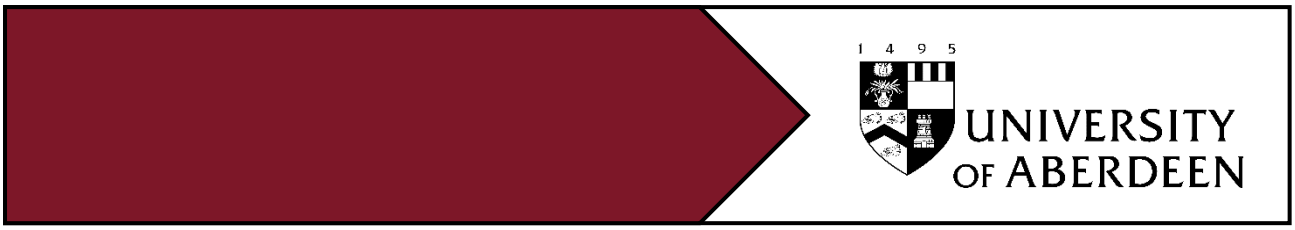

EPIDEMIOLOGY RESEARCH REPORT 2016a

Report title **Scotland Registry for Ankylosing Spondylitis (SIRAS) – Protocol**

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ABSTRACT

Background

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis predominantly affecting the spine and sacroiliac joints, although peripheral joints can be affected. It is commonly associated with a number of extra-articular manifestations, including psoriasis, uveitis and inflammatory bowel disease. The study of AS has increased, particularly since the advent of Tumour Necrosis Factor inhibition. Much of what is known about the epidemiology of AS comes from small clinical studies, or large randomised controlled trials, with highly selected populations. However, there remain a number of unresolved issues in terms of epidemiology. For example: the understanding of long-term quality of life, occupational outcomes, disease flares, and the link between other inflammatory conditions such as periodontal disease, is incomplete.

Methods / Design

Between October 2010 and October 2013, over 2,000 patients with a clinical diagnosis of AS were recruited to the Scotland Registry for Ankylosing Spondylitis (SIRAS) from rheumatology departments across Scotland. Clinical data was obtained through audits of patients' medical records, and patient-reported information was collected by postal questionnaire. Since then, participants who consented to follow-up have received questionnaires one years and two years after baseline. A further follow-up is planned, in 2016, to collect longer-term follow-up data on a number of disease outcomes, such as quality of life and occupational characteristics, and to collect new data on disease flares, periodontal disease and the presence of comorbid fibromyalgia.

Discussion

While randomised controlled trials undoubtedly have their place, we believe that there is still a need for large, rigorous, epidemiological studies of AS. Various analyses are planned, including an examination of long-term quality of life and occupational outcomes among persons with AS, the role of smoking cessation on disease outcomes, the epidemiology of disease flares, and the association between AS and periodontal disease. However, we hope that the greatest value will be achieved by creating a robust foundation upon which other studies can be built.

Keywords

Ankylosing spondylitis / Axial spondyloarthritis / Registry / Cohort

INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory arthritis that affects the axial skeleton and entheses, and is closely linked to a number of other spondyloarthropathies, including reactive arthritis, psoriatic arthritis, and arthritis associated with ulcerative colitis / Crohn's disease. Characteristically presenting in early adulthood, estimates of prevalence vary but are strongly associated with the frequency of the class 1 HLA antigen B27 in the population under study. Prevalence will also vary depending on which classification criteria are employed.

The classification of AS has changed over time. The modified New York criteria (1984) for AS require low back pain and stiffness which improves with exercise, but is not relieved by rest, various indicators of spinal limitation, and grade ≥3 unilateral or grade ≥2 bilateral sacroiliitis [1]. Since then, alternative criteria have been proposed [2,3]. Most recently (2009) the Assessment of SpondyloArthritis Society (ASAS) proposed a wider definition of axial spondyloarthritis – which incorporates AS – and is based upon evidence of sacroiliitis and / or HLA-B27 positivity, plus different combinations of additional clinical features, including enthesitis, uveitis, dactylitis, psoriasis, and elevated C-reactive protein (CRP) [4]. It is not known, however, the extent to which these criteria are applied in routine clinical practice – as opposed to being employed as inclusion criteria for randomised clinical trials – and, in practice, patients are often classified on the basis of a 'clinical diagnosis' of AS*. Most commonly mistaken for mechanical back pain, AS is frequently missed and under-diagnosed, and there is an average of eight to nine years between the onset of symptoms and clinical diagnosis [5].

From nine population-based European studies (mainly using clinical or modified New York criteria), we recently estimated the prevalence of AS to be 18.6 per 10,000 [6]. There is a significant impact of AS on functional mobility and employment, with 25% of patients having to retire early or cease work as a result of their disease [7]. Prognosis is variable, and is influenced, in part, by the presence of common extra-spinal manifestations of the disease (psoriasis, uveitis and inflammatory bowel disease) and, of course, treatment. Until the early part of the 21st century, the standard therapy for AS was a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, with disease-modifying anti-rheumatic drugs (DMARDs), such as Sulfasalazine and Methotrexate, showing limited efficacy in patients other than those with associated peripheral joint disease. However, since the early 2000s, Tumour Necrosis Factor (TNF) inhibition agents have been used in the treatment of AS, with significant improvement in functional indices and disease activity [8]. As these therapies are costly, there are understandable limitations regarding their

* By definition, a clinical diagnosis of AS will include patients who may not satisfy all or any of the recognised classification criteria. In this document, we will use 'AS' to refer to clinical diagnosed patients, unless otherwise stated.

use; TNF inhibition is only considered for those patients who have previously failed at least two NSAIDs and who have active disease, defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 and spinal pain Visual Analogue Scale (VAS) ≥4cm on two occasions, four weeks apart, without any change of treatment [9].

In 2007, a group of rheumatologists and scientists from Scotland and Northern Ireland met in Perth to plan the creation of a registry of patients with clinically diagnosed AS, to determine the aetiology and natural history of the disease and to identify predictors of poor outcome. This initiative received support and approval from the Scottish Society for Rheumatology and a steering group was formed to establish the collaboration. The aims were firstly, to enumerate the AS population seen in secondary care in Scotland, and secondly, to collect basic clinical and patient-reported data to allow epidemiological analyses including questions regarding natural history, disease severity, quality of life, and treatment.

METHODS

Study design overview

The Scotland Registry for Ankylosing Spondylitis (the SIRAS study) was initially designed as two discrete investigations:

- Phase 1 An audit of clinical data recorded in the medical notes of all patients seen in secondary care in Scotland with a clinical diagnosis of AS; and
- Phase 2 A postal questionnaire survey to collect patient-reported outcomes to allow epidemiological analysis.

However, both phases were subsequently expanded with, in Phase 1, more extensive clinical data; and in Phase 2, the addition of follow-up questionnaires plus the collection of genetic samples.

Although data collection was only from patients residing and being clinically managed in Scotland, patients who subsequently moved out of Scotland were (and remain) eligible for follow-up, and were invited to participate, providing they did not indicate their desire to withdraw from the study.

Clinical data

Audit 1

All National Health Service rheumatology clinics that assess AS patients within Scotland were approached for inclusion in SIRAS, and to assist in recruitment of patients.

There is international debate regarding the classification and diagnosis of AS, and other related diagnoses. Further, we believe that, in clinical practice, there is considerable variation in applying classification criteria. Therefore, patients were considered eligible if they had either:

- Received a diagnosis of AS according to the modified New York criteria [1]; or
- Had been given a clinical diagnosis of AS by a consultant rheumatologist;

and, in addition:

- Had attended clinic in the two years prior to data collection at each particular site.

Patients were identified as they attended their routine appointments, via the clinic lists (where available), or through a review of recent physician correspondence (covering the previous two years). Eligible patients had their medical notes reviewed by trained personnel from either the University of Aberdeen Clinical Research Facility (CRF), the University of Glasgow CRF, the Wellcome Trust CRF in Edinburgh, or the core SIRAS team at the University of Aberdeen. Information from patients' medical records was extracted on to

paper data collection forms, and subsequently entered into the study database at the University of Aberdeen. Details of the clinical information collected are shown in Table 1.

Audit 2

Audit 1 had gathered longitudinal data for some variables (for example, a full history of TNF inhibition therapy), but only cross-sectional data on many other clinical variables (for example, BASDAI from the most recent clinic attendance only). To allow a more detailed analysis of the natural history of AS, Audit 2 aimed to collect clinical data from routine medical notes in greater historical detail. Audit 1 began in August 2008. However, from October 2010, Audit 2 superseded Audit 1 such that any patients who had hitherto not been seen were only audited once with the new data extraction pro forma. Those who had previously been seen were re-audited to collect the additional information. Details of the clinical information collected are shown in Table 1.

Patient-reported data

Baseline questionnaire

All patients from whom clinical data were obtained, and for whom a current address was available, were invited to participate in a postal questionnaire survey. Potential participants were sent a questionnaire pack containing a SIRAS invitation letter, signed by one of their local consultants on the appropriate NHS-headed paper. Reminders were sent to non-responders. The questionnaire contained a number of generic and disease-specific instruments to assess general health, pain, function and quality of life, and various aspects of lifestyle. Details of the patient-reported information collected are shown in Table 2.

Follow-up questionnaires

Very little prospective data has been collected from AS patients, outside of randomised controlled trials. SIRAS, and specifically the willingness of participants to be invited to participate in future health studies (indicated in the baseline questionnaire), provided a valuable opportunity to collect 'real-life' data on a large cohort of AS patients including, for example, health status, quality of life, and occupational outcomes.

All patients who completed a baseline questionnaire and explicitly gave both (a) consent for further contact; and (b) their home address, were sent a follow-up questionnaire pack as close as possible to the first and second anniversaries of their baseline questionnaire completion. Reminders were sent to non-responders, as per the baseline questionnaire. The primary objective of the follow-up questionnaires was to track changes (or stability) in quality of life and health status and, thus, the questionnaires were largely similar to those used at baseline.

However, the opportunity was taken to gather additional self-reported information not previously collected, to enhance the cohort. This included (a) the EASiQoL, a recently developed disease-specific quality of life instrument, to enhance data on quality of life [10]; (b) the Ankylosing Spondylitis Work Instability Scale (AS-WIS [11]) and the Patient Acceptable Work State questionnaire (PAWS [12]), to augment the data on employment and employability and; (c) bespoke questions on sexual function, to determine the impact of AS on this life domain, and to collect preliminary data regarding how well (if at all) this is addressed in clinic. Details of the follow-up questionnaire are shown in Table 2.

Genetic samples

Participants who indicated their willingness to receive future questionnaires were also invited to donate a saliva sample to allow DNA extraction and analysis. The primary objective of this aspect of the study is to identify the variant genes involved in AS in order to understand disease susceptibility and develop better methods of diagnosis and treatment. SIRAS samples will be used to add to the data already collected by a large international consortium led by the universities of Oxford, Queensland, and Texas. This collaboration has already completed a genome-wide association study in 2009 and identified the ERAP1 and IL-23R genes as associated with this condition [13]. Replication of this work is now required.

All patients who completed a baseline questionnaire and explicitly gave both (a) consent for further contact; and (b) their home address, were sent an invitation to receive further information about genetic sample collection. Those who responded positively were sent further information and an Oragene® saliva sampling kit. Donated samples were initially returned to the SIRAS team at the University of Aberdeen, and then dispatched to the University of Oxford, along with some phenotype data, for processing and analysis.

Ongoing follow-up

An important clinical measurement in AS is disease activity, most commonly assessed using the BASDAI. Examining these measurements over time, from routine rheumatology clinic appointments, we have demonstrated that, at the group level, disease activity is relatively stable over time [14]. At the individual level, however, AS is seen to be characterised by transient periods of increased disease activity, pain, stiffness, fatigue and disability, often described as disease flares. Evidence, although limited, suggests that flares, and flare patterns, are an important determinant of poor quality of life [15], although little is known about their nature, timescale, extent or triggers.

The epidemiology of disease flares in AS is not only of academic and clinical interest but is also of key interest to patients. The National Ankylosing Spondylitis Society (NASS) is the only registered charity in the UK dedicated to the needs of people affected by AS. Recently, the NASS membership voted disease flares their number one research priority [16]. In response, and with input from patients, researchers and clinicians, we have developed a flares questionnaire. In 2016, we plan to collect information from a large group of patients (SIRAS participants) to assess the epidemiology of AS disease flares, as well as identifying a small group of patients for future study.

We decided, therefore, to take pragmatic advantage of the opportunity of another SIRAS follow-up to collect additional data in a number of areas – specifically: employment, fibromyalgia, and periodontal disease.

Employment

Previous studies have shown that the physical manifestations and disability associated with AS substantially impact on occupational status, with sick leave, work disability and complete work withdrawal expected to be common [17], particularly amongst those with manual professions [7,18]. Withdrawal from the workplace is associated with fatigue [19], poor spinal mobility, limited chest expansion and poor overall perception of health [7,17,20]. These factors are also associated with sick leave and work disability, and are potentially precursors of job loss. It is less clear how other, less objective factors, such as anxiety, depression and current work impairment affect the ability of patients with AS to remain in work in the long-term.

Identifying the factors associated with absenteeism or presenteeism (impaired whilst at work) may provide novel targets for future intervention. However, identifying the predictors of future work withdrawal may facilitate the characterisation of 'at risk' groups in whom targeted intervention may be the most effective. Although the current cross-sectional studies are useful, longitudinally collected data provide the best way of identifying such risk factors.

Fibromyalgia

The prevalence of fibromyalgia amongst patients with AS is unknown, but it is conservatively estimated to be around 15%, three to four times the prevalence in the general population [21]. Others have shown, using updated fibromyalgia classification criteria [22] that the prevalence may be as high as 34% [23], but these findings have not been replicated. Further, it is challenging in AS, however, to determine whether widespread pain (the cardinal feature of fibromyalgia) arises from AS directly, or is because of comorbid fibromyalgia. This is particularly important because the presence of fibromyalgia may distort responses to

some of the key patient-reported measures used in AS, including measures of disease activity (BASDAI) and function (Bath Ankylosing Spondylitis Functional Index; BASFI). As a result, patients may receive inappropriate management.

Therefore, the planned 2016 SIRAS follow-up questionnaire contains a battery of questions that will determine the prevalence of fibromyalgia as per the American College of Rheumatology 2011 modification of the preliminary diagnostic criteria for fibromyalgia [22]. This will also allow us to examine differences in characteristics of AS patients with, or without, fibromyalgia.

Periodontal disease

Periodontitis is inflammation of the periodontium that is accompanied by apical migration of the junctional epithelium, leading to destruction of the connective tissue attachment and alveolar bone loss [24]. Periodontitis, viewed for many years as primarily the outcome of infection, is now seen as resulting from a complex interplay between bacterial infection and host response, often modified by behavioural factors [25]. The host response is now seen as a key factor in the clinical expression of periodontitis [26].

The association of AS with periodontitis is not clear. A systematic review conducted by Ratz et al. (2015) for the possible link between AS and periodontitis, showed that the overall pooled estimate of the odds ratios for periodontitis, comparing persons with and without AS, was 1.85 (95%CI: 1.72–1.98) [27]. The study suggested a need for a larger study with, for example, sufficient statistical power to detect the desired effect size, taking into account potential confounding factors and using validated measures of AS and periodontitis.

Thus, the planned 2016 SIRAS follow-up questionnaire contains detailed questions on disease flares in AS, employment status and employability, and dental health.

Planned analysis / Statistical issues

In the first instance, the data collected within SIRAS will be analysed to produce simple descriptive epidemiological statistics about the prevalence, burden and natural history of AS. In addition, the nature of the data will allow important areas to be investigated further, particularly the assessment of long-term change in quality of life and work outcomes. Although designed as a platform for many potential questions, a number of specific analyses are planned.

- We will assess the quality of life of those with AS and identify the factors, particularly those that are modifiable, associated with reporting the poorest quality of life. Additionally, as work outcomes

are of primary concern to patients, the prevalence of absenteeism and presenteeism will be assessed, including identifying the factors most likely to predict these, and work withdrawal, in both the short- and medium-term.

- Although the effect of smoking among patients with AS has been shown to be associated with poorer outcomes [28], higher disease severity [29], and poorer quality of life [30], the effects of smoking cessation are less clear. In order to address this, firstly the previous findings on the association between smoking and disease characteristics (including quality of life) will be confirmed; and secondly the effect of smoking cessation on clinical and patient-reported factors will be examined.
- As a primary concern of patients, the current study will also collect information on AS disease flares, firstly to determine their prevalence, and to examine differences in flare characteristics between patients (e.g. frequency and duration); and secondly to examine differences between patients who do / do not report recent flare(s), in terms of demographic characteristics and disease-related factors.
- The link between periodontal disease and AS will be explored, firstly to confirm this association in a clinical population; secondly to evaluate if this differs according to the severity of AS; and lastly to determine the reliability and validity of self-reported periodontitis amongst AS patients.

Clinical data was available on 1,408 patients in Audit 1 with more detailed clinical information (Audit 2) on 1,868, including 1,215 patients who were audited twice. In total, audit data were available on 2,062 patients, 1,018 of whom also provided baseline questionnaire responses (49%). Of the questionnaire responders, the majority, 846 (83%), also provided consent for future follow-up, 528 (62%) and 350 (41%) of whom returned a one year and two year follow-up questionnaire, respectively.

The statistical power available for any specific analysis will depend on a number of assumptions, e.g. the prevalence of exposure and outcome, and the size of effect that one is trying to detect. However, as an indicative example, the baseline sample size gives more than 90% power to detect a doubling in the risk of any outcome, associated with the highest versus lowest quartile of any exposure, assuming the prevalence of the outcome in the non-exposed (lowest quartile) group is 15%.

Clearly, with fewer participants at follow-up, statistical power is reduced. However, at one year, the study still maintains 85% power to detect a doubling in the risk of any outcome, associated with the highest versus lowest tertile of any exposure, assuming the onset of the outcome in the non-exposed (lowest tertile) group is 15%.

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Funding

SIRAS was funded by unrestricted grants from Pfizer and AbbVie. The project was reviewed by both companies, during the award process, for Scientific merit, to ensure that the design did not compromise patient safety, and to assess the global regulatory implications and any impact on regulatory strategy.

Ethical issues

The SIRAS audit of medical records was registered, and received approval, from all 14 territorial NHS Health Boards in Scotland. The original baseline questionnaire survey was approved by the North of Scotland Research Ethics Service (reference: 09/S0802/7). This initial approval also permitted the collection of consent to link data from the questionnaire to the previously collected (or ongoing) audit data. All subsequent questionnaire surveys were approved by the same committee, as amendments to the original protocol, or by the University of Aberdeen College of Life Sciences and Medicine College Ethics Review Board (reference: CERB/2011/2/551 and CERB/2012/4/721). The current planned 2016 follow-up is, at the committee's request, being submitted as a *de novo* application to the North of Scotland Research Ethics Service (no reference assigned as yet).

Competing interests

The authors declare that:

- GT Jones Has received funds from AbbVie and Pfizer for the SIRAS study, and funds from the British Society for Rheumatology (BSR) for the conduct of the BSR Biologics Register for Ankylosing Spondylitis (BSRBR-AS), for which the BSR receives funds from AbbVie, Pfizer and UCB.

- Hunter Has received grants to enable attendance at international meetings from UCB, AbbVie and Pfizer.
- Macfarlane Has received funds from AbbVie and Pfizer for the SIRAS study, and funds from the British Society for Rheumatology (BSR) for the conduct of the BSR Biologics Register for Ankylosing Spondylitis (BSRBR-AS), for which the BSR receives funds from AbbVie, Pfizer and UCB. Chairs a Pfizer research grant panel, for which he receives an honorarium.

All other authors have no competing interests to declare.

References

1. van der Linden S, Valkenburg HA, Cats A: **Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria.** *Arthritis Rheum* 1984, **27:** 361-368.

2. Amor B, Dougados M, Mijiyawa M: **[Criteria of the classification of spondylarthropathies].** *Rev Rhum Mal Osteoartic* 1990, **57:** 85-89.

3. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A *et al*.: **The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy.** *Arthritis Rheum* 1991, **34:** 1218-1227.

4. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J *et al*.: **The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection.** *Ann Rheum Dis* 2009, **68:** 777-783.

5. Feldtkeller E, Bruckel J, Khan MA: **Scientific contributions of ankylosing spondylitis patient advocacy groups.** *Curr Opin Rheumatol* 2000, **12:** 239-247.

6. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ: **Global prevalence of ankylosing spondylitis.** *Rheumatology (Oxford)* 2014, **53:** 650-657.

7. Montacer KM, Mehdi GM, Hamdi W, Azzouz D, Kochbati S, Saadellaoui K *et al*.: **Impact of the ankylosing spondylitis on the professional activity.** *Joint Bone Spine* 2009, **76:** 378-382.

8. Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC, Jr., Dijkmans B *et al*.: **ASAS/EULAR recommendations for the management of ankylosing spondylitis.** *Ann Rheum Dis* 2006, **65:** 442-452.

9. Braun J, Davis J, Dougados M, Sieper J, van der Linden S, van der Heijde D: **First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis.** *Ann Rheum Dis* 2006, **65:** 316-320.

10. Haywood KL, Garratt AM, Jordan KP, Healey EL, Packham JC: **Evaluation of ankylosing spondylitis quality of life (EASi-QoL): reliability and validity of a new patient-reported outcome measure.** *J Rheumatol* 2010, **37:** 2100-2109.

11. Gilworth G, Emery P, Barkham N, Smyth MG, Helliwell P, Tennant A: **Reducing work disability in Ankylosing Spondylitis: development of a work instability scale for AS.** *BMC Musculoskelet Disord* 2009, **10:** 68.

12. Maksymowych WP, Richardson R, Mallon C, van der Heijde D, Boonen A: **Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis.** *Arthritis Rheum* 2007, **57:** 133-139.

13. Reveille JD, Sims AM, Danoy P, Evans DM, Leo P, Pointon JJ *et al*.: **Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci.** *Nat Genet* 2010, **42:** 123-127.

14. Dean LE: *Epidemiology of ankylosing spondylitis utilizing the Scotland and Ireland Registry for Ankylosing Spondylitis.* University of Aberdeen; 2015.

15. Stone MA, Pomeroy E, Keat A, Sengupta R, Hickey S, Dieppe P *et al*.: **Assessment of the impact of flares in ankylosing spondylitis disease activity using the Flare Illustration.** *Rheumatology (Oxford)* 2008, **47:** 1213-1218.

16. Cook D, Dickinson S, Garces-Bovett C, Goodacre L. National Ankylosing Spondylitis Society Research Priorities 2013 - 2018. 2015.

17. Boonen A: **Socioeconomic consequences of ankylosing spondylitis.** *Clin Exp Rheumatol* 2002, **20:** S23-S26.

18. Boonen A, Chorus A, Miedema H, van der Heijde D, Van Der Tempel H, van der Linden S: **Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients.** *Ann Rheum Dis* 2001, **60:** 353-358.

19. Boonen A, Chorus A, Miedema H, van der Heijde D, Landewe R, Schouten H *et al*.: **Withdrawal from labour force due to work disability in patients with ankylosing spondylitis.** *Ann Rheum Dis* 2001, **60:** 1033-1039.

20. Ariza-Ariza R, Hernandez-Cruz B, Collantes E, Batlle E, Fernandez-Sueiro JL, Gratacos J *et al*.: **Work disability in patients with ankylosing spondylitis.** *J Rheumatol* 2009, **36:** 2512-2516.

21. Azevedo VF, Paiva ES, Felippe LR, Moreira RA: **Occurrence of fibromyalgia in patients with ankylosing spondylitis.** *Rev Bras Reumatol* 2010, **50:** 646-650.

22. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS *et al*.: **Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia.** *J Rheumatol* 2011, **38:** 1113-1122.

23. Baraliakos X, Regel A, Kiltz U, Menne H-J, Dybowski F, Igelmann M *et al*.. Patients with fibromyalgia (FM) do not fulfill classification criteria for axial spondyloarthritis (axSpA) but patients with axSpA may fulfill classification criteria for FM. Arthritis Rheum 67[Suppl 10], 1383-1384. 2015.

24. Flemmig TF: **Periodontitis.** *Ann Periodontol* 1999, **4:** 32-38.

25. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS: **Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions.** *Periodontol 2000* 1997, **14:** 216-248.

26. Darveau RP, Tanner A, Page RC: **The microbial challenge in periodontitis.** *Periodontol 2000* 1997, **14:** 12-32.

27. Ratz T, Dean LE, Atzeni F, Reeks C, Macfarlane GJ, Macfarlane TV: **A possible link between ankylosing spondylitis and periodontitis: a systematic review and meta-analysis.** *Rheumatology (Oxford)* 2015, **54:** 500-510.

28. Reed MD, Dharmage S, Boers A, Martin BJ, Buchanan RR, Schachna L: **Ankylosing spondylitis: an Australian experience.** *Intern Med J* 2008, **38:** 321-327.

29. Mattey DL, Dawson SR, Healey EL, Packham JC: **Relationship between smoking and patient-reported measures of disease outcome in ankylosing spondylitis.** *J Rheumatol* 2011, **38:** 2608-2615.

30. Bodur H, Ataman S, Rezvani A, Bugdayci DS, Cevik R, Birtane M *et al*.: **Quality of life and related variables in patients with ankylosing spondylitis.** *Qual Life Res* 2011, **20:** 543-549.

31. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A: **A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index.** *J Rheumatol* 1994, **21:** 2286-2291.

32. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P *et al*.: **A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index.** *J Rheumatol* 1994, **21:** 2281-2285.

33. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A: **Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index.** *J Rheumatol* 1994, **21:** 1694-1698.

34. Jones SD, Steiner A, Garrett SL, Calin A: **The Bath Ankylosing Spondylitis Patient Global Score (BAS-G).** *Br J Rheumatol* 1996, **35:** 66-71.

35. Ware J, Jr., Kosinski M, Keller SD: **A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.** *Med Care* 1996, **34:** 220-233.

36. **EuroQol--a new facility for the measurement of health-related quality of life.** *Health Policy* 1990, **16:** 199-208.

37. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ *et al*.: **Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis.** *Ann Rheum Dis* 2003, **62:** 20-26.

38. Von KM, Dworkin SF, Le RL: **Graded chronic pain status: an epidemiologic evaluation.** *Pain* 1990, **40:** 279-291.

39. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D *et al*.: **Development of a fatigue scale.** *J Psychosom Res* 1993, **37:** 147-153.

40. Reilly MC, Zbrozek AS, Dukes EM: **The validity and reproducibility of a work productivity and activity impairment instrument.** *Pharmacoeconomics* 1993, **4:** 353-365.

41. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D: **Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger.** *Assessment* 2011, **18:** 263-283.

Tables

Table 1 Data extracted from patient medical records

		Audit 1	Audit 2
Demographic characteristics			
Date of birth		☑	☑
Sex		☑	☑
Employment status		☑	☑
Height and weight		☑	☑
Clinical and family history			
Date of diagnosis and date of symptom onset		☑	☑
Family history of AS		☑	☑
Extra-spinal manifestations of disease			
	Uveitis	☑	☑
	Psoriasis	☑	☑
	Inflammatory bowel disease	☑	☑
	Enthesitis		☑
	Peripheral joint disease	☑	☑
Smoking status		☑	☑
Alcohol consumption		☑	☑
Laboratory markers			
HLA-B27 status		☑	☑
CRP		☑	☑ [1]
ESR / Plasma viscosity		☑	☑ [1]
Imaging			
X-rays	Cervical spine images		☑ [2]
	Lumbar spine images		☑ [2]
	Thoracic spine images		☑ [2]
	Pelvic images		☑ [2]
MRI	Cervical spine images		☑ [2]
	Lumbar spine images		☑ [2]
	Thoracic spine images		☑ [2]
	Pelvic images		☑ [2]
Evidence of sacroiliitis		☑	☑
Disease measures			
Bath Ankylosing Spondylitis Disease Activity Index [31]		☑	☑ [1]
Bath Ankylosing Spondylitis Functional Index [32]		☑	☑ [1]
Bath Ankylosing Spondylitis Metrology Index [33]		☑	☑ [1]
Bath Ankylosing Spondylitis Global Score [34]			☑ [1]
Spinal pain visual analogue scale		☑	☑ [1]
Treatment history			
Tumour Necrosis Factor (TNF) inhibition agents		☑ [1]	☑ [1]
Disease-modifying anti-rheumatic drugs (DMARDs)		☑	☑ [1]
Oral corticosteroids		☑	☑
Physiotherapy		☑	☑

[1] Data collected from >1 time point. Generally, all available data was collected (as many data points as were available in the medical records). Unless indicated, data collected from the most recent clinical visit only.

[2] Data recorded = Dates of images taken. Actual images not recorded – although these could be retrieved at a later date.

Table 2 Questionnaire data

		Questionnaire			
		Baseline	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**
Demographics / Lifestyle					
	Date of birth	☑	☑	☑	☑
	Sex	☑	☑	☑	☑
	Education	☑			
	Smoking status	☑			☑
	Alcohol consumption	☑			☑
Family history					
	AS	☑			
	Other seronegative disease [1]	☑			
General health / quality of life					
	SF-12 Health Survey [35]	☑	☑	☑	☑
	EQ-5D [36]	☑	☑	☑	
	ASQoL [37]	☑	☑	☑	☑
	EASiQoL [10]		☑	☑	
Symptoms					
	Chronic pain grade [38]	☑	☑	☑	
	Presence of night pain	☑	☑	☑	
	Chalder Fatigue Scale [39]	☑	☑	☑	
	Fibromyalgia (ACR modified 2010 criteria) [22]				☑
Disease measures					
	Bath Ankylosing Spondylitis Disease Activity Index [31]				☑
	Bath Ankylosing Spondylitis Functional Index [32]				☑
	Bath Ankylosing Spondylitis Global Score [34]				☑
	Spinal pain visual analogue scale				☑
Employment					
	Employment status				
	Work Productivity Activity and Impairment [40]	☑	☑	☑	☑
	AS Work Instability Scale [11]		☑	☑	
	Patient Acceptable Work State [12]		☑	☑	☑

Other					
	Driving limitations	☑			
	Childhood experiences			☑	
	Threatening life events		☑	☑	
	Sexual function		☑ [2]	☑ [2]	
	PROMIS anxiety and depression scale [41]				☑
	Flares				☑
	Diet				☑
	Oral health				☑

[1] Specific question asked about other seronegative spondyloarthropathies (a list was provided).

[2] Separate questionnaire on sexual function was included for all patients, in the next available questionnaire. For some this was one year, and for others two years, after baseline.