Assessment Questionnaire (HAQ)

Association of HPED with QoL in patients with axSpA at baseline: cross-sectional analyses

As shown in Table 16, patients with HPED had poorer QoL as shown by higher ASQoL scores (4.6±4.5 vs 2.3±2.9; p<0.01) when compared to patients without. Patients with HPED also had lower scores for all SF-36 domains except GH (51.5±21.5 vs 58.1±21.8; p=0.08), MH (69.4±17.4 vs 75.2±16.5; p=0.05) and MCS (42.7±11.5 vs 46.3±12.2; p=0.08) compared to patients without HPED.

Table 16. Quality of life of patients with axSpA with and without extra-spinal features (HPED) at baseline: cross-sectional analyses

Characteristics	**Total (n=138)**	**HPED (n=85)**	**Without HPED (n=53)**	**P value**
Primary outcome (0-18, lower value indicates better QoL)				
ASQoL	3.7±4.1	4.6±4.5	2.3±2.9	<0.01
SF-36 Eight domains (0-100, higher value indicates better QoL)				
Physical function	77.6±20.9	72.7±22.1	85.5±16.1	<0.01
Role physical	76.3±23.5	70.1±24.4	86.3±18.3	<0.01
Bodily pain	60.3±21.0	55.4±21.7	68.1±17.4	<0.01
General health	54.0±21.8	51.5±21.5	58.1±21.8	0.08
Vitality	58.1±19.8	54.1±19.2	64.5±19.1	<0.01
Social functioning	80.0±19.9	74.7±20.1	88.6±16.4	<0.01
Role emotional	81.8±22.3	76.5±24.3	90.6±15.0	<0.01
Mental health	71.7±17.2	69.4±17.4	75.2±16.5	0.05
SF-36 Norm-based summary (0-100, higher value indicates better QoL)				
Physical component summary	43.8±11.3	40.5±11.6	49.3±8.4	<0.01
Mental component summary	44.1±11.9	42.7±11.5	46.3±12.2	0.08

Date presented as mean ± standard deviation

Abbreviation: Presence of peripheral arthritis, enthesitis or dactylitis, ever (HPED), Ankylosing Spondylitis Quality of Life (ASQoL), axial Spondyloarthritis (axSpA), quality of life (QoL), Ankylosing Spondylitis Quality of Life (ASQoL), Short Form-36 Health Surveys (SF-36)

Association of HPED with QoL at baseline and 1-year post-baseline in patients with axSpA using linear mixed model: longitudinal analyses

The multivariate analysis using linear mixed model in Table 17 (Model 1) showed that HPED was associated with ASQoL and 6 SF-36 domains (PF, RP, BP, VT, SF and RE) and PCS. After adjustments with confounders (Model 2), HPED was associated with ASQoL and 4 SF-36 domains (PF, RP, SF and RE) and PCS.

Table 17. Extra-spinal symptoms (HPED) on quality of life outcomes: linear mixed model analyses

Outcome	**Model 1 n=138**	**Model 2 n=138**	**Model 3 n=138**		
	HPED on QoL at baseline	HPED on QoL at baseline	β_1	$\beta_1 + \beta_3$	β_3
ASQoL	2.20**	1.24*	0.85	1.61**	0.76
PF	-12.50**	-6.72*	-3.64	-9.60**	-5.96*
RP	-14.15**	-10.34**	-8.38*	-12.17**	-3.79
BP	-8.94**	-3.57	-3.35	-3.79	-0.44
GH	-3.50	-1.25	-1.36	-1.14	0.22
VT	-7.12*	-3.13	-4.03	-1.78	2.25
SF	-10.57**	-6.11*	-6.74*	-5.42	1.32
RE	-10.67**	-8.58**	-9.37**	-7.87*	1.50
MH	-2.82	0.32	-0.64	1.25	1.89
PCS	-7.34**	-5.06**	-4.52**	-5.61**	-1.09
MCS	-1.34	0.59	-0.25	1.46	1.71

Data presented as β. Time referred to time of assessment (baseline or 1-year). β_1, $\beta_1 + \beta_3$ and β_3 represented the effect of HPED on QoL at baseline, one year and that of the interaction with time respectively.

* <0.05; **<0.01

Model 1 – Unadjusted analysis
Model 2 – Model 1 with adjustment for age, gender, comorbidities, disease duration, disease activity and treatment
Model 3 – Model 2 with inclusion of time of assessment and interaction between time of assessment and HPED

Higher ASQoL β refers to poorer quality of life while higher PF, RP, BP, GH, VT, SF, RE, MH, PCS and higher MCS β refer to better quality of life.

Abbreviation: Presence of peripheral arthritis, enthesitis or dactylitis, ever (HPED), physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), mental health (MH), physical component summary of SF-36 (PCS), mental component summary of SF-36 (MCS), Ankylosing Spondylitis Quality of Life (ASQoL), axial Spondyloarthritis (axSpA), quality of life (QoL), presence of peripheral arthritis, enthesitis, or dactylitis, ever (HPED)

After inclusion of the time of assessment and interaction between HPED and time of assessment (Model 3), HPED was associated with 3 SF-36 domains (RP, SF and RE) and PCS at baseline. At 1-year post-baseline, HPED was associated with ASQoL, 3 SF domains (PF, RP and RE) and PCS. BP, GH, VT, MH and MCS were not associated with HPED at baseline or at 1-year post-baseline. Although the interaction term between HPED and time of assessment was significant only for PF, the directions of the associations were largely positive for physical domains of QoL while negative for mental domains of QoL (Model 3).

6.5 Discussion

This is the first study to examine the association between HPED and QoL among patients with axSpA over a 1-year period. In the cross-sectional analyses, HPED in patients with axSpA was associated with poorer QoL across all outcomes except SF-36 GH, MH and MCS. Also, HPED was associated with poorer physical health at 1-year post-baseline. The findings in the chapter were consistent with the results of a study by van der Heijde et al which has shown that improvement in extra-spinal symptoms may indirectly improve QoL.(137)

HPED in axSpA was shown to have a negative impact on most domains of QoL. This was similar to the finding by Yilmaz et al that peripheral arthritis in patients with ankylosing spondylitis resulted in poorer QoL.(128) Patients with HPED experience pain in areas such as hands or feet which may adversely affect QoL during walking, locomotion and usage of hands.(3) The cross-sectional analyses in this chapter did not show an association between HPED and SF-36 GH, MH and MCS – this may be due to the fact that patients in our cohort already had low SF-36 GH, MH and MCS scores as axSpA has a strong impact on GH, MH and MCS due to the systemic nature of the disease.(5) Patients with axSpA have mental health scores comparable to patients on dialysis (138) as well as a higher prevalence of depression and anxiety compared to the general population.(139) As the patients had low HAQ and BASMI scores suggesting good functioning and metrology measurements respectively, the poor QoL observed in this study demonstrated that other factors such as pain and HPED may be influencing QoL. Therefore, clinicians should try to screen for HPED, as this can result in poorer QoL in patients with axSpA. Also, the presence of enthesitis and dactylitis might not result in the patient having a BASDAI greater than 4, but these patients might still benefit from biologics, thus improving their QoL.

Disease activity, as expected, was the main driver of QoL.(140) Despite this, at 1-year, HPED was still shown to have a persistent negative impact on QoL especially the physical domains. This showed that over 1-year, the impact of HPED on physical health increased while the impact of HPED on mental health decreased. Possible

reasons could be due to response shift seen or development of coping strategies in patients with HPED.(141) Nevertheless, patients should be followed up over a longer duration and more qualitative studies are needed to understand the true impact of HPED on the QoL of patients with axSpA in order to develop suitable interventions to improve their QoL.

This chapter revealed that patients with axSpA and extra-spinal symptoms can have significant impairment on QoL. Rheumatologists may consider early screening of extra-spinal symptoms and to implement interventions to reduce extra-spinal symptoms to reduce impact on QoL. In terms of learning points to health services researchers, this chapter revealed the importance of a well managed registry in order to study QoL using a longitudinal approach. Although I started out wanting to understand the impact of individual symptoms or biologics on QoL over 3 years, I cannot proceed because the registry has a significant number of dropouts over the years. However, this is a similar problem met by registries worldwide.(142) Researchers may consider using less burdensome approach in data collection to sustain patient participation over the long run. Students using longitudinal data for analysis can learn from the thought process of how the analytical method was selected in this chapter.

The strength of this chapter is that both generic (SF-36) and disease specific QoL PROMs (ASQoL) were utilised which allow further comparison of QoL with other diseases in future. This chapter has several limitations. Firstly, the number of Malay and Indian patients in this cohort was relatively small; as such, the effect of ethnicity could not be adjusted for fully. However, the low representation of minorities in this chapter is comparable to the ethnic composition of the axSpA cohort in this center and in Singapore.(5, 80, 81) Also, no significant difference in QoL was found among different ethnic groups in patients with rheumatoid arthritis and psoriatic arthritis.(113, 143) Furthermore, the data was re-analysed with BASMI as a confounder and the results were similar to that presented in this chapter. Secondly, structural changes in the spine were not adjusted for in our modeling. However, this was appropriate in this chapter because structural changes are known to be very

slow and are reported to be not associated with QoL.(136) Thirdly, less than 10% of the patients were on biologics at the time of analysis as the patients had generally lower disease activity (mean BASDAI of 3.3 as compared to 4.6 in the DESIR cohort)(144) and Singapore's healthcare system requires patients to co-pay, thus limiting financial accessibility to biologics.(145) Fourthly, HPED did not reflect extra-spinal symptoms at the time of assessment but rather the presence of extra-spinal symptoms at any time during the disease course. However, only 5 patients developed extra-spinal symptoms over the 1-year follow-up. The results of the sensitivity analysis, when we excluded these patients, were similar to those shown in Table 17. Finally, the separate effects of peripheral arthritis, heel enthesitis and dactylitis were not presented because of the limited number of patients with single symptoms, and the treatment algorithm currently hinges on whether patients presented with peripheral symptoms.(12) My analyses revealed that there are no associations between the individual symptoms of peripheral arthritis, heel enthesitis and dactylitis with QoL and this may be due to the small sample size of each symptom.

In conclusion, HPED was associated with poorer QoL outcomes in patients with axSpA. After one year, patients with HPED have poorer QoL especially in physical health domains, compared to patients without HPED. This chapter combines the findings of Chapter 2 to 4. In Chapter 2 and 3, I wrote that patients who have both axial and peripheral symptoms may have poorer QoL and this chapter corroborates this finding. SF-36 was validated in Chapter 4 and was used as a PROM in this chapter.

Chapter 7: Traditional Chinese Medicine (TCM) collaborative care in the management of patients with axial Spondyloarthritis (AcuSpA): Protocol for a pragmatic randomized controlled trial

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7.1 Abstract

Objectives: AxSpA is a chronic disease which results in fatigue and pain and affects QoL. TCM, especially acupuncture, has shown promise in managing pain and may serve as a complementary modality to improve QoL. Although a TCM-collaborative model of care (TCMCMC) has been studied in cancer, no study has explored the involvement of a TCM physician in the care of patients with AxSpA. Therefore, a pragmatic trial will be conducted to determine the clinical effectiveness, safety and cost-effectiveness of TCMCMC versus usual rheumatologic care for patients with AxSpA. TCMCMC was defined as standard TCM history taking and physical examination, acupuncture and TCM non-pharmacological advice and communications with rheumatologists in addition to usual rheumatologic care. This chapter aimed to describe in detail the rationale and methodology of this trial.

Methods: A pragmatic randomized controlled trial will be conducted. 160 patients who have been diagnosed with AxSpA and have inadequate response to stable doses of NSAIDs for at least 4 weeks will be recruited. Women who are pregnant or breastfeeding, on anti-platelets or anti-coagulants or have blood-borne communicable diseases will be excluded. Patients will be randomly allocated to receive usual rheumatologic care or the intervention on a 1:1 basis via random permuted block randomization. Ten 30-minute acupuncture sessions will be provided by TCM physicians registered with Singapore Traditional Chinese Medicine Practitioners Board to patients assigned to the TCMCMC arm. All participants will continue to receive usual rheumatologic care. The primary end-point of spinal pain will be evaluated at week 6. Secondary end-points include clinical, QoL, and economic outcome measures. Adverse events will be documented. Patients will be followed up for up to 52 weeks.

Discussion: This trial in this chapter may contribute evidence for the clinical and cost effectiveness and safety of a TCM collaborative model of care for patients with AxSpA.

Trial registration: Clinical Trials.gov number, NCT03420404, registered on 14 February 2018.

7.2 Introduction

AxSpA is a chronic debilitating disease, often affecting the quality of life of patients (57, 146). To date, there is no cure for axSpA and the pathophysiology of the disease remains unclear (84, 147). The treatment for patients with axSpA who remain symptomatic after initial treatment with NSAIDs usually involves biologics which cost more than USD$20,000 per year and only provides short-term relief of symptoms (148). Biologics also have significant side effects, in particular infections and risk of malignancies e.g. melanoma (149, 150).

TCM is one of the most commonly used complementary and alternative medicine modalities (151-153). TCM modalities, especially acupuncture, have shown promising results thus far in the management of pain (154, 155). Acupuncture has frequently been promoted for lower back pain and osteoarthritis (156), and rheumatic diseases are, according to survey data, frequently treated by acupuncturists (157-159). Previous studies have demonstrated efficacy of acupuncture in pain relief for osteoarthritis, fibromyalgia and back pain (160). For patients with irritable bowel syndrome, acupuncture plus usual care can provide additional benefit over usual care alone, and the magnitude of the effect is sustained (161).

However, till date, there is no study of the effectiveness of TCM, in addition to usual care, for patients with axSpA.(162) Given this evidence gap, and the unmet need of the patients with axSpA who do not respond well to current conventional treatment, further investigations of a collaborative model of care involving TCM is merited. Hence, a pragmatic trial to assess the clinical effectiveness, safety and cost-effectiveness of a TCMCMC in patients with axSpA using a pragmatic trial approach will be conducted. This trial aim to provide a TCMCMC as close as possible to how it will be provided in the real-world. This design can provide evidence for policy and decision-makers considering TCM physicians as a referral option for patients with axSpA. This chapter will describe the rationale and the detailed methodology of this trial.

7.3 Methods/Design

Study design and setting

This study is a two-arm pragmatic, randomized controlled trial to evaluate the clinical effectiveness, safety and cost-effectiveness of TCMCMC, in particular acupuncture, for patients with axSpA with inadequate response to NSAIDs (163-166). It is anchored in the Pragmatic Explanatory Continuum Indicator Summary Framework-2 (PRECIS-2) criteria and the extended CONSORT guidelines for pragmatic trials as well as the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) statement for acupuncture. The two arms are: TCMCMC (including acupuncture) plus usual rheumatologic care, and usual rheumatologic care alone. Participants will be recruited from dedicated clinics in a tertiary hospital setting. Patients will be randomly allocated to receive usual rheumatologic care or the intervention (TCMCMC) on a 1:1 basis via random permuted block randomization. Although participants and TCM physicians will be aware of the allocation arm, the rheumatologist and the data analysts will be kept blinded to the allocation. The SPIRIT figure was detailed in Figure 5.

Inclusion/exclusion criteria

Patients with axSpA who have spinal pain and active disease despite standard medical therapy will be recruited. Patients are eligible for the study if they are 21 years of age or older; have axSpA, diagnosed according to the 2009 ASAS criteria for axSpA (167); have active disease based on BASDAI score ≥4 on a 11-point Numerical Rating Scale (NRS) and spinal pain score ≥4 on a 11-point NRS (168); have failed 2 sequential NSAIDs (including cyclooxygenase-2 inhibitor) at maximal tolerated doses for ≥ 4 weeks in total; and have received no biologics (i.e. tumour necrosis factor blocker or anti-interleukin 17) within the past three months. No concomitant DMARD therapy or corticosteroid therapy is allowed. Patients with a BASDAI 50% response to NSAIDs will be recruited in one block, whilst patients who did not have BASDAI 50% response to NSAIDs will be recruited in another block.

Figure 5. SPIRIT Figure for the schedule of enrolment, interventions, and assessments.

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**					**Close out**
TIMEPOINT (Week)**	***0***	**0**	***1***	***6***	***12***	***24***	***52***	***> 52***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Baseline Assessment	X							
Allocation		X						
INTERVENTIONS:								
Usual rheumatologic care			⟷	⟷				
TCM collaborative care			⟷	⟷				
ASSESSMENTS:								
Spinal pain score	X			X	X	X	X	
QoL scores (SF-36, AsQoL)	X			X	X	X	X	
BASDAI	X			X	X	X	X	
BASFI	X			X	X	X	X	
BASG	X			X	X	X	X	
HAQ	X			X	X	X	X	
Costs				X	X	X	X	
Adverse events			X	X	X	X	X	
Analysis of study outcomes								X

Abbreviation: Short Form-36 Health Survey (SF-36), Ankylosing Spondylitis Quality of Life (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global score (BASG), Health Assessment Questionnaire (HAQ), quality of life (QoL) (169)(168)(167)(166)(166)(166)(166)

Patients who are pregnant or breastfeeding; on anti-platelet agents (i.e. aspirin, clopidogrel, dipyridamole, etc.) or anti-coagulants (i.e. warfarin, enoxaparin, rivaroxaban, dabigatran, etc.); have bleeding disorders; or have blood-borne communicable diseases (e.g. hepatitis B, hepatitis C, human immunodeficiency virus, etc) will be excluded.

Procedures

The attending rheumatologist will identify eligible patients according to the inclusion and exclusion criteria. Informed consent will be taken by the attending rheumatologist and the patients will be referred to the research coordinator who will randomly assign them to the intervention or control arm. The research coordinator will keep custody of the randomization list that was pre-generated by the biostatistician using a computerized random number generator, and assign treatment accordingly to the intervention listed. All patients will receive routine counseling on medical adherence. Bias due to attrition will be minimized by carefully following up all the patients including drop-outs. The trial work plan is summarized in Figure 6.

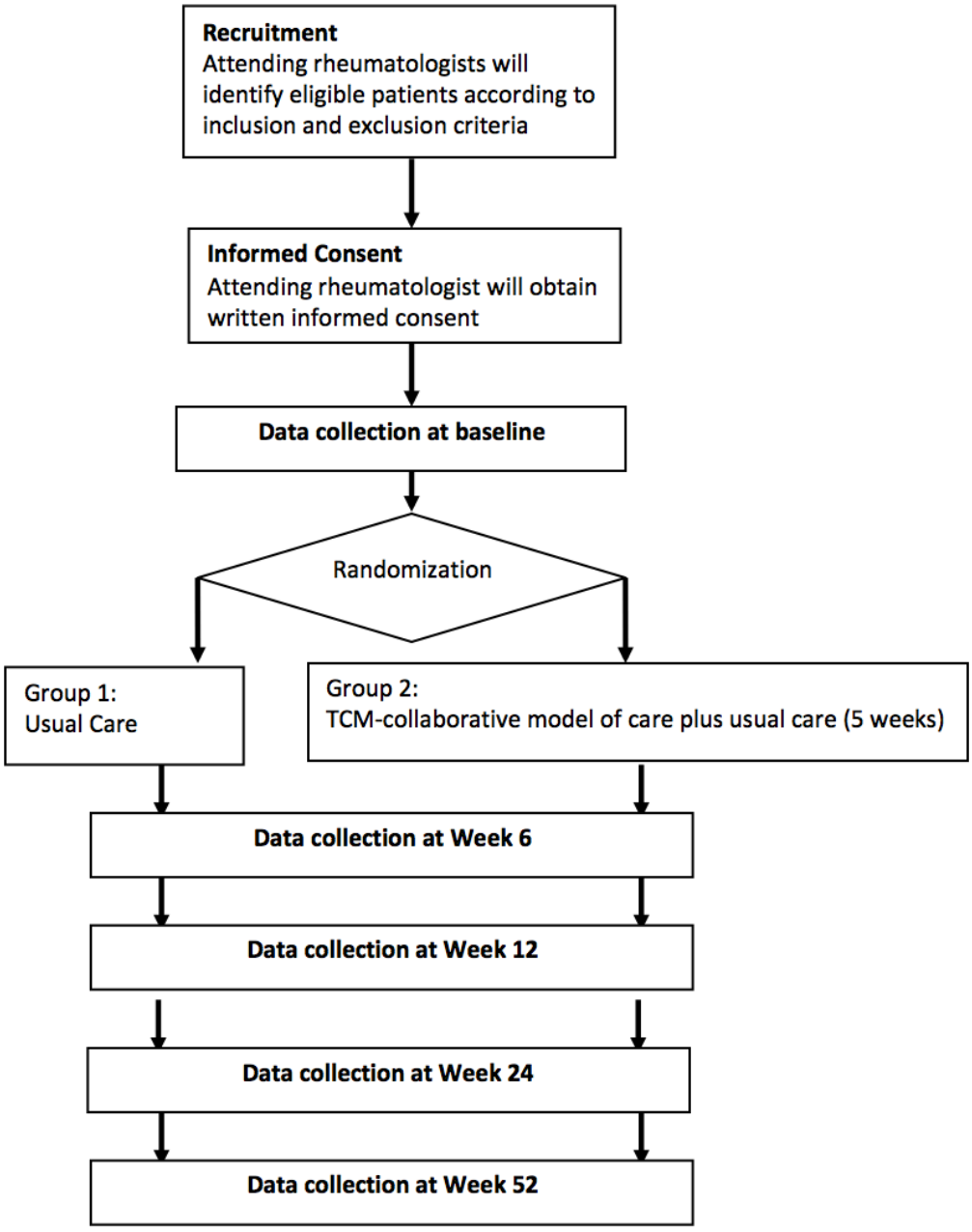

Figure 6. Trial work plan. Follow-up will be performed at week 6, week 12, week 24 and week 52 after baseline visit. Pain score at week 6 is the primary outcome of this study. Outcome measures at week 52 serve as exploratory data. The remaining outcome measures are the secondary outcomes of the study. Abbreviations: Traditional Chinese Medicine (TCM)

Control

Usual rheumatologic care consists of a referral to the physiotherapist for therapeutic exercise, medications including NSAIDs, and regular monitoring for complications which may arise from axSpA such as uveitis, interstitial lung disease, risk factors for cardiovascular disease and osteoporosis. In this trial, the attending rheumatologist will see each patient at 6 weekly to 6 monthly intervals depending on the patient's condition as per routine care. At each session, the attending rheumatologist will conduct a thorough physical examination and monitor the disease activity using validated patient-reported outcome instruments. The rheumatologist will be allowed to prescribe the full range of medications, including biologics, as per routine care and according to local treatment guidelines. The rheumatologist will remind patients not to visit any TCM physician and not to seek alternative therapy for the duration of the study.

To avoid potential contamination of the study results, all healthcare staff will be reminded to treat the patients in both interventional and control arms in a consistent manner.

Intervention

TCM physicians registered with the Singapore TCM Practitioners Board with at least 3 years of experience will participate in the study. Prior to the treatment sessions, all the acupuncturists will undergo training to ensure standardization of acupuncture techniques. The intervention arm will involve the TCM physicians in the management of the patients, in addition to usual rheumatologic care. The clinical interventions carried out by the TCM physicians include counseling, diagnosis based on TCM clinical syndromes and the prescription of acupuncture.

The main acupuncture points are *Jiaji, Shenshu, Yaoyangguan, Mingmen,* and *Huantiao*. We will use sterile disposable stainless-steel needles of 0.25 mm diameter, 25 mm or 40 mm length and 0.30 mm diameter, 50 mm or 70 mm length depending on the acupuncture points. In addition to the main acupuncture points specific for the treatment of AxSpA, the TCM physicians will be allowed to make minor adjustments

to the acupuncture points in view of the differing constitution of the patients as per the holistic treatment philosophy of TCM as shown in Figure 7. The acupuncture treatment will consist of a total of 10 sessions (or 2 courses) in total. Each course of treatment will consist of 5 acupuncture sessions held over 2 weeks, each session lasting 30 minutes in duration. The patient will have a break of at least 3 days to 1 week in between each course of acupuncture. TCM physicians will document components of treatment and adherence in logbooks.

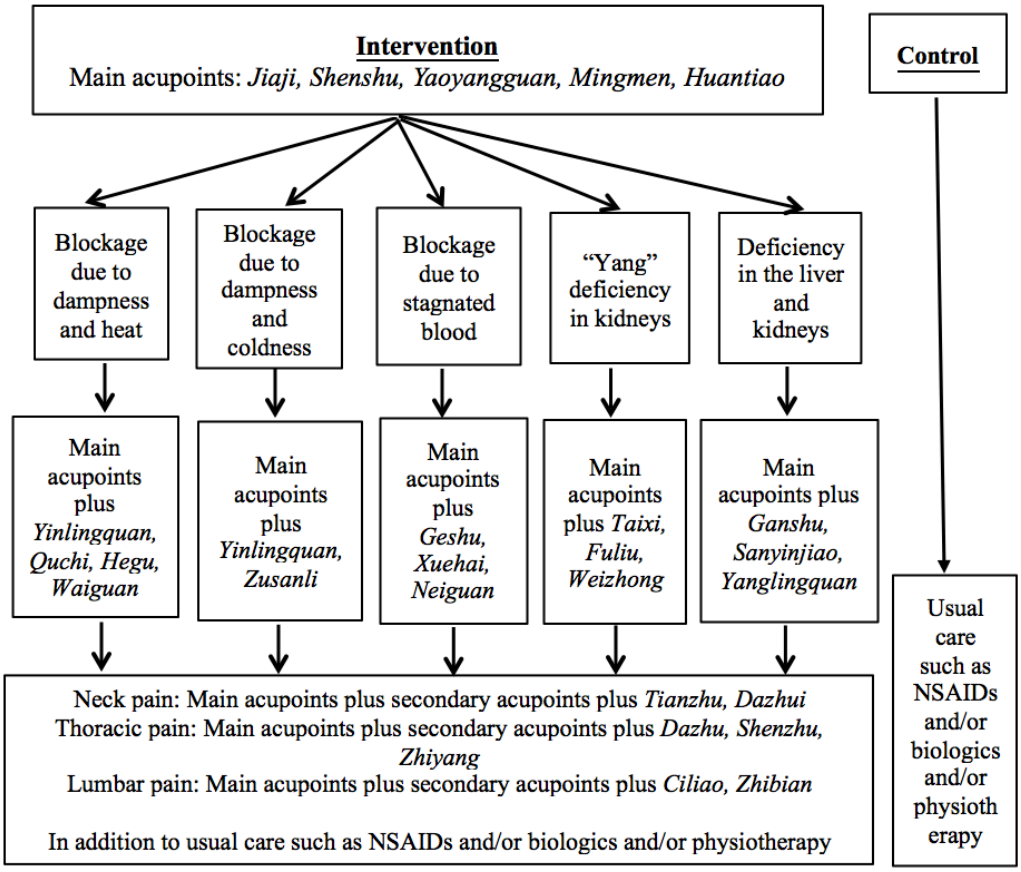

Figure 7. The acupuncture points employed in AcuSpA. The main acupuncture points are *Jiaji, Shenshu, Yaoyangguan, Mingmen, Huantiao*. The patients in the intervention group will be classified into one of the five syndromes based on their clinical presentation and have secondary acupuncture points chosen based on their respective syndromes. There will also be additional acupuncture points for patients with neck pain, thoracic pain and/or lumbar pain. Patients in both intervention and control group will be given usual care consisting of as NSAIDs and/or biologics and/or physiotherapy as deemed necessary by the attending rheumatologists.
Abbreviations: Acupuncture points (Acupoints); Non-steroidal anti-inflammatory drugs (NSAIDs)

Primary outcome

Spinal pain score at week 6 is the primary outcome of this study. The pain NRS will be used since pain is what matters most to patients with axSpA, and it is widely used and has been validated across many settings (170). This was selected to investigate if there is short-term effectiveness of the intervention. The primary and secondary outcome measures are shown in Table 18.

Main secondary outcome

Spinal pain score at week 24 is the main secondary outcome in this study. This was selected to investigate if there is sustained long-term effectiveness in the intervention.

Other secondary outcomes

Clinical outcomes, quality of life outcomes and economic outcomes will be collected. Other secondary clinical outcomes include spinal pain at week 12 and week 24; clinical parameters, including BASDAI (171), BASFI (172), BASG (173), and HAQ (6, 169) at week 6, 12 and 24.

QoL will be assessed using the SF-36 (5) and ASQoL (131, 174), which will be administered at baseline, week 6, and at week 12, and week 24. Both PROMs have been validated in the Singapore population (5).

For secondary economic outcomes, axSpA-related and non-axSpa-related health care use such as rheumatologist's consultation fees, costs of laboratory procedures, and number of inpatient days will be collected. Healthcare use will be obtained through questionnaires administered to patients in both control and interventional arms at week 6, and at week 12, and week 24. In addition, this information will be supplemented by medical records and data from the electronic databases. Non-health care financial consequences will be captured in the questionnaires by recording self-reported travel costs incurred by the patients to receive treatment, patient income and salary, the number of days patients missed work due to illness, and work status (active, inactive, retired).

Table 18: Summary of Primary, Secondary and Exploratory Outcome Measures

Outcomes	Definition	Time			
		Week 6	Week 12	Week 24	Week 52
1. Primary outcome					
1.1 Spinal pain score	Overall level of pain at neck, back or hip	✓			
2. Main secondary outcome					
2.1 Spinal pain score	Overall level of pain at neck, back or hip			✓	
3. Other secondary outcomes					
3.1 Clinical outcomes					
3.1.1 Spinal pain score	Overall level of pain at neck, back or hip		✓		
3.1.2 BASDAI	Disease activity of patient	✓	✓	✓	
3.1.3 BASFI	Disease-specific physical function	✓	✓	✓	
3.1.4 BAS-G	Global assessment of disease	✓	✓	✓	
3.1.5 HAQ	Disability	✓	✓	✓	
3.2 Quality of life outcomes					
3.2.1 SF-36	General QoL assessment	✓	✓	✓	
3.2.2 ASQoL	Disease-specific QoL assessment	✓	✓	✓	
3.3 Economic outcomes					
3.3.1 Costs	Direct and indirect costs of disease	✓	✓	✓	
4. Exploratory outcomes					
4.1 Clinical outcomes					
4.1.1 Spinal pain score	Overall level of pain at neck, back or hip				✓
4.1.2 BASDAI	Disease activity of patient				✓
4.1.3 BASFI	Disease-specific physical function				✓
4.1.4 BAS-G	Global assessment of disease				✓
4.1.5 HAQ	Disability				✓
4.2 Quality of life outcomes					
4.2.1 SF-36	General QoL assessment				✓
4.2.2 ASQoL	Disease-specific QoL assessment				✓
4.3 Economic outcomes					
4.3.1 Costs	Direct and indirect costs of disease				✓

Baseline data will be collected for all outcome measures except for costs.

Exploratory outcomes

The spinal pain, BASDAI, BASFI, BASG, HAQ, SF-36, ASQoL, rheumatologist's consultation fees, cost of laboratory procedures, and number of inpatient days at week 52 will serve as exploratory outcomes.

Instruments and definitions

BASDAI (ranges from 0 to 10) is a disease-specific questionnaire to measure disease activity, with higher values indicating more active disease (97). BASFI (ranges from 0 to 10) is a disease-specific questionnaire used to measure physical functioning, with higher values indicating worse functioning (97). BASG (ranges from 0 to 100) is a disease-specific questionnaire to give a global assessment of well-being, with higher score reflecting poorer well-being (173).

HAQ (ranges from 0 to 3) is a generic questionnaire used to assess function, with a higher score reflecting worse function (96). It includes 8 domains namely dressing, arising, eating, walking, hygiene, reach, grip and daily activities. HAQ is a valid and reliable measure for use in patients with axSpA in Singapore (6).

SF-36 version 2 is a generic questionnaire used to measure QoL in eight areas of perceived health. The 36 individual questions make up 8 subscales with lower scores reflecting poorer QoL. Norm-based scores were used whereby 50 represent the mean and 10 represent the standard deviation. The eight subscales are: physical functioning, role limitation due to physical problem, bodily pain, general health, vitality, social functioning, and role limitation due to emotional problem and mental health. These eight scales were summed with different weights to give two summary scores – PCS and MCS (95). The SF-36 has been shown to be valid and reliable in patients with axSpA in Singapore (5).

ASQoL is a patient-derived and disease-specific measure of QoL for AS. It consists of 18 items with a "yes" (scored as 1) or "no" (scored as 0) response to each item. All item scores are summed to a total score ranging from 0 to 18 (132), with higher scores

indicating worse QoL. The English version of ASQoL has been shown to be a valid and reliable measure for use in patients with axSpA, also in Singapore (131).

Process measurement

Adherence to treatment defined as the number of acupuncture sessions attended by the patients in the intervention arm will be assessed. The number of acupuncture and rheumatology consultations, and number of needles used in each acupuncture session will be recorded. The TCM physicians will complete a checklist to ensure standardization of acupuncture treatment across all sessions. The checklist is available in Supplementary Figure 6.

Safety

Adverse events will be recorded throughout the study up to week 52. Acupuncture-related adverse events are defined as symptoms or complications related to acupuncture that begin or worsen after the first session of acupuncture through the last session of acupuncture (175). The adverse events were adapted from a systematic review of adverse events of acupuncture treatment, including broken needles, fainting during session and local infections at the site of acupuncture.

Adverse events related to usual rheumatologic care were adapted from previously conducted randomized controlled trials performed in patients with axSpA (176, 177). Adverse effects related to usual rheumatologic care include abdominal distension and pain, nausea, diarrhea, gastrointestinal disease, headache, giddiness, upper respiratory tract infection, nasopharyngitis, malignancy, infections, and hepatic-related adverse events will be recorded.

Sample size justification

As this is the first trial to explore a collaborative model between TCM physicians and rheumatologists in the field of axSpA, sample size calculation was based on a study by Meng et al. (154) With a conservative estimate of 0.6 point difference on a 11-point scale in pain score between the two arms, and assuming a standard deviation of 1.2 for both arms, approximately 64 patients are needed for each arm to obtain a

statistical power of 80% (two sided Type I error rate of 0.05) based on a 1:1 treatment allocation. After taking into account a dropout rate of approximately 20%, a total of 160 patients with 80 patients per arm will be needed for this trial. According to Cohen, this effect size is considered “moderate” (178).

Statistical analysis

The statistical analysis will be performed on the intention-to-treat (ITT) basis. The primary outcome of interest is the difference in pain score at week 6 between the interventional and control arms. The baseline characteristics will be shown as the mean ± SD (or median and interquartile range where adequate) for continuous variables (e.g. age), and n (%) for categorical variables (e.g. gender). Primary outcome of pain score at week 6 will be analyzed using Student’s t-test. Further adjustment will be made with baseline pain score using analysis of covariance. Multiple imputations will be used to account for missing values. All evaluations will be made assuming a two-sided type I error rate set at 0.05.

For secondary outcomes with repeated measurements, we will use a linear mixed model to account for within-individual correlation among measurements and the sandwich estimator to obtain robust standard error estimates. The intervention indicator and time factor will be included among the linear predictors adjusting for baseline covariates.

To assess safety of the intervention, the frequency of adverse events that occurred will be presented in frequency and percentages in both intervention and control arms within the study period of 52 weeks.

The economic evaluation will be conducted from both the health care system and societal perspectives. Both cost-effectiveness analysis (i.e. cost of reduction in 1 pain score point) and cost-utility analysis (i.e. cost of reduction in 1 quality-adjusted life year saved) will be performed (179, 180). Costs will include direct healthcare-related costs of the TCM physician, rheumatologist, hospital stays and any drugs. The indirect costs caused by lost workdays will also be taken into account. Health utility will be

measured using the Short Form-6 Dimensions (SF-6D) which is a derivation from the SF-36 (181). The cost-effectiveness and cost-utility analyses will be performed by calculating the incremental cost-effectiveness ratio and incremental cost-utility ratio respectively. The analysis period will be at week 6, week 12, week 24 and week 52.

The incremental cost-effectiveness ratio will be calculated by dividing the between-group difference in costs by the between-group difference in effects (i.e. costs per pain score reduced). The incremental cost-utility ratio will be calculated by dividing the between-group difference in costs by the between-group difference in utility (i.e. costs per SF-6D unit improvement). Sensitivity analysis will be conducted on the most important cost drivers to assess the robustness of the results.

An independent data and safety monitoring board will meet annually to provide interim monitoring of the un-blinded safety and efficiency data for the study. The data and safety monitoring board, comprising independent senior clinical experts and external biostatisticians, will help ensure the availability of appropriate expertise in trial design, execution, interim monitoring, analysis and reporting.

7.4 Ethics and Dissemination

This trial has been approved by the SingHealth Centralised Institutional Board Review (CIRB) (Reference number: 2017/2088). Independent clinicians and biostatisticians with extensive research experience in clinical trials will serve as the Data and Safety Monitoring Committee. Study participation is voluntary, can be discontinued at any time, and deciding not to take part will not affect a patient's care. Protocol amendments, adverse effects reporting and annual review will be overseen by the CIRB. The information provided by the patients will only be shared with members of the research team. Every effort will be made to keep patient information confidential. All personal identifying information and research data will be stored on SingHealth Research Electronic Data Capture (REDCap), which is a password-protected network. All research-related paper documents will be in a locked cabinet. All patient information will be kept strictly confidential. All members of the research team are

required to complete a biomedical research training module offered by the Collaborative Institutional Training Institute on human subjects' protection and data security.

The results of this trial will be submitted for publication to a journal for international audit with all actively collaborating investigators acknowledged.

7.5 Discussion

This is the first trial to assess the impact of involving TCM, in particular acupuncture, in the management of patients with axSpA with inadequate response to NSAIDs. By utilizing a pragmatic trial approach, this trial aims to understand the effect of this intervention in the real-world setting. Pursuant to the PRECIS-2, our design reflects key pragmatic dimensions: (1) This trial will recruit patients who are most likely to use TCM (i.e. patients who have inadequate disease control despite NSAIDs and declined or are unable to afford biologics); (2) treatment setting reflects the situation where the patients will receive their treatment in real life; (3) extra resources are not provided for the treatment and this reflects what will be done currently in clinical practice; (4) relevant outcomes which are important to the patients and stakeholders in healthcare are chosen; (5) no extra follow up is scheduled with the patients but any extra data needed from the data collection will be collected in their home or over telephone; and (6) follow an ITT analysis (14, 164). With these features, this trial balances the issues of internal and external validity, with the goal of assessing real-world effectiveness of a TCMCMC involving both a TCM physician and a rheumatologist in the management of patients with axSpA with inadequate response to NSAIDs (182).

For axSpA, NSAIDs are often the first-line treatment, and biologics are the step-up treatment for patients who have inadequate response to NSAIDs (12). However, the cost difference between NSAIDs and biologics is significant (183). Patients who have inadequate response to NSAIDs but cannot afford biologics often experience

significant pain and impairment in QoL (3). Hence, this trial will provide an evidence for a novel model of care for this group of patients.

In conclusion, a pragmatic trial of a TCMCMC involving both a TCM physician and rheumatologist in the management of patients with axSpA may provide evidence to support the referral of patients with axSpA to TCM physicians for better management of pain and QoL. This may aid policy and decision-makers considering TCM physicians as a referral option for patients with axSpA. This chapter combines the learning points of chapter 2 to 6. From chapter 2 and 3, I know that pain is the main area of impact of QoL in patients with SpA. In chapter 3, through the FGDs, I know that TCM is a modality that I can consider when my team develop an intervention to improve QoL for patients with axSpA. I also gain the confidence that recruitment will be feasible if my team conduct a study on TCM in patients with axSpA. From chapter 4 to 5, I validated SF-36 and HAQ for use as PROMs in this trial. Last, from chapter 6, I know that there exists significant heterogeneity in patients with axSpA, therefore, myteam developed an intervention that allow for heterogeneity of symptoms. A positive trial can allow the rheumatologists to use TCMCMC as a potential treatment modality. Health services researchers can derive learning points from this pragmatic trial and conduct future RCTs with implementation in mind to facilitate greater uptake of interventions with strong evidence.

Chapter 8: Conclusions, learning points and future directions

8.1 Major findings and contributions

Through this thesis, I have studied 4 major themes to better understand and improve the QoL of patients with SpA. First, **I** established the QoL domains and items relevant to patients with SpA and how currently-used PROMs are measuring them.(3) I also found that since the QoL domains and items relevant to patients with axSpA and pSpA are similar, there may be a possibility of harmonizing the PROMs used in both groups of patients.(3) I then further established the QoL domains relevant to patients with SpA in Singapore and found they are similar to patients in other part of the world except for domains such as financial freedom, work satisfaction and positive feelings, which were of greater relevance in patients with SpA in Singapore possibly due to the local socio-cultural context.(4) This study also further re-iterated the possibility of harmonizing the PROMs used in both groups of patients.(4)

Based on these findings, I validated 2 commonly used PROMs in rheumatology, the SF-36 and the HAQ.(5, 6) These two PROMs are also part of the PROMs that are routinely used in clinical trials in SpA. I found that both SF-36 and HAQ are valid and reliable to be used in patients with SpA.(5, 6) , supporting their use in measuring QoL and physical functioning in these patients in clinical practice and research. This also adds to the worldwide evidence base of PROMs available to measure QoL in patients with SpA, allowing a timely update of the core set of domains and outcome measures of the ASAS-OMERACT workgroup.(14, 184) I was honored to be invited to participate in the ASAS-OMERACT workgroup to update the core set of domains and outcome meaures of SpA whereby QoL was being put forth as a core domain to be measured in future studies on SpA.

With validated outcomes, I delved deeper to identify modifiable factors that are associated with a poorer QoL in patients with SpA. Due to the heterogeneity of patients with SpA, I focused our analysis on patients with axSpA. This study found that history of peripheral arthritis, enthesitis or dactylitis (HPED) was associated with poorer QoL at baseline and one year later. Rheumatologists who manage patients with

axSpA should consider the impact of HPED on their treatment plans and aim to reduce peripheral arthritis, enthesitis or dactylitis in their patients.

Lastly, as the main symptom of patients with axSpA is back pain, I sought to improve the pain relief and hence the QoL of patients with axSpA. Using acupuncture as the main mode of intervention and a collaborative model of care with TCM physicians and rheumatologists, I was part of the multidisciplinary team which submitted a grant to the Ministry of Health whereby Dr Warren Fong is the PI while Prof Truls Østbye and Prof Julian Thumboo are the co-investigators of the trial. The Ministry of Health TCM Research Grant was awarded to our team, and I was deeply involved with the planning and execution of the study. The study was ongoing at time of thesis submission. We published the protocol paper detailing the plans for the trial. I hope that this collaborative model of care will become a foundational component for management of axSpA, and that clinicians treating other rheumatological diseases will similarly be willing to explore a new model of care for their patients.

I hope that with the above contributions from the thesis, the QoL of patients with SpA can be improved, and this thesis can be used as a future model for researchers seeking to improve the QoL of their patients.

8.2 Limitations

In writing this thesis, some limitations were encountered. The limitations relevant to specific chapters were listed separately in the discussions of the individual chapters. I list the limitations that apply broadly to my work across SpA here.

First, although Singapore is a multi-ethnic country, my patients with SpA are predominantly Chinese. I had difficulties recruiting Malays and Indians as SpA is less prevalent among Malays and Indians. This is likely due to HLA-B27 being more prevalent in Chinese as is suggested by large registries of Chinese patients with SpA in the literature.(182) Future research in SpA should focus on other races in Asia in order to improve the QoL of these patients.

Second, as SpA is a rare disease with prevalence of less than 1%,(185) I could not explore other hypotheses such as the the impact of biologics on QoL because biologics is more expensive and less than 30 patients are on biologics in our cohort . In the future, SpA researchers should consider recruiting from multi-centers and to have joint multi-national registries in order to test these hypotheses.

Third, as much as I would like to have a holistic package of TCM modalities, I was restricted by ethical and logistics issues because of poor understanding of other modalities of TCM such as moxibustion and electro-acupuncture. The journey to integrate conventional medicine with TCM remains to be explored. Philosophical, financial, operational and safety concerns need to be addressed before further implementation into the current healthcare system.(186) Future research can use our current protocol paper as a base to test other interventions in order to optimize the management of patients with axSpA.

8.3 Learning Points

This thesis allowed me to learn a wide range of skills to answer a breadth of research questions in rheumatology and health services research.

In working on theme 1, I wrote and was awarded my first research grant as a principal investigator from the Asia-Pacific League of Rheumatology. I learnt how to conduct a systematic review and qualitative study and how to bring the studies to completion. In theme 2, I learnt psychometric skills and how to utilize the COSMIN checklist for PROMs in conducting such studies. I also learnt about PROMs in depth and how to use them in research. In theme 3, I learnt about linear mixed models and how to conduct a longitudinal study. In theme 4, I learnt how to write a national level competitive grant on TCM, which is a complex intervention. Furthermore, with the support from Duke University and Duke-NUS Medical School, I managed to embark on a fellowship with Prof Hayden Bosworth to learn about implementation science. I also learnt how to conduct a pragmatic trial and to manage the relationships and perspectives of

different stakeholders. The difficulty of this trial was the drastically different viewpoints between the TCM physicians, rheumatologists and scientists. Despite these challenges, we managed to successfully complete the trial and are planning a follow up project with the same group of researchers.

In addition to the "hard" skills learnt, I learnt "soft" skills such as negotiation, time management, grant management, staff management and stakeholder management. These skills were essential to me to complete these projects and to further my career as a clinician scientist. I am grateful for my mentors to allow me to explore my interest and to learn about these areas, which are beyond what I expected when I started my PhD programme.

8.4 Future Directions

This thesis brought together a series of publications that improved the understanding of QoL in patients with SpA. One potential future direction that can be pursued is to develop a computer adaptive test that can measure QoL across all SpA subtypes. Computer adaptive tests allow us to measure a latent construct with fewer questions while maintaining precision. This reduces cognitive burden as patients will only need to answer questions that are relevant to them. Also, larger data sets from joint international registries should be obtained to answer questions relevant to this rare disease. This is especially important as certain symptoms like extra-spinal symptoms occur in small numbers, making it difficult to draw substantial conclusions in my dataset. Lastly, more modalities of TCM such as electroacupuncture, moxibustion and herbs can be investigated in patients with SpA to expand the therapeutic toolbox that a rheumatologist can use to treat patients with SpA.

8.5 Conclusion

This thesis explored various themes to improve the QoL of patients with SpA. I explored the impact of disease on patients, conducted psychometric analyses on PROMs related to QoL, explored factors that were associated with QoL in a

longitudinal study, and developed a collaborative model of care involving TCM in the management of SpA patients. I hope that such a model can be used as a foundation for future researchers interested in QoL work in various chronic diseases.

Appendix A: List of Abbreviations

List of Abbreviations

Full Form of Word	Abbreviation
Ankylosing Spondylitis	AS
Ankylosing Spondylitis Quality of Life	ASQoL
Assessment of Spondyloarthritis International Society	ASAS
Axial Spondyloarthritis	axSpA
Bath Ankylosing Spondylitis Disease Activity Index	BASDAI
Bath Ankylosing Spondylitis Functional Index	BASFI
Bath Ankylosing Spondylitis Global Score	BASG
Bath Ankylosing Spondylitis Metrology Index	BASMI
Bodily Pain	BP
Centralised Institutional Board Review	CIRB
CLASsification for Psoriatic ARthritis	CASPAR
Computer-Adapted Test	CAT
COnsesus-based Standards for the selection of health status Measurement INstruments	COSMIN
Dermatology Life Quality Index	DLQI
Disease Modifying Anti-Rheumatic Drug	DMARD
Dougados Functional Index	DFI
Focus Group Discussion	FGD
Functional Assessment of Chronic Illness Therapy - Fatigue	FACIT-F
General Health	GH
Health Assessment Questionnaire	HAQ
Health Assessment Questionnaire- Spondyloarthritis	HAQ-S
History of Peripheral Arthritis, Enthesitis or Dactylitis	HPED
Inflammatory Bowel Disease	IBD
Intention-To-Treat	ITT
Mental Component Summary	MCS
Mental Health	MH
Modified Stoke Ankylosing Spondylitis Spinal Score	mSASSS

Non-Steroidal Anti-Inflammatory Drug	NSAID
Numerical Rating Scale	NRS
Outcome Measures in Rheumatology	OMERACT
Peripheral Spondyloarthritis	pSpA
Physical Component Summary	PCS
Physical Functioning	PF
Psoriatic Arthritis	PsA
Psoriatic Arthritis Impact of Disease	PsAID
Psoriatic Arthritis Quality of Life	PsAQoL
Patient Global Assessment	PGA
Patient-Reported Outcome	PRO
Patient-Reported Outcome Measure	PROM
Patient-Reported Outcome and Quality of Life Instruments Database	PROQOLID
PREcision medicine in SPondyloarthritis for better Outcomes aNd Disease remission	PRESPOND
Preferred Reporting Items for Systematic Reviews and Meta-Analyses	PRISMA
Quality of Life	QoL
Role Emotional	RE
Role Physical	RP
Short Form-36	SF-36
Short Form-6 Dimensions	SF-6D
Social Functioning	SF
Spondyloarthritis	SpA
Traditional Chinese Medicine	TCM
Traditional Chinese Medicine Collaborative Model of Care	TCMCMC
Visual Analogue Scale	VAS
Vitality	VT
World Health Organization Quality of Life	WHOQOL

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Appendix C (Supplementary Tables and Figures)

Supplementary Table 1. Domains and items relevant to QoL categoreised by continent, type of SpA and coverge by commonly used PROs

Items	Commonly used PROs in axial SpA							Axial SpA						Peripheral SpA						Commonly used PROs in peripheral SpA						
Types of SpA	**BASFI**	**BASG**	**PGA**	**Pain**	**ASQoL**	**HAQS**	**DFI**	**E**	**NA**	**SA**	**A1**	**O**	**A2**	**E**	**NA**	**SA**	**A1**	**O**	**A2**	**Pain**	**PGA**	**SF36**	**DLQI**	**PsAQoL**	**HAQ**	**FACITF**
Physical - general																										
Strength	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Weight and tone	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Physical - pain and discomfort																										
General pain	0	0	0	1	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	1	0	1	0	0	0	1
Back pain	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Neck pain	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Hip pain	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Joint pain	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Leg pain	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rib pain	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
Chest and abdomen pain	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tender to touch	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other discomfort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
Physical- energy and fatigue																										
Fatigue	0	0	0	0	1	0	0	1	1	0	1	1	1	1	1	0	0	1	0	0	0	1	0	1	0	1
Time to recover	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Easily tired	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	1
Weakness	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Physical - sleep and rest																										
Sleep quality	0	0	0	0	0	0	0	1	1	0	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	1
Ability to sleep on certain position	0	0	0	0	0	0	1	1	1	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0
Daytime sleepiness	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Waking from pain	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Need for rest	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Insomnia	0	0	0	0	1	0	0	1	1	0	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0
Physical - symptom																										
General	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Headache	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Swelling	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Stiffness	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Muscle cramps	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

Visual problems	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Hearing problem	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Digestive problems	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Skin and nail problems	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Other musculoskeletal problems	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Psychological - positive feelings																											
Drive and motivation	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0
Optimism	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
New perspective	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Psychological - thinking, learning, memory and concentration																											
Concentration	0	0	0	0	0	0	0	1	1	0	1	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0
Memory	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Problem solving	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Learning	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Psychological - self-esteem																											
Low self-esteem	0	0	0	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Embarrassment	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0
Psychological - bodily image and appearance																											
Self-image	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Psychological - negative feelings																											
Stress	0	0	0	0	0	0	0	1	0	0	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0
Anxiety	0	0	0	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	1
Worry	0	0	0	0	1	0	0	1	1	0	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1
Fear	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Hopelessness	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Injustice	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Premature ageing	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Resigned	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Frustrated	0	0	0	0	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	0	0	0	0	1	0	0	1
Depressed	0	0	0	0	1	0	0	1	1	0	0	1	0	1	1	0	0	1	0	0	0	1	0	1	0	0	1
Withdrawn	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Guilt	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Irritated	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Lack of motivation	0	0	0	0	0	0	0	1	1	0	1	1	1	1	0	0	0	0	0	0	0	1	0	1	0	0	0
Missing out	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Level of independence - general																											
General depenence	0	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	

Level of independence - mobility																											
Decreased mobility	0	0	0	0	0	0	1	1	1	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Bending	1	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0
Climbing stairs	1	0	0	0	0	1	1	1	1	1	1	0	0	1	0	0	0	1	0	0	0	1	0	0	1	0	0
Sitting	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Reaching	1	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0
Arising	1	0	0	0	0	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Standing	1	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Opening door	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Twisting and turning	0	0	0	0	0	1	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0
Turning head	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Running	0	0	0	0	0	0	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Walking	0	0	0	0	0	1	0	1	1	1	1	1	1	1	0	0	0	1	0	0	0	1	0	0	1	0	0
Balancing	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carrying or lifting	0	0	0	0	0	1	0	1	1	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0
Fine hand use	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0
Kneeling	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0
Squatting	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0
Level of independence - activities of daily living																											
Decreased activities	0	0	0	0	0	0	0	1	1	0	0	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1
Drinking and eating	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Personal care	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	1	0	1	1	0	
Caring for dependent	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Household chores	1	0	0	0	1	1	1	1	1	1	0	1	0	1	0	0	0	1	0	0	0	1	1	0	1	0	
Caring for pets	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Toileting	0	0	0	0	0	1	0	1	1	0	1	1	1	0	0	0	0	1	0	0	0	0	0	0	1	0	
Transferring	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Running errands	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	
Level of independence - dependence on medicinal substances and medical aid																											
Medicine	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Assistive device	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	
Personal products such as alcohol and cigarette	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Level of independence - work capacity																											
Affected your work	1	0	0	0	0	1	0	1	1	1	1	0	1	1	1	0	0	1	0	0	1	1	0	0	1		
Social relationship - personal relationships																											
Activities with family and friends	0	0	0	0	1	0	0	1	1	0	1	1	1	1	0	0	0	1	0	0	0	1	0	1	0	1	

Relationship with family and friends	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	1	0	0	0	0	1	1	0	1
Relationship with acquintance	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Social relationship - social support																										
Being understood	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Emotional support	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Physical support	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Social relationship - sexual activity																										
Impaired sexual life	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1
Relationship with partner	0	0	0	0	0	0	0	1	1	0	1	0	1	0	1	0	0	1	0	0	0	0	1	0	0	1
Discomfort during sexual intercourse	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Sexual function impairment	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Sex drive	0	0	0	0	0	0	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Environment - freedom, physical safety and security																										
Design of environment	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ability to do what you want to do	0	0	0	0	1	0	0	1	1	0	0	1	1	1	0	0	0	1	0	0	1	0	1	0	0	0
Environment - home environment																										
Design of home	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Family culture	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0
Environment - work satisfaction																										
Work culture	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Environment - financial resources																										
Financial losses	0	0	0	0	0	0	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Environment - health and social care																										
Being dismissed by healthcare professional	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0
Being prepared by healthcare professional	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0
Environment - opportunities for learning																										
Education	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Environment - participation in leisure activities																										
General recreation activities	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	1	0	0	0	0	1	1	0	1
Travelling	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Sports such as exercise, swimming, cycling	1	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	0	0	0	0	1	1	0	0
Socialisation	0	0	0	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0	0	0	0	1	1	1	0	1
Hobbies	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Environment - physical environment																										

Climate and temperature	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Environment -transport																											
Turning head while reversing	0	0	0	0	0	1	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Driving	0	0	0	0	0	0	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Looking into rear view mirror	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Getting in and out of car	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Taking public transportation	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Spirituality/religious/personal beliefs																											
Community/culture/religion	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Overall QoL and general health perception - general																											
Being able to adapt/cope	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1
General quality of life	0	1	1	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	1
Overall QoL and general health perception - treatment burden																											
Medication side effect	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1

Abbreviations: Spondyloarthritis (SpA), Quality of Life (QoL), Health Assessment Questionnaire – Spondyoarthritis (HAQ-S), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global (BASG), Patient Global Assessment (PGA), Pain Visual Analogue Score (Pain), Ankylosing Spondylitis Quality of Life (ASQoL), Patient-Reported Outcomes (PRO), Dougados Functional Index (DFI), Short-Form 36 (SF-36), Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQoL), Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), Europe (E), North America (NA), South America (SA), Africa (AF), Oceania (O), Asia (AS).

Supplementary Table 2: Topic guide for focus group discussions

1. Please take a few minutes individually to think about symptoms or effects of Spondyloarthritis?
    a. Could you please share the items on your paper with the group?

2. What are the different ways in which Spondyloarthritis affects your life?
    a. Prompt
        i. Physical symptoms
        ii. Emotional symptoms
        iii. Social and life roles
        iv. Variation in disease states
        v. Disease manifestations
        vi. World Health Organization Quality of Life Domains

3. In what ways has your life changed since you were diagnosed with Spondyloarthritis?

4. Is there anything you will like to add?

Supplementary Table 3. QoL domains and subdomains relevant to patients with SpA by subtype of SpA and compared with commonly used PROMs

Subbdomains	Commonly used PROMs in axial SpA[1]								Axial SpA[1] (N=34, FGD=6)	PsA[2] (N=17, FGD=3)	Commonly used PROMs in PsA[3]						
	BASFIS	BASG	PGA	Pain	ASQoL	HAQS	DFIS	SF-36G			Pain	PGA	SF36	DLQI	PsAQoL	HAQ	FACITF
General or disease specific PROM																	
Physical - general																	
Strength									✓	✓✓							
Weight and tone									✓✓	✓✓							
Physical - pain and discomfort																	
General pain				✓	✓	✓		✓	✓✓✓✓✓✓	✓✓✓	✓		✓			✓	✓
Back pain									✓✓✓✓✓✓	✓✓✓							
Neck pain									✓✓✓✓✓✓	✓							
Hip pain									✓✓✓✓	✓✓							
Joint pain									✓✓✓✓✓✓	✓✓✓							
Leg pain									✓✓✓✓✓	✓✓✓							
Rib pain		*Not found to be relevant to patients*										*Not found to be relevant to patients*					
Skin pain		*Not found to be relevant to patients*										*Not found to be relevant to patients*					
Chest and abdomen pain									✓	✓							
Tender to touch									✓	✓							
Other discomfort									✓✓✓✓	✓✓				✓			
Physical- energy and fatigue																	
Fatigue					✓			✓	✓✓✓✓✓	✓✓✓			✓		✓		✓
Time to recover		*Not found to be relevant to patients*										*Not found to be relevant to patients*					
Easily tired					✓				✓✓			*Not found to be relevant to patients*					
Weakness		*Not found to be relevant to patients*										*Not found to be relevant to patients*					
Physical - sleep and rest																	
Sleep quality									✓✓✓	✓✓							✓
Ability to sleep on certain position							✓		✓✓✓✓✓	✓✓✓							
Daytime sleepiness		*Not found to be relevant to patients*										*Not found to be relevant to patients*					
Waking from pain									✓✓	✓✓✓							

Need for rest			✓		*Not found to be relevant to patients*	
Insomnia	✓		✓✓✓✓			
			Physical - symptom			
General			✓✓	✓✓		✓
Headache	*Not found to be relevant to patients*				*Not found to be relevant to patients*	
Swelling			✓✓✓✓✓	✓✓✓		
Stiffness			✓✓✓✓✓✓	✓✓✓		
Muscle cramps			✓			
Visual problems			✓✓✓✓✓	✓✓		
Hearing problem	*Not found to be relevant to patients*				*Not found to be relevant to patients*	
Digestive problems	*Not found to be relevant to patients*				*Not found to be relevant to patients*	
Skin and nail problems			✓✓	✓✓✓		
Other musculoskeletal problems			✓✓✓✓✓	✓✓✓		
			Psychological - positive feelings			
Drive and motivation	*Not found to be relevant to patients*				*Not found to be relevant to patients*	
Optimism			✓✓✓✓✓	✓✓		✓
New perspective			✓✓✓✓	✓✓✓		✓
			Psychological - thinking, learning, memory and concentration			
Concentration			✓✓	✓✓		
Memory			✓			
Problem solving	*Not found to be relevant to patients*				*Not found to be relevant to our patients*	
Learning	*Not found to be relevant to patients*				*Not found to be relevant to our patients*	
			Psychological - self-esteem			
Low self-esteem			✓✓	✓✓✓		
Embarrassment		✓	✓✓	✓✓✓	✓	
			Psychological - bodily image and appearance			
Self-image			✓	✓✓✓		
			Psychological - negative feelings			
Stress	*Not found to be relevant to patients*			✓✓	✓	
Anxiety		✓	✓	✓✓	✓	✓
Worry	✓		✓✓✓✓	✓		✓
Fear			✓✓✓	✓		

Hopelessness					✓			*Not found to be relevant to patients*		
Injustice		*Not found to be relevant to patients*						*Not found to be relevant to patients*		
Premature ageing		*Not found to be relevant to patients*				✓✓			✓	
Resigned		*Not found to be relevant to patients*						*Not found to be relevant to patients*		
Frustrated		✓			✓				✓	✓
Depressed		✓		✓	✓✓✓✓✓	✓✓		✓	✓	✓
Withdrawn		*Not found to be relevant to patients*				✓✓				
Guilt					✓	✓				
Irritated		*Not found to be relevant to patients*		✓		✓✓		✓		
Lack of motivation		*Not found to be relevant to patients*						*Not found to be relevant to patients*		
Missing out		*Not found to be relevant to patients*						*Not found to be relevant to patients*		
					Level of independence - general					
General depenence		*Not found to be relevant to patients*						*Not found to be relevant to patients*		
					Level of independence - mobility					
Decreased mobility			✓		✓✓✓✓✓	✓✓				
Bending	✓	✓	✓	✓	✓✓✓✓	✓		✓	✓	
Climbing stairs	✓	✓	✓	✓	✓✓✓✓	✓✓✓		✓	✓	
Sitting		✓	✓		✓✓✓✓✓	✓				
Reaching	✓	✓			✓✓✓				✓	
Arising	✓	✓	✓		✓✓	✓✓			✓	
Standing	✓		✓		✓✓✓	✓				
Opening door		*Not found to be relevant to patients*				✓			✓	
Twisting and turning		*Not found to be relevant to patients*						*Not found to be relevant to patients*		
Turning head	✓				✓✓✓✓✓			*Not found to be relevant to patients*		
Running			✓	✓	✓✓✓	✓✓		✓		
Walking		✓		✓	✓✓✓✓✓✓	✓✓✓		✓	✓	
Balancing					✓			*Not found to be relevant to patients*		
Carrying or lifting		✓		✓	✓✓✓✓✓✓	✓✓		✓		
Fine hand use		✓			✓✓	✓✓✓			✓	
Kneeling					✓✓			*Not found to be relevant to patients*		
Squatting					✓✓✓✓			*Not found to be relevant to patients*		
					Level of independence - activities of daily living					
Decreased activities					✓✓✓	✓✓				✓

Drinking and eating				✓			✓			*Not found to be relevant to patients*				
Personal care	✓		✓	✓	✓		✓✓✓			*Not found to be relevant to patients*				
Caring for dependent							✓✓			*Not found to be relevant to patients*				
Household chores	✓		✓	✓	✓	✓	✓✓✓✓		✓	✓		✓		
Caring for pets		*Not found to be relevant to patients*								*Not found to be relevant to patients*				
Toileting				✓			✓		✓				✓	
Transferring		*Not found to be relevant to patients*								*Not found to be relevant to patients*				
Running errands				✓			✓			*Not found to be relevant to patients*				
Level of independence - dependence on medicinal substances and medical aid														
Medicine							✓✓✓✓✓✓	✓✓✓						
Assistive device				✓			✓			*Not found to be relevant to patients*				
Personal products such as alcohol and cigarette		*Not found to be relevant to patients*								*Not found to be relevant to patients*				
Level of independence - work capacity														
Affected your work	✓			✓		✓	✓✓✓✓✓✓	✓✓✓	✓	✓				✓
Social relationship - personal relationships														
Activities with family and friends			✓			✓	✓	✓			✓			✓
Relationship with family and friends		*Not found to be relevant to patients*								*Not found to be relevant to patients*				
Relationship with acquintance		*Not found to be relevant to patients*								*Not found to be relevant to patients*				
Social relationship - social support														
Being understood							✓✓✓✓	✓✓✓						✓
Emotional support							✓✓✓✓✓✓	✓✓✓						✓
Physical support							✓✓✓	✓						✓
Social relationship - sexual activity														
Impaired sexual life							✓✓✓✓	✓		*Not found to be relevant to patients*				
Relationship with partner							✓✓			*Not found to be relevant to patients*				

Discomfort during sexual intercourse				✓			*Not found to be relevant to patients*			
Sexual function impairment				✓✓✓	✓		*Not found to be relevant to patients*			
Sex drive				✓	✓✓					
Environment - freedom, physical safety and security										
Design of environment	*Not found to be relevant to patients*						*Not found to be relevant to patients*			
Ability to do what you want to do	*Not found to be relevant to patients*						*Not found to be relevant to patients*			
Environment - home environment										
Design of home				✓✓✓✓✓			*Not found to be relevant to patients*			
Family culture	*Not found to be relevant to patients*						*Not found to be relevant to patients*			
Environment - work satisfaction										
Work culture				✓✓✓✓✓			*Not found to be relevant to patients*			
Environment - financial resources										
Financial losses				✓✓✓✓✓✓	✓✓✓					
Environment - health and social care										
Being dismissed by healthcare professional				✓✓	✓					
Being prepared by healthcare professional				✓	✓✓					
Environment - opportunities for learning										
Education	*Not found to be relevant to patients*						*Not found to be relevant to patients*			
Environment - participation in leisure activities										
General recreation activities	*Not found to be relevant to patients*						*Not found to be relevant to patients*			
Travelling				✓	✓					
Sports such as exercise, swimming, cycling	✓		✓	✓✓✓✓✓	✓✓✓		✓	✓		
Socialisation			✓	✓✓	✓✓		✓	✓	✓	✓
Hobbies				✓✓	✓					
Environment - physical environment										
Climate and temperature				✓✓	✓✓					

Environment -transport									
Turning head while reversing		✓	✓✓✓			*Not found to be relevant to patients*			
Driving			✓✓✓			*Not found to be relevant to patients*			
Looking into rear view mirror	*Not found to be relevant to patients*					*Not found to be relevant to patients*			
Getting in and out of car	*Not found to be relevant to patients*					*Not found to be relevant to patients*			
Taking public transportation			✓✓✓	✓					
Spirituality/religious/personal beliefs									
Community/culture/religion			✓✓✓✓✓	✓✓					
Overall QoL and general health perception - general									
Being able to adapt/cope			✓✓✓✓	✓✓✓					✓
General quality of life	*Not found to be relevant to patients*		✓	✓		✓	✓		✓
Overall QoL and general health perception - treatment burden									
Medication side effect			✓✓✓✓✓	✓✓✓				✓	✓

[1]Classified to have axial SpA using the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria for axial Spondyloarthritis. [2]Diagnosed with psoriatric arthritis using 2006 classification criteria for psoriatic arthritis (CASPAR).
The number of ticks in the cells refers to the number of focus group discussions reporting the affected main effect of SpA or meant that the PROM captured the respective main effects of SpA. Empty boxes meant that the main effect was not relevant to the patients or not captured by the PROMs.
Abbreviations: Spondyloarthritis (SpA), Psoriatic Arthritis (PsA), Quality of Life (QoL), Health Assessment Questionnaire – Spondyoarthritis (HAQ-S), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global (BASG), Patient Global Assessment (PGA), Pain Visual Analogue Score (Pain), Ankylosing Spondylitis Quality of Life (ASQoL), Patient-Reported Outcome Measures (PROM), Dougados Functional Index (DFI), Short-Form 36 (SF-36), Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQoL), Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), general PROM (G), disease specific PROM (S).

Supplementary Table 4. QoL domains and subdomains relevant to patients with SpA and their supporting quotes

Subdomains	Quotes
Physical - general	
Strength	"It was so painful and it affects my legs and back, my legs are deformed, both feet. I don't have strength to walk." - Chinese speaking patient with axSpA "ya, I just feel that I don't have any strength to get up" – English speaking patient with PsA
Weight and tone	"On average, I only eat 1 meal a day. And I don't really feel like eating for that one meal, I really have no appetite. I lost more than 20kg." -Chinese speaking patient with axSpA "Yeah, I lost a lot of weight. And my legs were very skinny." - English speaking patient with axSpA
Physical - pain and discomfort	
General pain	"Not really its just that its sitting too long then you will feel the.. actually the pain is not that very sharp pain but its like the pain is just go off lor so just have to move abit if you are too busy you just continue on for like 1-2h then get up" – English speaking patient with axSpA "I have the same experience like Ms Z. in the morning, when you need to wake up even you have to really stretch out first, with the pain, even though you are pain but you still have to do some stretching before you can move about." – English speaking patient with PsA
Back pain	" Mine is lower back pain" – English speaking patient with axSpA "Basically then I also have body aches. My body felt very stiff. But I think prior to that, 2011, about three years before that, I actually have a lot of my pain in my back." – English speaking patient with axSpA
Neck pain	"Lower back, chest, neck" – English speaking patient with axSpA "Ya, is the joints and my neck, pain, but it cannot turn, that time, because for my case, my my, most of my joints actually." – English speaking patient with PsA
Hip pain	"Yea so no more problems with the knees no more pain anywhere else other than the hip" – English speaking patient with axSpA "Develop skin rashes on my head, my fingers, and some parts of my legs and toes, then I have stiff fingers, swelling, besides this, I got joints pain on my hips"- English speaking patient with PsA
Joint pain	"I had the problem for about 11 years it was about 2005 when I was still a student an initially the pain affected actually my knee, just one knee, my left knee" – English speaking patient with axSpA "when it started it started with the major joints like the knees and the ankles, and, but every joint would would be painful"- English speaking patient with PsA
Leg pain	"Because when you are in pain, the way you walk, you limp and you cannot walk properly and people will stare at you" – English speaking patient with axSpA "My feet hurt, the upper part, I felt pain even walking." – Chinese speaking patient with PsA
Rib pain	*Not found to be relevant to patients*
Skin pain	*Not found to be relevant to patients*
Chest and abdomen pain	"Uh back leg chest so just don't lie" – English speaking patient with axSpA "The pain concentrate in the chest area" – English speaking patient with PsA
Tender to touch	"Ya, when you just step only you can feel the pain" – English speaking patient with PsA "You touch the scalp you can feel pain" – English speaking patient with PsA
Other discomfort	" You can feel, some part of the scalp will be normal, some part will be scaly, so you can feel there is a difference in the texture. And that part there is scaly will become more itchy" – English speaking patient with PsA :"I was in discomfort for an hour" – Chinese speaking patient with axSpA

Physical- energy and fatigue	
Fatigue	"I will feel tired when walking. But I will take a break and sit down when I feel tired after walking" – Chinese speaking patient with PsA "Really feel drained because I am not taking medications" – English speaking patient with axSpA
Time to recover	*Not found to be relevant to patients*
Easily tired	"Yes. As long as I go out, I will be very tired. AS takes up a lot of my energy. It will. I get tired very easily. Maybe I leave at 8am, by 8pm I am so tired but I still have to work. So by the time I go home, I enjoy lying down on my bed. There are definitely still restrictions. Unlike my friend who can pull all-nighter. It suck up a lot of my energy" – Chinese speaking patient with axSpA "Maybe I just walk from here, like normal walk. But a bit faster, maybe within two to three minutes, I will get tired" – English speaking patient with axSpA
Weakness	*Not found to be relevant to patients*
Physical - sleep and rest	
Sleep quality	"Ask you whether you sleep well or not last night then we will tell them ah I pain cannot sleep well last night then you know the condition already what because I think that sleep is very important once you get pain you cannot sleep well, I ankle pain I also cannot sleep well" – English speaking patient with axSpA
Ability to sleep on certain position	"You cannot stand up you cannot do anything you cannot turn you lie on the bed you turn abit its like something poke you like that its very painful" – English speaking patient with axSpA "Uh, arthriits, sometimes it was because of leg pain. I can only sleep sideways, then will press onto the legs, pain, I have to change my sleeping position. Now, I am visiting for sleep disorder" – Chinese speaking patient with PsA
Daytime sleepiness	*Not found to be relevant to patients*
Waking from pain	"When I wake up I don't know what to do because it is as pain as hell" – English speaking patient with axSpA "It is the swelling of one side, so cannot really sleep on that side. If you have any sudden movement, then you will feel the pain and then you wake up. For now it is fine." – English speaking patient with axSpA
Need for rest	" Anyway, so sleep is a huge problem for me. Some morning, the sky gets bright, the birds start singing, I am still like you know, need sleep. So this interferes with my work, and it has for many years" – English speaking patient with axSpA
Insomnia	" I have the problem for 10 years, I mean ihave been taking medications, I take small doses everyday I take it so that I can sleep at night because if I don't take and I cant get a proper night sleep then the next day you just can't do things properly" – English speaking patient with axSpA "One of the side effect is insomnia, so you are in pain and you have insomnia, it will affect my perfomance"- Chinese speaking patient with axSpA
Physical - symptom	
General	" Normally, I can climb. It's just that my balance is affected because of this problem." Chinese speaking patient with axSpA "In 2008, I started to have nose bleed. Then I have back pain, it started to radiate to the front." Chinese speaking patient with PsA
Headache	*Not found to be relevant to patients*
Swelling	" Because I have swollen knee cap so they help me to extract the fluid from the ankle I went to A&E a lot of times its really very bad until I have the infliximab drip that was actually back to 2013 the disease has been quite well controlled la at the same time I also control my weight not to put on too much weight and too much pressure" English speaking patient with axSpA "And this leg, this leg swollen in March 2014" English speaking patient with PsA
Stiffness	"Means you are not able to bend so become la hokkien term kiauku. Become very fixed position" English speaking patient with axSpA "Pain will get very strong then your leg… become very stiff" English speaking patient with PsA
Muscle cramps	"Cramp. Sleeping position" Chinese speaking patient with axSpA "If not we will feel cramp, numb" Chinese speaking patient with axSpA
Visual problems	"Senstitive to light. Pain till I cry. That is when I close my eyes, I can sense light. It was so painful that when I close my eyes, made me tearful" Chinese speaking patient with axSpA " Then the other thing, I notice I have but none of you all raised is because I do have uveitis, the eyes. Which is linked to the condition. It has flared up quite a few times alr. So what the eye centre, what I am seeing, they give me some kind of steroid eyedrops" English speaking patient with axSpA

Hearing problem	*Not found to be relevant to patients*
Digestive problems	*Not found to be relevant to patients*
Skin and nail problems	"Of course, my psoriasis affect whole body from head to toe" English speaking patient with PsA "My skin, I started to have rashes. Then I got referred to dermatology" Chinese speaking patient with axSpA
Other musculoskeletal problems	"I think my toes does somewhat deformed because of the arthritis, I can't wear court shoes" English patient with PsA "See, my bones. I have hammer toes. It was so serious" Chinese speaking patiet with axSpA
Psychological - positive feelings	
Drive and motivation	*Not found to be relevant to patients*
Optimism	"Positive attitude because you are already in this situation I mean you only can help yourself" English speaking patient with axSpA "There's some hope" English speaking patient with PsA
New perspective	"Especially when you know you need to rely on medication for long term especially the painkiller you will come to accept" English speaking patient with axSpA "Yes, because I always feel that, I always think positive that we have now, other people might be more worse than me" English speaking patient with PsA
Psychological – thinking, learning, memory and concentration	
Concentration	"I think I had quite short attention span" English speaking patient with PsA "Not memory, but concentration. I get fatigued when I lack sleep." English speaking patient with axSpA
Memory	"Yes. Sometimes, I forgot to take something, no memory" Chinese speaking patient with axSpA
Problem solving	*Not found to be relevant to patients*
Learning	*Not found to be relevant to patients*
Psychological - self-esteem	
Low self-esteem	"Ya. In the beginning where it really flaring all the time, and with my arthritis, with my psoriatic, psoriatic arthritis together, then they really flare up, I feel really useless that time" English speaking patient with PsA "And it's not about, erm, well, one you you feel very self-conscious, you wonder what people will think. Because, I mean, if somebody else had it, you look, is a natural human instinct, is that something different about somebody, you take a second look" English speaking patient with PsA
Embarrassment	"I have all kind of symptoms sometimes numb sometimes you can feel the cracking sound you know when I get up from the seat you need to adjust if not will piak its really very loud even on the MRT people will look at me eh the sound is It from where its really very loud" English speaking patients with axSpA "Unless you, sometimes I really want to walk with a cane but I'm embarrassed" Chinese speaking patient with axSpA
Psychological - bodily image and appearance	
Self-image	"So I stop meeting, I stop meeting friends, because you go to friend's house, you take your shoes, right? Then your your nails are deformed, so very unsightly, so I stop" English speaking patient with PsA "People are afraid to look at when I go out and walk" Chinese speaking patient with PsA
Psychological - negative feelings	
Stress	"Ah yea yea, and I agree with Ms Z, I think stress pain place a very important part for the disease also." English speaking patient with PsA "Very stressful" English speaking patient with PsA
Anxiety	"Correct, correct. There is this feeling, there is always this thinking, when am I going to get better? Because the medicine just don't work, I tried a lot, then I, really try to stay away from taking oral medication or injection if possible actually that kind. Ya." English speaking patient with PsA "Not concern about that, but what what I, I would like to know is whether the doctor can predict in advance the certain certain state, at certain time, this particular symptoms will flare up then you can plan in advance, whether to travel or not. Am I able to that?" English speaking patient with PsA

Worry	"Worried about financial burden and medical fees" Chinese speaking patient with axSpA "Yes, I am very worried about how it will affect my future children. More or less" Chinese speaking patient with axSpA
Fear	"I am afraid my kids will inherit this illness" Chinese speaking patient with axSpA "Yea… actually I am fearful. I actually brought him to the orthopedic about a year ago to get it checked up so far thank goodness its not" English speaking patient with axSpA
Hopelessness	"Hopeless, helpless" English speaking patient with axSpA
Injustice	*Not found to be relevant to patients*
Premature ageing	"And plus I have like high cholesterol also, so like, like my body is older than my grandmother's body. Ya, so is like, I just don't tell them anything at all also" English speaking patient with PsA "Because before I went onto the biologics, as I said earlier, I felt I aged from being in my mid 40s to 70s, you know" English speaking patient with PsA
Resigned	*Not found to be relevant to patients*
Frustrated	"And then when you pain you very frustrated because you have to go out and you have to cancel appointment, family can understand, friends don't understand, affected our lifestyle because we need social friends so that does affect also la then people will start to ask you how come when you walk you start to limp then you have to explain all over again yea that kind of thing so you affected also" English speaking patient with axSpA
Depressed	"For me ah, I don't feel much fatigue but feel depressed" English speaking patient with PsA "Just cry" English speaking patient with axSpA
Withdrawn	"Especially the patches on my head, wa, last time is red, I lost my self-confidence, I go out I scared, all the people look at me" English speaking patient with PsA "And then you just don't want to talk to them" English speaking patient with PsA
Guilt	"Because it's genetical for me, so my dad felt very bad because he felt that it was his genes but the thing is that for me it's both sides so he was actually felt quite guilty about it" English speaking patient with axSpA "And and, this is the hereditary in their perception, so parents don't have it how come kids have it" English speaking patient with PsA
Irritated	"She can walk at 5-6 years old. I will lose my temper when I am in pain" Chinese speaking patient with PsA "I just don't want it to flare up, and now it's flaring up so that the, that's, that's upsetting sometimes, ya, is very irritating" English speaking patient with PsA
Lack of motivation	*Not found to be relevant to patients*
Missing out	*Not found to be relevant to patients*
Level of independence - general	
General depenence	*Not found to be relevant to patients*
Level of independence - mobility	
Decreased mobility	"Yea, you cannot move" English speaking patient with axSpA "Movement. There's some restrictions because I am unable to turn to the left. So it's inconvenient" Chinese speaking patient with axSpA
Bending	"For some reason, the eye doctor told me to bend down in front of her. I was not able to reach my toes, and she was quite shocked" English speaking patient with axSpA "I have trouble cutting my toe-nails. I have trouble bending over, I cannot reach. Maybe because of the stiffness at the back. I can't reach, cannot bend over" English speaking patient with axSpA

Climbing stairs	"Both knees climb up and down the stairs are painful" English speaking patient with PsA "Last time I can still climb, now it is very difficult" Chinese speaking patient with axSpA
Sitting	"Yea and aircon room so I think that is the pain problem keep sitting and the whole day sitting and go back sleep already so never do any exercise" English speaking patient with axSpA "So far when I starting, cannot cope, because the body will feel like burning, cannot sit too long on the chair" English speaking patient with axSpA
Reaching	"Housework, you can't reach you have got to get the long poles with the clap because you can't quite stretch" English speaking patient with axSpA "I have trouble cutting my toe-nails. I have trouble bending over, I cannot reach" Chinese speaking patient with axSpA
Arising	"Yes, it's all of my joints. And especially, I need help to to even wake up. My husband need to pull me up" English speaking patient with PsA "I cannot sit because once I sit, I can't get up. I have to sleep on higher bed, so I have to sit down to shower" Chinese speaking patient with axSpA
Standing	"You cannot stand up you cannot do anything you cannot turn you lie on the bed you turn abit its like something poke you like that its very painful" English speaking patient with axSpA "Even fifteen minutes, if I stand stationary, if I waiting for a train or bus, for fifteen minutes not moving, my knees after that I got problem walking" English speaking patient with PsA
Opening door	"You cannot even like hold things, open the door, no, all that cannot" English speaking patient with PsA
Twisting and turning	*Not found to be relevant to patients*
Turning head	"You are in stand position and moving suddenly it's just like oh shit something is wrong you can't turn, you turn it's like" English speaking patient with axSpA "There's some restrictions because I am unable to turn to the left. So it's inconvenient." Chinese speaking patient with axSpA
Running	"Some days can't run lor or you notice your endurance is less than your classmates" English speaking patient with axSpA "So I thought that maybe because of my regular jogging that caused some injury to the knees. But it did not hit in the first place, so I just continue as usual until following that the pain slowly set in" English speaking patient with PsA
Walking	"People will start to ask you how come when you walk you start to limp then you have to explain all over again yea that kind of thing so you affected also" English speaking patient with axSpA "I couldn't walk, I cannot do anything" English speaking patient with PsA
Balancing	"I will have difficulty walking because my balance is very bad. So I suspect it's the stiffness, I cannot balance." Chinese speaking patient with axSpA "If I squat, I will lose my balance." Chinese speaking patient with axSpA
Carrying or lifting	"Means normal as long as I don't carry heavy things then it's okay" English speaking patient with axSpA "But if I need to carry heavy stuff or my hands need to touch my back then it will be very painful" Chinese speaking patient with axSpA
Fine hand use	"Yes, even pen. After the neurosurgery, it got better but I still have trouble holding things that are thin like" Chinese speaking patient with axSpA "Ya, your hands all will be like sausage. And you can't even clench your fist" English speaking patient with PsA
Kneeling	"Even I mean, as the age goes by because the inflammation goes upwards it will reach ¾ of my spine recently I just had a….prayer so you cannot kneel too long" English speaking patient with axSpA

	"Yeah the knee is very important, cannot kneel" English speaking patient with axSpA
Squatting	"When I stand up I cannot squat because you felt your legs are stretched" Chinese speaking patient with axSpA "Those chores that requires to bend, squat, those I don't do" English speaking patient with axSpA
Level of independence - activities of daily living	
Decreased activities	"I cannot do anything" English speaking patient with PsA "Like I like to go for aerobics, then dance and all these. So I was quite restricted in a lot of activities" English speaking patient with axSpA
Drinking and eating	"The joints here because I cannot open my mouth to eat and my hands are twisted, I cannot raise them up, my fingers are deformed" Chinese speaking patient with axSpA
Personal care	"I have trouble cutting my toe-nails" Chinese speaking patient with axSpA "It is difficult. Sometimes I cannot touch my toes. Putting on socks, I have no problem but I cannot cut my toenail" English speaking patient with axSpA
Caring for dependent	"And the last case, when I tried to teach a two year old to ride a tricycle, I had to bend over, practically drag this one. I could not move for a couple of days. The back was so painful" English speaking patient with axSpA
Household chores	"Don't need to do house work. The moment I mope the entire house I need to rest the whole day already" English speaking patient with axSpA "For half a month, I was at home when I couldn't walk, I sit on the floor to mop it. How do I mop? No need mop, I always use a cloth to clean the floor. When my legs hurt, I kneel down and mop slowly" Chinese speaking patient with axSpA
Caring for pets	*Not found to be relevant to patients*
Toileting	"I cannot sit up also, so that is my, during my first 2 years, is a very bad where I can't even even when I need to go to toilet, somebody must really hold me back, bring me to the toilet" English speaking patient with PsA "When I went to toilet and squat, I realized my knee were very swollen, very painful. I cannot stand up. I slowly pushed myself to stand up, then I realized it was very swollen" Chinese speaking patient with axSpA
Transferring	*Not found to be relevant to patients*
Running errands	"My joints, when carrying groceries and cutting my toenails, it was very painful for me" English speaking patient with axSpA
Level of independence - dependence on medicinal substances and medical aid	
Medicine	"I have the problem for 10 years, I mean I have been taking medications, I take small doses everyday I take it so that I can sleep at night because if I don't take and I can't get a proper night sleep then the next day you just can't do things properly" English speaking patient with axSpA "It affects me, I need sleeping pills" Chinese speaking patient with axSpA
Assistive device	"Walking is really tiring, I will sweat a lot after a short walk. I used the cane for many years" Chinese speaking patient with axSpA
Personal products such as alcohol and cigarette	*Not found to be relevant to patients*
Level of independence - work capacity	

Affected your work	"So initially it affected my job because I keep taking MC I try a lot of medicine I also cannot stop the pain so my boss is also not a very understanding boss la my job was also being terminated that time I say what is the reason of termination she say because you take too many MC because one year only limited to 14 days more than that is unpaid leave so I can take up to 2 months of unpaid leave so she not very happy so she terminated my services" English speaking patient with axSpA "That time, I stopped working for half a year because I cannot work anymore" Chinese speaking patient with axSpA
Social relationship - personal relationships	
Activities with family and friends	"But like I said, I am the favourite aunt in the clan. So it is a bit depressing. because I can't- I do try to teach them how to ride bicycle, and climb the jungle gym and all that. So I am very much limited in that direction" English speaking patient with axSpA "Because on weekends, like Saturday and Sunday, I don't feel like going out at all, my wife, let's go out for lunch or meal, I said I'm sorry" English speaking patient with PsA
Relationship with family and friends	*Not found to be relevant to patients*
Relationship with acquintance	*Not found to be relevant to patients*
Social relationship - social support	
Being understood	"Ah so whenever we have any activities, I know my symptoms is coming or I have schedule for infliximab drip I will tell my teammate I have this thing happening on this day they are very nice they change the date for me or sometimes my MD I tell my MD I cannot participate in this game" English speaking patient with axSpA "Ya, You so hygienic, how come you got this skin disease and all these things, they don't understand, and even.." English speaking patient with axSpA
Emotional support	"For family wise I think we getting stronger because brother and sister they are concerned" English speaking patient with axSpA "Ya, during the time where re-flaring up all that, of course relationship, my husband, right. So, but then, he is the one very supportive husband, so er, I'm very lucky" English speaking patient with PsA
Physical support	"Whenever I need help, the church friends will help or if I want to go somewhere, they will give me a lift" Chinese speaking patient with axSpA "My relative will come over to help look after my child" Chinese speaking patient with PsA
Social relationship - sexual activity	
Impaired sexual life	"Definitely sexual drive is lot less and active sexual life is compromised" English speaking patient with axSpA "Might have arousal and penis erection difficulties" Chinese patient with PsA
Relationship with partner	"I am worried, if I were to have a girlfriend, how she would think of me. Will she accept me?" Chinese speaking patient with axSpA "I have had a partner before, who didn't accommodate at all. It was very tiresome" English speaking patient with axSpA
Discomfort during sexual intercourse	"Performance is sometimes affected by stiffness of neck, shoulder, back and limb joints" English speaking patient with axSpA
Sexual function impairment	"It will be passed on, so play safe" English speaking patient with axSpA "The condition of the spine or back affect intimacy with my wife – mobility" English speaking patient with axSpA
Sex drive	"Reduced sex drive after consumption of medication" Chinese speaking patient with PsA "As my body feels unwell, there is no mood for sex" Chinese speaking patient with axSpA
Environment - freedom, physical safety and security	
Design of environment	*Not found to be relevant to patients*

Ability to do what you want to do	*Not found to be relevant to patients*
Environment - home environment	
Design of home	"The matteress is extremely important for me. It has to be very hard, a lot support not the support" English speaking patient with axSpA "I have to choose the chair for me to sit. because if it is not suitable, the pain will come. The back here will ache" English speaking patient with axSpA
Family culture	*Not found to be relevant to patients*
Environment - work satisfaction	
Work culture	"Basically its actually 6 weeks I have to go back but this is actually under my company claim so my company has been treating me quite well I have been staying in this company for 9 years" English speaking patient with axSpA "There was once when I had to go for consultation every 2 weeks later, because I still don't know what is the problem, I have to keep going for doctor's appointment. So you will keep taking medical leave, keep going for consultation. Then the boss cannot decide to give you more work or not. Sometimes, I look well but they don't understand it's because of the painkillers. When the boss stress me, my condition worsen." Chinese speaking patient with axSpA
Environment - financial resources	
Financial losses	"Cause it's very expensive that one one year at least 20k. Now the new drug, the medicine itself is already 5k which is more expensive than infliximab so after deduct medisave I still have to pay cash" English speaking patient with axSpA "So then medicine the jab one is very expensive, which I can't afford, it will drain up my savings, so thanks God that time was they, there's a clinical trial, so I was put on the clinical trial, and thanks God again" English speaking patient with PsA
Environment - health and social care	
Being dismissed by healthcare professional	"Because if the doctors are very umm… you know very… I guess not very umm… encouraging, not caring, I understand that doctors have to take a step back, but I think patients when they come, and when they're in a lot of pain, er expect some kind of empathy" English speaking patient with PsA "The doctor see me, he ask me to do the back exercise but as a doctor you need to know what's happening to me, every time I come to see you, you patronize me, the patient is still in pain" Chinese speaking patient with axSpA
Being prepared by healthcare professional	"That's why I really appreciate her for for taking care of me. Is really really very good. She give me a lot of encouragement. Whenever I see her she gave me, a lot of encouragement, a lot of hope" English speaking patient with PsA "Ya, I guess I'm part of the Psoriasis Association in Singapore. So there are support groups around and you can participate in the activities and get to know other patients and share your experience" English speaking patient with PsA
Environment - opportunities for learning	
Education	*Not found to be relevant to patients*
Environment - participation in leisure activities	
General recreation activities	*Not found to be relevant to patients*
Travelling	"If you want to be a third world country to be a missionary or what with no access to medical care then that maybe an issue. My friends are going to highlands for 3 weeks kind of thing I mean I can go but maybe not" English speaking patient with axSpA "So ya, I don't go travelling to those places. That's the kind of restriction for me" English speaking patient with PsA

Sports such as exercise, swimming, cycling	"Some days can't run or you notice your endurance is less than your classmates" English patient with axSpA "So at first the pain was still bearable, so continue jogging, then after that slowly became worst, so I have to, after a few months, two or three months down the road, I find that cannot jog anymore. Just too painful" English speaking patient with PsA
Socialisation	"And then when you pain you very frustrated because you have to go out and you have to cancel appointment, family can understand, friends don't understand, affected our lifestyle because we need social friends so that does affect also then people will start to ask you how come when you walk you start to limp then you have to explain all over again yea that kind of thing so you affected also" English speaking patient with axSpA "So I stop meeting, I stop meeting friends, because you go to friend's house, you take your shoes, right? Then your your nails are deformed, so very unsightly, so I stop meeting people" English speaking patient with axSpA
Hobbies	"They can tell you even the person who massage you can tell you your back is really stiff so that is something that you can't enjoy" English speaking patient with axSpA "Last time I used to knit" Chinese speaking patient with axSpA
Environment – physical environment	
Climate and temperature	"I find I go to cold places, no pain, better" English speaking patient with axSpA "Yea you feel more aches I mean the Chinese say its like some superstition but you do feel in colder condition whether if the aircon is very cold or it rains a lot you feel abit more tight" English speaking patient with axSpA
Environment -transport	
Turning head while reversing	"When I drive, I cannot turn over the shoulders to see, it's very difficult" Chinese speaking patient with axSpA "So I learnt to reverse with just using the mirrors" English speaking patient with axSpA
Driving	"My legs have no strength and it's very pain to step on the clutch" Chinese speaking patient with axSpA "For those with AS, driving is a problem. And then for me, especially the neck, I cannot turn. I am not saying people with AS shouldn't drive, but you know the condition" English speaking patient with axSpA
Looking into rear view mirror	*Not found to be relevant to patients*
Getting in and out of car	*Not found to be relevant to patients*
Taking public transportation	"In the northeast line cannot even find a handle sometimes when I flared up ah cannot stand cannot sit don't know what to do you know" English speaking patient with axSpA "It is actually difficult you know people see me as a able person I am not an old auntie or someone" English speaking patient with axSpA
Spirituality/religious/personal beliefs	
Community/culture/ religion	"Healing from God" English patient with PsA "Take your mind away from the problem" Chinese speaking patient with axSpA
Overall QoL and general health perception - general	
Being able to adapt/cope	"It's just to get your life on, and not let this to hamper you and like oh what I have got this it doesn't help you you see why I got this" English speaking patient with axSpA

	"Ya, so you must adjust to life that was I really have to face, so you need to adjust to it" English speaking patient with PsA
General quality of life	"Because at the start, there is physiotherapy, so you need to make frequent trips. And my camp is not very accessible" English speaking patient with axSpA "For my my depressive, because no quality of life" English speaking patient with PsA
Overall QoL and general health perception – treatment burden	
Medication side effect	"So for me I never miss appointment because I got renal problem also so these infliximab drip and arcoxia will affect your kidney and the steroid that you inject will affect your bone" English speaking patient with axSpA "Then the impact on work is, I also take a high dose of prednisolone. One of the side effect is insomnia, so you are in pain and you have insomnia, it will affect my performance" Chinese speaking patient with axSpA

Abbreviations: Spondyloarthritis (SpA), axial spondyloarthritis (axSpA) psoriatic arthritis (PsA)

Dependent variable (QoL_T): QoL score at Time T
Exposure variable ($Peripheral$): Presence of extra-spinal symptoms, ever.

$$E(QoL_T) = \beta_0 + \beta_1 Peripheral + \beta_2 T + \beta_3 Peripheral \times T + \beta_4 Age + \beta_5 Male + \beta_6 Hypertension + \beta_7 Disease\ Activitiy + \beta_8 Sulphasalazine + \beta_9 Disease\ Duration$$

where $T = \{1,0\}$ and Age and $Disease\ duration$ are continuous variables.

At	Time Variables	Effect of presence of peripheral arthritis, enthesitis or dactylitis on QoL at time T
T_0 Baseline	$T = 0$	β_1
T_1 1-year	$T = 1$	$\beta_1 + \beta_3$

Supplementary Figure 5. The linear predictor of the linear mixed model

Supplementary Figure 6: Quality checklist for each acupuncture session

No	Description	Done?
1	Patient counselling before acupuncture	Yes/ No/NA
2	Sanitization of the patient's skin	Yes/ No/NA
3	Sterile disposable needles of 0.25 mm diameter, 25 mm or 40 mm length and 0.30 mm diameter, 50 mm or 70 mm length depending on the acupuncture points.	Yes/ No/NA
4	Main acupoints: *Jiaji* (EXB2 华佗夹脊穴), *Shenshu* (BL23 肾俞穴), *Yaoyangguan* (DU3 腰阳关穴), *Mingmen* (DU4 命门穴), *Huantiao* (GB30 环跳穴), *Ashixue* (阿是穴)	Yes/ No/NA
5	Secondary acupoints: Blockage due to dampness and heat: Main points plus *Yinlingquan* (SP9 阴陵泉), *Quchi* (LI11 曲池), *Hegu* (LI4 合谷), *Waiguan* (SJ5 外关) Blockage due to dampness and coldness: Main points plus *Yinlingquan* (SP9 阴陵泉), *Zusanli* (ST36 足三里) Blockage due to stagnated blood: Main points plus *Geshu* (BL17 膈俞), *Xuehai* (SP10 血海), *Neiguan* (PC6 内关) "Yang" deficiency in kidneys: Main points plus *Taixi* (KI3 太溪), *Fuliu* (KI7 复溜), *Weizhong* (BL40 委中) Deficiency in the liver and kidneys: Main points plus *Ganshu* (BL18 肝俞), *Sanyinjiao* (SP6 三阴交), *Yanglingquan* (GB34 阳陵泉)	Yes/ No/NA
6	Acupoints for symptoms: Neck pain: Main points plus secondary points plus *Tianzhu* (BL10 天柱), *Dazhui* (DU14 大椎) Thoracic pain: Main points plus secondary points plus *Dazhu* (BL11 大杼), *Shenzhu* (DU12 身柱), *Zhiyang* (DU9 至阳) Lumbar pain: Main points plus secondary points plus *Ciliao* (BL32 次髎), *Zhibian* (BL54 秩边)	Yes/ No/NA
7	After eliciting the deqi sensation, the needles are left in place for 30 minutes.	Yes/ No/NA
8	Turn the needles every 10 minutes	Yes/ No/NA
9	After 30 minutes, take out the needles on the acupoints.	Yes/ No/NA
10	Patient counselling after acupuncture	Yes/ No/NA
11	Unintended/ side effects of treatment are noted	Yes/ No/NA

12. Remarks:

Appendix D (Publications)

Publications from this thesis (6)

For all these publications, I took the main role *in designing the study, data collection, analysis of data, interpretation of data and writing the paper* with guidance from my mentors.

- Kwan, Y. H., Fong, W., Tan, V. I. C., Lui, N. L., Malhotra, R., Ostbye, T., & Thumboo, J. (2017). A systematic review of quality-of-life domains and items relevant to patients with spondyloarthritis. *Semin Arthritis Rheum*, 47(2), 175-182.

- Kwan, Y. H., Fong, W., Leung, Y. Y., Tan, V. I. C., Yap, A. F., Lui, N. L., Yoon, S., Malhotra, R., Thumboo, J., & Ostbye, T. (2018). A qualitative study of Quality of Life domains and subdomains relevant to patients with Spondyloarthritis *International Journal of Rheumatic Diseases (In Review)*.

- Kwan, Y. H., Fong, W. W., Lui, N. L., Yong, S. T., Cheung, Y. B., Malhotra, R., Ostbye, T., & Thumboo, J. (2016). Validity and reliability of the Short Form 36 Health Surveys (SF-36) among patients with spondyloarthritis in Singapore. *Rheumatol Int*, 36(12), 1759-1765.

- Kwan, Y. H., Fong, W., Lui, N. L., Yong, S. T., Cheung, Y. B., Malhotra, R., Thumboo, J., & Ostbye, T. (2018). Validity and reliability of the Health Assessment Questionnaire among patients with spondyloarthritis in Singapore. *Int J Rheum Dis*, 21(3), 699-704.

- *Kwan, Y. H., Fong, W., Leung, Y. Y. Lui, N. L., Tan, C.S., Malhotra, R., Ostbye, T., & Thumboo, J. (2019). Are extra-spinal symptoms associated with poorer quality of life in patients with axial Spondyloarthritis? A 1-year follow up study. Clin Rheum. 38(7):1881-1887.*

- Kwan, Y. H., Fong, W., Ang, X.L., Tan, C.S., Tai, B.C., Huang, Y.Y., Bilger, M., Phang, J.K., Tan, H.C., Lee, J.V., Sun, L.M., Tan, C.T., Dong, B.Q., Koh, H.L., Leung, Y.Y., Lui, N.L., Yeo, S.I., Ng, S.C., Fong, K.Y., Thumboo, J., & Ostbye, T. (2018). Traditional Chinese Medicine (TCM) collaborative care in the management of patients with axial Spondyloarthritis (AcuSpA): Protocol for a pragmatic randomized controlled trial. *Trials*, 20:46

Publications of direct relevance to the thesis (15)

- Wang CTM, **Kwan YH**, Fong W, Xiong SQ, Leung YY. Factors associated with patient-physician discordance in a prospective cohort of patients with psoriatic arthritis: An Asian perspective. 2019. International Journal of Rheumatic Disease (Epub ahead of print)
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Hong C, **Kwan YH**, Leung YY, Lui NL, Fong W. Comparison of ankylosing spondylitis and non-radiographic axial spondyloarthritis in a multi-ethnic Asian population in Singapore. 2019. International Journal of Rheumatic Diseases. (Epub ahead of print)
    - *Role: Analysis support and data interpretation*

- Xiang L, Teo EPS, Low AHL, Leung YY, Fong W, Xin X, Gandhi M, **Kwan YH**, Uy EJB, Hamilton L, Thumboo J. Cross-cultural adaptation of the Hamilton axial spondyloarthritis questionnaire and development of a Chinese version in a multi-ethnic Asian population. 2019. International Journal of Rheumatic Diseases. (Epub ahead of print)
    - *Role: Data interpretation*

- **Kwan YH*,** Aw FF*, Fong W*, Phang JK, Klitz U, Lim KK, Chew EH, Lui NL, Tan CS, Thumboo J, Ostbye T, Leung YY. Validity and reliability of the Assessment of Spondyloarthritis International Society Health Index in English-Speaking patients with axial spondyloarthritis in Singapore. 2019. International Journal of Rheumatic Diseases. (Epub ahead of print) (*Co-first authors)
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- **Kwan YH,** Fong W, Cheng GHL, Phang JK, Leung YY, Lui NL, Thumboo J, Ostbye T. The mediating role of pain and function in the association between stiffness and quality of life in patients with axial spondyloarthritis. 2019. Seminars in Arthritis and Rheumatism. (Epub ahead of print)
    - *Role: Design, data collection, data analysis, data interpretation and manuscript writng*

- **Kwan YH*,** Ng A*, Lim KK*, Fong W, Phang JK, Chew EH, Lui NL, Tan CS, Thumboo J, Ostbye T, Leung YY. Validity and reliability of the ten-item Connor-Davidson Resilience Scale (CD-RISC10) instrument in patients with axial spondyloarthritis (axspa) in Singapore. 2018. Rheumatology International. (Epub ahead of print) *Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Wang CTM*, Fong W*, **Kwan YH**, Phang JK, Lui NL, Leung YY, Thumboo J, Cheung PP. A cross-sectional study on factor associated with patient-physician discordance in global assessment of patients with axial

spondyloarthritis: an Asian perspective. 2018. International Journal of Rheumatic Disease. (Epub ahead of print) *Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- **Kwan YH**, Fong W, How P, Wee HL, Leung YY, Phang JK, Tan CS, Malhotra R, Ostbye T, Thumboo J. The impact of axial spondyloarthritis on quality of life (QoL): A comparison with the impact of moderate to end-stage chronic kidney disease on QoL. 2018. Quality of Life Research. 27:2321-2327
    - *Role: Design, data collection, data analysis, data interpretation and manuscript writng*

- Png WY*, **Kwan YH***, Lee YX, Lim KK, Chew EH, Lui NL, Tan CS, Thumboo J, Osbyte T, Fong W. Factors associated with initiation of biological in patients with axial Spondyloarthritis in an urban Asian city: A PRESPOND study. Journal of Clinical Rheumatology. 2018. *Co-first author (Epub ahead of print)
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Png WY*, **Kwan YH***, Lim KK, Chew EH, Lui NL, Tan CS, Ostbye T, Thumboo J, Fong W. A systematic review of the factors associated with the initiation of biological in patients with rheumatological conditions. European Journal of Hospital Pharmacy. 2018. *Co-first author (In Press)
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Png K*, **Kwan YH*,** Leung YY, Phang JK, Lau JQ, Lim KK, Chew EH, Low LL, Tan CS, Thumboo J, Fong W, Ostbye T. Measurement properties of patient-reported outcomes for spondyloarthritis: A systematic review. 2018. Seminars in Arthritis and Rheumatism (Epub ahead of print) *Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Phang JK*, **Kwan YH*,** Goh H, Tan VIC., Thumboo J, Østbye T, Fong, W. Complementary and alternative medicine for rheumatic diseases: A systematic review of randomized controlled trials. *Complementary Therapies in Medicine*. (Epub ahead of print) *Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Lee XY*, **Kwan YH*,** Png WY, Lim KK, Tan CS, Lee NL, Chew EH, J Thumboo, T Ostbye, W Fong. Association of obesity with patient-reported outcomes in patients with axial spondyloarthritis: a cross-sectional study in an urban Asian population. Clinical Rheumatology. 2017. 36(10): 2365-2370.* Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Seng JJB*, **Kwan YH*,** Low LL, Thumboo J, Fong W. Role of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) in assessing disease control in Asian patients with axial spondyoarthritis. Biomarkers. 2018. (Epub ahead of print) * Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Goh H*, **Kwan YH***, Seah Y*, Low LL, Fong W, Thumboo, J. A systematic review of barriers affecting medication adherence in patients with rheumatic diseases. Rheumatology International. 2017. 37(10): 1619-1628. * Co-first authors
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Other publications (40)

- Seng BJJ*, Lim VZK*, **Kwan YH**, Thumboo J, Low LL. Outpatient primary and tertiary healthcare utilization among public rental housing residents in Singapore. 2019. BMC Health Services Research. 19:227. *Co-first authors.
    - *Role: Data interpretation*

- Yan S, Seng BJJ, **Kwan YH**, Tan CS, Quah JHM, Thumboo J, Low LL. Identifying heterogenous health profiles of primary care utilisers and their differential healthcare utilization and mortality. A retrospective cohort study. 2019. BMC Family Practice. 20:54.
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- Xiang L, Teo EPS, Low AHL, Leung YY, Fong W, Xin X, Gandhi M, **Kwan YH**, Uy EJB, Sparks JA, Karlson EW, Thumboo J. Cross-cultural adaptation of the connective tissue disease screening questionnaire and development of a Chinese version in a multi-ethnic Asian population. 2019. Clinical Rheumatology. (Epub ahead of print)
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    - *Role: Data interpretation and manuscript writing*

- Lee YX*, **Kwan YH*,** Lim KK, Tan CS, Lui NL, Phang JK, Chew EH, Ostbye T, Thumboo J, Fong W. A systematic review of the association of obesity with the outcomes of inflammatory rheumatic diseases. 2019. Singapore Medical Journal. 60(6):270-280. (*Co-first authors)

- *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Low LL, **Kwan YH**, Ma CA, Yan S, Chia EHS, Thumboo J. Predictive ability of an expert-defined population segmentation framework for healthcare utilization and mortality – a retrospective cohort study. 2019. BMC Health Services Research. 19(1): 401.
  - *Role: Data interpreation*

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- Ho AFW, Zheng H, Earnest A, Cheong KH, Pek PP, Seok JY, Liu N, **Kwan YH**, Tan JWC, Wong TH, Hausenloy DJ, Foo LL, Tan BYQ, Ong MEH. Time-stratified case crossover study of the association of outdoor ambient air pollution with the risk of acute myocardial infarction in the context of seasonal exposure to the southeast Asian haze problem. 2019. Journal of American Heart Association. 8:e011272.
  - *Role: Data interpreation*

- Choo HMC*, Cher WQ*, **Kwan YH**, Fong W. Risk factors for cytomegalovirus disease in systemic lupus erythematosus (SLE): a systematic review. 2019. Advances in Rheumatology. 59:12. *Co-first authors
  - *Role: Design, data interpretation, supervision and mentoring*

- Lim KK*, Ang HT*, **Kwan YH**, Tan CS, Ostbye T, Low LL. Authors' Reply to Kahlaee et al: "A systematic review and meta-analyses of the association beween anti-hypertensive classes and the risk of falls among older adults". 2018. Drugs and Ageing. (Epub ahead of print) *Co-first authors
  - *Role: Design, data interpretation and mentoring*

- Yeam CT, Chia S, Tan HCC, **Kwan YH**, Fong W, Seng JJB. A systematic review of factors affecting medication adherence in patients with osteoporosis. 2018. Osteoporosis International (Epub ahead of print)
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- Lee WC, Zainul-Abidin S, **Kwan YH**, Lam KY, Mahadev A. Predicting subsequent displacement of lateral condyly of humerus fractures based on soft tissue swelling. 2018. Journal of Shoulder and Elbow Surgery. (Epub ahead of print)
  - *Role: Design, guidance of analysis and data interpretation*

- **Kwan YH*,** Png K*, Phang JK*, Leung YY, Goh H, Seah Y, Thumboo J, Ng SC, Fong W, Lie D. A systematic review of quality and utility of observer-based instruments for assessing medical professionalism. 2018. Journal of Graduate Medical Education (Epub ahead of print). * Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Yan S, **Kwan YH**, Tan CS, Thumboo J, Low LL. A systematic review of the clinical application of data-driven population segmentation analysis. 2018. BMC Medical Research Methodology. 18: 121
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Lee YX*, **Kwan YH*,** Lim KK, Tan CS, Lui NL, Chew EH, Ostbye T, Thumboo J, Fong W. A systematic review of the association of obesity on the outcomes of inflammatory rheumatic diseases. 2018. Singapore Medical Journal (In Press) * Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Banu Z*, Lim KK*, **Kwan YH**, Yap KZ, Ang HT, Tan CS, Fong W, Thumboo J, Lee KH, Ostbye T, Low LL. Anti-hypertensive medications and injurious falls in an older population of low socioeconomic status: a nested case-control study. 2018. BMC Geriatrics. *Co-first authors
    - *Role: Design, guidance of analysis, data interpretation, supervision and mentoring*

- Ang HT*, Lim KK*, **Kwan YH**, Tan PS, Yap KZ, Banu Z, Tan CS, Fong CS, Thumboo CS, Ostbye T, Low LL. A systematic review and meta-analyses of the association between anti-hypertensive classes and the risk of falls among older adults. 2018. Drugs and Ageing. (Epub ahead of print) *Co-first authors
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- Seng BJJ*, **Kwan YH*,** Goh H, Thumboo J, Low LL. Public rental housing and its association with mortality – a retrospective, cohort study. BMC Public Health. 2018. 18:665. *Co-first authors
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- Chia S, Wong XY, Toon ML, Seah Y, Yap AF, Lim C, Tay HY, Fong W, Low LL, **Kwan YH**. Patient preferences for types of community-based cardiac rehabilitation programme. Heart Asia. 2018. 10:1-5
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision, mentoring and funding solicitation*

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- Ruan XC, Low LL, **Kwan YH**. Association of aspartate aminotransferase in statin-induced rhabdomyolysis. Journal of primary health care. 2017. 9(4): 316-220.
    - *Role: Design, data collection, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

- Lim KK*, **Kwan YH*,** Tan CS, Low LL, Chua AP, Lee WY, Pang L, Tay HY, Chan SY, T Ostbye. The association between distance to public amenities and cardiovascular risk factors among lower income Singaporeans. Preventive Medicine Reports. 2017. 8: 116-121. *Co-first authors
    - *Role: Design, data collection, guidance of analysis, data interpretation and manuscript writng.*

- **Kwan YH**, Chua CJ, JXL Kian, Fong W. The top 100 cited articles in the field of rheumatology. European Journal of Rheumatology. 2017. 4(4):294-304.
    - *Role: Design, data collection, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

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    - *Role: Design, data collection, guidance of analysis, data interpretation, manuscript writng, supervision, mentoring and funding solicitation*

- Yap AF, **Kwan YH**, Tan CS, Ibrahim S, Ang SB. Rhythm-centred music making in community living elderly: A randomized pilot study. BMC Complementary and Alternative Medicine. 2017. 17:311
    - *Role: Design, data collection, guidance of analysis, data interpretation, manuscript writng and mentoring*

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    - *Role: Design, data collection, guidance of analysis, data interpretation, manuscript writng and mentoring*

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- Goh XTW, Tan YB, Thirumoorthy T, **Kwan YH.** A systematic review of factors that influence treatment adherence in paediatric oncology patients. Journal of Clinical Pharmacy and Therapeutics. 2017. 42(1):1-7. doi: 10.1111/jcpt.12441
    - *Role: Design, data interpretation, manuscript writng and mentoring*

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    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

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- Lee WC, **Kwan YH**, Yeo SJ. Severe Bilateral Fixed Flexion Deformity-Simultaneous or Staged Total Knee Arthroplasty? Journal of Arthroplasty. 2016. 31(1):128-31.
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng and mentoring*

- Ong KY, **Kwan YH**, Tan SYD, Tay HC, Chang JY. Prevalence of dysglycemic events among inpatients with diabetes: an Asian perspective. Singapore Medical Journal. 2015; 56(7): 393-400
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    - *Role: Design, data collection, data interpretation, manuscript writng and supervision*

- Teo V, Toh MR, **Kwan YH**, S Raaj, Tan DSY, Tan JZY. Association between total daily doses with duration of hospitalization among readmitted patients in a multi-ethnic Asian population. Saudi Pharmaceutical Journal. 2015 Sep;23(4):388-96.
    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

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    - *Role: Design, guidance of analysis, data interpretation, manuscript writng, supervision and mentoring*

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    - *Role: Design, data collection, guidance of analysis, data interpretation and manuscript writng.*

- **Kwan YH**, Tung YK, Singh Kochhar J, Li H, Poh AL, Kang L. Handbook of Cosmecutical Excipients and their safeties. Woodhead Publishing. 2014 (Book)
    - *Role: Design, data collection, guidance of analysis, data interpretation and book writng.*

- **Kwan YH**, Koh ET, Leong KP, Wee HLAssociation between helplessness, disability, and disease activity with health-related quality of life among rheumatoid arthritis patients in a multiethnic Asian population. Rheumatology International. 2014. 34(8):1085-93.
    - *Role: Design, data collection, guidance of analysis, data interpretation and manuscript writng.*

- Tan JZY, **Kwan YH**. Stability of chronic medicines in dosage administration aids. How much have been done? Saudi Pharmaceutical Journal. 2016 Jan;24(1):21-8. doi: 10.1016/j.jsps.2014.02.002.
    - *Role: Design, data collection, guidance of analysis, data interpretation and manuscript writng.*

Appendix E (Abstract presentations, Grants and Awards)

Abstract presentations

- Effectiveness of transitional care program on mortality and healthcare utilization: A systematic review of pragmatic trials. Royal College of Physician. 2019. (*Poster*)
- The mediating role of pain and function in the association between stiffness and quality of life in patients with axial spondyloarthritis. SGH ASM 2019. (*Oral*)
- The mediating role of pain and function in the association between stiffness and quality of life in patients with axial spondyloarthritis. ASCI 2019. (*Poster*)
- The validity and reliability of work productivity and activity impairment (WPAI) among patients with axial spondyloarthritis in Singapore. SGH ASM 2019. *(Nominated for best poster in clinical research)*
- Factors associated with patient-physician discordance in global assessment of patients with axial spondyloarthritis: An Asian Perspective. EULAR. 2018. (*Poster*)
- Factors associated with patient-physician discordance in a cohort of patients with psoriatic arthritis: An Asian Perspective. EULAR. 2018. (*Poster*)
- A systematic review of indicators to measure population health. Global Conference on Integrated Care. 2018*. (Oral)*
- A systematic review of quality of life domains and items relevant to patients with Spondyloarthritis. International Society of Pharmacoeconomics and Outcomes Research 2017. *(Poster)*
- A systematic review of quality of life domains and items relevant to patients with Spondyloarthritis. SGH Annual Scientific Meeting 2017. *(Finalist for oral presentation)*
- Factors associated with initiation of biologics in patients with axial spondyloarthritis in an urban Asian City: A PRESPOND study. International Society of Pharmacoeconomics and Outcomes Research 2017. *(Poster)*
- Association of obesity with patient-reported outcomes in patients with axial spodyloarthritis: A cross-sectional study in an urban Asian population. International Society of Pharmacoeconomics and Outcomes Research 2017. *(Poster)*
- A systematic review of the association between obesity and outcome of rheumatic diseases. International Society of Pharmacoeconomics and Outcomes Research 2017. *(Poster)*
- A systematic review of the factors associated with the initiation of biologics in patients with rheumatological conditions. International Society of Pharmacoeconomics and Outcomes Research 2017. *(Poster)*
- Factors of cardiovascular disease risk screening uptake among populations with low socioeconomic status: a systematic review. International Society of Pharmacoeconomics and Outcomes Research 2017. *(Poster)*
- Association between access to health-promoting facilities and participation in cardiovascular disease (CVD) risk screening among populations with low socioeconomic status (SES) in Singapore. International Society of Pharmacoeconomics and Outcomes Research 2017. *(Poster)*

- Validity and reliability of Health Assessment Questionnaire (HAQ) in patients with Spondyloarthritis in Singapore. Asia-Pacific International Society of Pharmacoeconomics and Outcomes Research 2016 *(Oral presentation* ***– Best Podium Presenter Award****)*
- Validity and reliability of Short Form-36 Survey (SF-36) in patients with Spondyloarthritis in Singapore. Asia-Pacific International Society of Pharmacoeconomics and Outcomes Research 2016 *(Award finalist)*
- Developing item banks for physical functioning, social relationships, and positive mindset to measure health-related quality of life (HRQoL) in the Singapore population. Asia-Pacific International Society of Pharmacoeconomics and Outcomes Research 2016 *(Poster)*
- Systematic review of factors affecting medication adherence in older population. American Geriatrics Society Meeting 2016*. (Poster)*
- Severe Bilateral Fixed Flexion Deformity-Simultaneous or Staged Total Knee Arthroplasty? SingHealth-Duke NUS Congress 2016 *(Poster)*
- Severe bilateral fixed flexion deformity-simultaneous or staged total knee arthroplasty? Singapore Orthopedics Associations 38th Annual Scientific Meeting 2015. *(Oral presentation)*
- Impact of community-based cardiac rehabilitation on clinical parameters of patients with cardiovascular diseases. Singapore Prevention and Cardiac Rehabilitation Symposium 2015. *(Selected for oral presentation and* ***awarded merit award****)*

Grants (SGD 2,373,738.40)

- EMPOWERing patients with chronic disease using profiling and targeted feedbacks delivered through wearable device (EMPOWER). (Co-I/ 2019/ NIC on Active and Confident Ageing Grant, MOH, SGD2,050,274.40)
- Investigating factors of non-compliance with referral recommendations in individuals with undiagnosed chronic conditions following a community-based screening: A mixed-method study. (Co-I/ 2019/PULSES Centre Grant, SingHealth, SGD 50,000)
- The impact of age on the time to complications and the cost-effectiveness of Type 2 Diabetes Mellitus screening among adults in Singapore. (Co-I/ 2019/PULSES Centre Grant, SingHealth, SGD 35,700)
- A pragmatic randomized controlled trial of a novel TCM physician-involved collaborative care model in the management of patients with axial Spondyloarthritis (AxSpA) in Singapore (AcuSpA) (Co-I/2017/Ministry of Health Traditional Chinese Medicine Research Grant / SGD$213,564)
- Evaluation of Medical Professionalism for postgraduates using the Professional Mini-Evaluation Exercise (P-MEX). (Co-I/ 2017/ SingHealth Duke-NUS JOAM/ SGD$123,000)
- SingHealth medical student talent development award 2017 – Travel (PI/2017/SingHealth Duke-NUS JOAM/ SGD$3000)

- SingHealth medical student talent development award 2016 – Project (PI/2016/SingHealth Duke-NUS JOAM/ SGD$5000)
- Conjoint analysis (PI/2016/Sawtooth Software Inc/ USD$12,000 software grants)
- What are the domains important to Quality of Life in Spondyloarthritis? A Qualitative Study. (PI/2016/Asia Pacific League of Associations for Rheumatology/USD $12,000)

Awards

SingHealth Duke-NUS Academic Medical Centre Bunsen Burner Award **2019**

- Awarded to young researcher who is conscientious and inspiring

Duke-DukeNUS Pre-Doctoral and Post-Doctoral Research Exchange Program **2019**

- Awarded to researchers to participate in research exchange in Duke Univerity in Durham for a month

Publons Top 1% Reviewer **2019**

- Top 1% reviewer of the social science, clinical science and cross-fields
- Reviewed more than 60 manuscripts from peer reviewed journals in a year

Publons Top 1% Reviewer **2018**

- Top 1% reviewer of the social science, general field
- Reviewed more than 30 manuscripts from peer reviewed journals in a year

SingHealth Medical Student Talent Development Award - Travel **2017**

- Awarded to promising medical students to provide developmental opportunities

SingHealth Medical Student Talent Development Award - Project **2016**

- Awarded to promising medical students to provide developmental opportunities

ISPOR 7th Asia-Pacific Conference Best Podium Presenter Award **2016**

- Awarded to top presenter for podium presentation

Singapore Prevention and Cardiac Rehabilitation Symposium Best Oral Presentation **2015**

- Awarded to top presenter for oral presentation during the breakout session

Duke-NUS 10th Anniversary Scholarship **2015**

- Awarded to individuals who had contributed significantly in advancing the school's mission in research and education

Duke-NUS Unsung Heroes Award **2015**

- Awarded to individuals who had contributed in student activities, community work and programs significantly