AXIAL SPONDYLOARTHROPATHIES IN THE WESTERN CAPE

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DECLARATION PAGE

The research presented here is based on independent work performed by the primary investigator, Dr. Robert B. Smith. No part of this work has, or will be, submitted for another degree to any other university. This research has not been reported or published prior to registration for the above-mentioned degree. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Dr. Robert B Smith

Date: 21 November 2018
ABSTRACT

Impaired Health-Related Quality of Life and Work Productivity amongst South African patients with Axial Spondyloarthritis.

Background:
No studies have investigated health-related quality of life (HRQoL) or work productivity in patients with axial spondyloarthritides (axSpA) living in sub-Saharan Africa.

Methods:
This cross-sectional study of adults with axSpA collated demographic particulars and patient questionnaires: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Bath Ankylosing Spondylitis Functional Index (BASFI); Bath Ankylosing Spondylitis Global Score (BASG); Medical Short Form (SF)-36; and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP).

Results:
Of 36 patients, the mean (SD) age was 40.3 (13.3) years and mean (SD) diagnostic delay was 8.7 (8.4) years. Most patients were male (80.6%) and of mixed racial ancestry (69.4%). Most (66.7%) patients were smokers and only 5 (13.9%) patients received tumor necrosis factor inhibitor (TNFi) therapy. The mean (SD) BASDAI was 5.3 (2.1), and 72.2% had a BASDAI ≥ 4. Patients with a high BASDAI (i.e. BASDAI ≥ 4) had higher BASG scores ($p=0.003$), higher WPAI:SHP activity impairment scores ($p=0.003$), and poorer SF-36 scores, particularly in the role-physical, bodily pain, and social functioning domains ($p=0.0001$, 0.001 and 0.02 respectively). Activity impairment according to the WPAI:SPH was 57.4%, with the BASDAI and activity impairment correlating closely ($p=0.006$). The SF-36 scores were low in physical (particularly role-physical, bodily pain, and general health) and mental (notably vitality and role emotional) domains.
Conclusion:
This study describes a cohort of South African patients with axSpA who have poor prognostic features including diagnostic delay and cigarette smoking. Active disease, impaired function, poor physical- and mental HRQoL, and work disability are unmet needs.
ACKNOWLEDGEMENTS AND CONTRIBUTIONS

We thank the participants enrolled into this study at George Regional Hospital and Groote Schuur Hospital.

Contributions:
- Prof. Bridget Hodkinson (primary supervisor): conceptualisation, planning, data synthesis, interpretation of results and manuscript preparation;
- Dr. Trevor Gould (supervisor at George Regional Hospital): data collection and manuscript preparation;
- Ms. Kathryn Manning (University of Cape Town Department of Medicine Statistical Support Team): assistance with data analysis.
INTRODUCTION AND LITERATURE REVIEW

BACKGROUND
The spondyloarthritides (SpA) are a family of disorders that are grouped together by common clinical features and an association with the human leucocyte antigen-B27 (HLA-B27). The prototypical disorder in this family is known as ankylosing spondylitis, but others include are psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease and undifferentiated arthritis [1]. A recent, revised classification of SpA that was proposed by the Assessment of Spondyloarthritis International Society (ASAS), separates the disorders into those presenting with predominantly axial symptoms and those presenting with predominantly peripheral symptoms. According to this classification, axial spondyloarthritis (axSpA) includes ankylosing spondylitis (AS) and non-radiographic (nr) axSpA [2-4].

In axSpA, young adults typically present with inflammatory back pain and progressively worsening stiffness of the spine. Other associated symptoms include peripheral arthritis, enthesitis (inflammation of the entheses, the tendinous or ligamentous insertions on bone) and dactylitis (inflammation of the digits). There are also numerous associated extra-articular manifestations, including uveitis, inflammatory bowel disease, psoriasis, cardiovascular- and pulmonary disease [1].

The course of the disease is variable. Disease progression leads to stiffness and varying degrees of spinal fusion, which causes marked functional impairment. Pain and limitation of physical function has a negative impact on health-related quality of life (HRQoL) [1]. This also impacts on work productivity in affected individuals. This was illustrated in a systematic literature review describing work status in patients with AS done by Boonen et al. [5]. The authors concluded that there was substantial work disability and sick leave. The findings were, however, limited by the marked heterogeneity of the patient populations that were studied, as well as of the designs of the various studies that were included in the analysis. In the review, employment in AS ranged between 34-96%, with half of the studies reporting employment of less than 70% [5]. In addition to the physical impairment and the impact on work productivity, the disease also results in fatigue and psychological disturbance (depression and anxiety) in many. [6]
DIAGNOSIS

The diagnostic delay in axSpA has been recognised in several studies, with reports of delays between 5 - 10 years [7-9]. As shown in Figure 1, the 1984 Modified New York Classification Criteria for Ankylosing Spondylitis were historically used to aid in the diagnosis of the disorder [10]. However, for the diagnosis of AS to be made according to these criteria, sacroiliitis must be present on plain film radiographs. These plain film radiological changes may take several years to develop, resulting in a delay in the diagnosis. As will be discussed later, this is of importance as early diagnosis and initiation of therapy may improve outcome.

Figure 1: The 1984 Modified New York Criteria for the diagnosis of Ankylosing Spondylitis [10].

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<td>Low back pain for at least 3 months duration that is improved with exercise and not relieved by rest</td>
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<td>Limited lumbar spinal motion in sagittal and frontal planes</td>
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<td>Limitation of chest expansion relative to normal values correlated for age and sex</td>
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<td>Sacro-iliitis grade 2 bilaterally or grade 3-4 unilaterally</td>
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The ASAS classification criteria for axSpA attempts to address this problem. It was developed to diagnose patients with early axial disease, or non-radiographic axSpA (nr-axSpA) [2-4]. These criteria are shown in Figure 2. As the name implies, patients with nr-axSpA lack the plain film radiographic changes to the sacroiliac joints that is necessary to meet the diagnosis according to the 1984 Modified New York Criteria. Although patients with nr-axSpA may have normal plain films, inflammation suggestive of sacroiliitis is visible on MRI.
Recently, there has been a decline in the diagnostic delay [11-12] likely due to the new ASAS classification criteria [3] and the recognition of nr-axSpA.

In the majority of cases, the initial presenting complaint in patients with axSpA is inflammatory back pain (IBP). Recognising IBP is therefore an important first step in the diagnosis of the disorder and health care professionals should be aware of its characteristics. IBP should be considered in individuals younger than 40 years of age with insidious onset back pain for a period of more than three months. Characteristically, IBP improves with exercise, does not improve with rest and is experienced at night [13]. Rudwaleit et al. showed that in patients younger than 45 years of age with chronic lower back pain, identifying IBP or testing for HLA-B27, with referral to a rheumatologist if either of these are positive, may be an approach to reducing the delay in diagnosing patients with axSpA [14].

**ASSESSMENT OF DISEASE STATUS**

Accurate assessment of disease status in SpA is important as it guides management decisions. Patient completed questionnaires specific to the condition are widely used in daily practice to assess disease activity and functional status [15-16]. These include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Global score (BASG), which assess disease activity, functional impairment and general health,
respectively. The Ankylosing Spondylitis Disease Activity Score (ASDAS) measures disease activity and incorporates acute phase reactants [17]. Use of the BASDAI, BASFI, BASG and ASDAS has been validated in AS. Another validated self-reported questionnaire, the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), is used to assess work productivity and impairment in daily activities [18]. In employed individuals, the WPAI:SHP reports on absenteeism (sick leave related to disease), presenteeism (impairment in productivity related to disease) and overall impairment at work.

The Medical Short Form (SF)-36 is an instrument used to measure HRQoL [19]. This questionnaire is not disease specific. It has been validated in numerous diseases, including rheumatologic diseases such as rheumatoid arthritis [20] and AS. The questionnaire contains 36 items that can be grouped into eight domains. Four of these are physical domains and four are mental domains. The physical domains are: physical functioning, bodily pain, role physical, and general health perceptions; whereas the mental domains are: vitality, role emotional, social functioning, and mental health [19]. A meta-analysis was conducted by Yang et al. [21] to evaluate the impact of AS on the HRQoL as assessed by the Medical SF-36 questionnaire. The authors concluded that the measurement of HRQoL using the SF-36 should be considered as an essential part of the overall assessment of health status of patients with AS. Importantly, it guides improved management. Of note, none of the studies included in the meta-analysis were conducted in South Africa [21]. The above-mentioned questionnaires are included in the appendix (Appendix C-G).

MANAGEMENT
The optimal management of axSpA requires a combination of treatment modalities, both non-pharmacological and pharmacological [22-23]. Non-pharmacological management refers to patient education, smoking cessation and exercise. Exercise has been shown to be of benefit, whether it is individual home-based exercise or supervised group therapy [24-25]. The first line of pharmacotherapy for all patients is non-steroidal anti-inflammatory drugs (NSAIDs), and in many patients it may be the only medication required [26]. The current recommendations for the use of NSAIDs are that, in the absence of contra-indications or side-effects, they should be used at the maximum dose in a continuous manner for patients with active disease [23]. In patients with
persistently high disease activity despite an adequate trial of 4 weeks of NSAIDs, a biological disease modifying anti-rheumatic drug (bDMARD) is considered [23]. The tumor necrosis factor inhibitors (TNFi) have been associated with significant improvements in disease activity and function [27]. The highest remission rates are observed when used in patients with early disease, therefore earlier diagnosis improves outcome [28-29]. The non-biological, or conventional synthetic DMARDs often used include sulfasalazine and methotrexate. In patients with peripheral arthritis, sulfasalazine has been shown to be of benefit. Use of sulfasalazine, however, is not recommended in the absence of peripheral arthritis [30]. Although it is widely used, a meta-analysis evaluating the efficacy of methotrexate in AS found no evidence of benefit for its use in this disease [31].

PROGNOSTIC INDICATORS
Various factors are associated with poor outcomes in patients with axSpA. These include age, male sex, cigarette smoking, a history of uveitis, lower educational level, presence of other diseases related to SpA, presence of HLA-B27, active disease as assessed by a disease activity index, self-reported functional impairment, the presence of enthesitis, increasing severity of radiographic changes and elevated C-reactive protein (CRP) [32-34]. Elevated CRP levels, baseline severity of radiographic change and cigarette smoking are associated with increased risk of radiographic progression [35-36].

AXIAL SPONDYLOARTHRITIDES IN SUB-SAHARAN AFRICA
SpA is uncommon in sub-Saharan Africa. Dean et al. reported the mean prevalence of AS in Africa at 7.4 per 10000 [37]. This estimate was based on a single cross-sectional study of 1352 persons conducted in South Africa [37]. In comparison, the mean prevalence per 10000 in Europe, Asia, North America and Latin America is 23.8, 16.7, 31.9 and 10.2, respectively [37]. The reason for the low prevalence in Sub-Saharan Africa is likely due to the low frequency of HLA-B27 in the African Black population [39]. Studies done in Togo, Zambia and Burkino Faso, have identified other HLA alleles, namely HLA-B 14:03 and HLA-B 27:05, to be associated with an increased risk for the development of axSpA in sub-Saharan African populations [40].
There are numerous challenges to the diagnosis and treatment of the SpA in sub-Saharan Africa. The diagnosis is often delayed until late in the course of the disease. Various reasons may include low public awareness resulting in late presentation, inadequate health care service access by the general population, lack of health care professionals with rheumatology skills to recognise the condition early, and limited access to specialised investigations. Furthermore, there is doubt as to whether the new ASAS classification criteria will be of clinical value in sub-Saharan Africa, due to the rarity of HLA-B27 and the limited access to magnetic resonance imaging (MRI) [39].

Once the diagnosis is made, treatment is mostly limited to exercise and NSAIDs. TNFi agents are not only prohibitively expensive, but exposure to these agents has been shown to be an independent risk factor for tuberculosis (TB) in high burden areas [41]. There are also concerns with regards to safety in the setting of human immunodeficiency virus (HIV) infection [42]. A cross-sectional study from Zambia showed 98% of SpA cases were HIV associated rather than HLA-B27 associated [43].

Few studies have investigated the characteristics of patients living with axSpA in South Africa. A retrospective survey of 100 patients with AS seen between January 1988 and January 1995 at the Rheumatic Diseases Unit of the University of Cape Town, concluded that the spectrum of SpA in South Africa is comparable to that found in other parts of the world [44]. A more recent cross-sectional study in Kwazulu-Natal described the ethnicity of 248 patients with AS. It was found in this cohort that 74% of patients were White, 26% were Indian, and that there were no Black patients [45]. No study in South Africa has described the HIV- and HLA-B27 associations, or the disease status, HRQoL and work productivity of patients with axSpA.

OBJECTIVES
The objective of this cross-sectional study is to investigate a cohort of consenting adults with axSpA residing in the Western Cape, South Africa.

Firstly, the following will be described:

1. The demographics and characteristics of the group, including age, gender and self-reported ethnicity;
2. The disease history, including presenting symptom(s), age at symptom onset, symptom duration and diagnostic delay;
3. Employment history;
4. The association with HLA B-27 and HIV infection, when available;
5. The poor prognostic indicators identified; and
6. Treatment exposure, side-effects and response.

Following this, the disease activity, functional impairment, work productivity and health related quality of life will be determined using the validated, self-reported questionnaires that were discussed under the heading Assessment of Disease Status above. Together, the information gathered will provide insight on the challenges involved in the diagnosis and management of patients with axSpA in South Africa, and will be the first to report on work productivity and HRQoL in this setting.

REFERENCES:


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Impaired Health-Related Quality of Life and Work Productivity amongst South African patients with Axial Spondyloarthritis

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RS: Planning, data synthesis, interpretation, manuscript preparation
TG: Manuscript preparation
BH: Conceptualisation, planning, data synthesis, interpretation, manuscript preparation

Conflict of Interest Statement
The authors declare that there is no conflict of interest.
Impaired Health-Related Quality of Life and Work Productivity amongst South African patients with Axial Spondyloarthritis

Background
Axial Spondyloarthritides (axSpA) are chronic inflammatory disorders primarily affecting the axial skeleton in young adults, typically presenting with inflammatory back pain. Disease progression may result in spinal fusion. Other features of axSpA include peripheral arthritis, enthesitis and dactylitis, together with extra-articular complications, such as uveitis, inflammatory bowel disease, psoriasis, cardiovascular and pulmonary disease [1]. Untreated disease may lead to functional impairment, poor health-related quality of life (HRQoL) and impaired work productivity [2-4].

There are numerous challenges to the diagnosis and treatment of axSpA in sub-Saharan Africa. These diseases are somewhat uncommon, and have been described as mild in the African population, attributed to the low frequency of the HLA-B27 gene [5-6]. The diagnosis is often delayed until late in the course of the disease. Reasons for this include low public awareness and inadequate training of health care professionals to recognise the condition, together with limited access to specialised investigations such as magnetic resonance imaging (MRI) [7]. The Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA were developed to aid in the diagnosis of patients with early axial disease, but these may be of limited clinical value in sub-Saharan Africa, due to the rarity of HLA-B27 and the limited access to MRI [8]. Once the diagnosis of axSpA is made, treatment includes exercise and non-steroidal anti-inflammatory drugs (NSAIDs). Biologic disease modifying anti-rheumatic (bDMARD) agents, including tumour necrosis factor inhibitors (TNFi) are prohibitively expensive and therefore not widely available in resource-constrained settings such as ours, and also infer a significant risk of tuberculosis (TB) which is of major concern in TB endemic regions such as South Africa (SA) [9].

There are few papers published on axSpA from sub-Saharan Africa, and none have investigated HRQoL. We undertook this study to investigate clinical features, HRQoL
including function and work productivity in a cohort of axSpA patients from the Western Cape, SA.

**Patients and methods**

A cross-sectional study of consenting adult patients (≥18 years of age) with a diagnosis of axSpA according to the ASAS classification criteria were enrolled from the outpatient departments of a regional and a tertiary academic hospital. The University of Cape Town Human Research Ethics Committee approved the study, and all participants signed informed consent.

Demographic information including self-reported ethnic background, HLA-B27, HIV status and C-reactive protein (CRP) level were documented, where available. Disease status was assessed using patient completed questionnaires, namely: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Bath Ankylosing Spondylitis Functional Index (BASFI); and Bath Ankylosing Spondylitis Global score (BASG). The Medical Short Form (SF)-36 was used to assess HRQoL [10-12]. Thirty age- and sex-matched healthy controls completed the Medical SF-36 questionnaire. The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) was used to assess work and home productivity [13].

Statistical analysis was performed using data analysis software in Microsoft Excel. Pearson correlation coefficients were calculated to show relationship between variables. The Students t-test was applied to compare continuous variables, and in the case of categorical variables, the Pearson’s Chi-Square test, or where indicated, the 2-tailed Fishers’ Exact test was used. A p value < 0.05 was considered significant.

**Results**

Of 36 patients, the mean (SD) age was 40.3 (13.3) years and symptom duration was 16.8 (11.2) years (Table 1). Most patients were male (80.6%) and of mixed racial ancestry (69.4%). There were only 2 (5.6%) black African patients. There was significant diagnostic delay, with a mean (SD) lag between symptom onset to disease diagnosis of 8.7 (8.4) years. Patients had a poor socio-economic background: all were attending state-sector hospitals, none had medical insurance, and more than half (58.3%) were unemployed.
The majority of patients presented with lower back pain without peripheral arthritis (55.6%), followed by lower back pain and peripheral arthritis (30.6%), and the minority with peripheral arthritis alone (13.9%). Fourteen (38.9%) patients had a history of uveitis, and enthesitis was documented in 6 (16.7%) patients. All the patients fulfilled the ASAS classification criteria for ankylosing spondylitis, and none had psoriasis, inflammatory bowel disease or reactive arthritis. Most (66.7%) patients were cigarette smokers with a mean (SD) pack year smoking duration of 14.9 (16.8) years. HLA-B27 was positive in 25 of 27 (92.6%) patients tested, and 9 (25.0%) patients reported a family history. The HIV status was unknown in 20 (55.6%) patients, and of the 16 patients tested, none were HIV positive. Nine (25.0%) patients had a history of pulmonary TB.

Disease Activity
The mean (SD) BASDAI was 5.3 (2.1) and the mean (SD) BASG was 6.4 (2.3). Most (72.2%) patients had a BASDAI ≥ 4. The mean (SD) CRP at the time of the study was 16.5 (18.2) g/L, and 71.4% had a CRP ≥ 6 g/L. Plain X-rays, scored according to the modified New York grading for sacroiliitis [14], showed grade 4 sacroiliitis in 23.1% of those available. Three patients had undergone hip arthroplasty (unilateral = 1; bilateral = 2). An MRI had been performed in 7 patients (19.4%) and confirmed sacroiliitis in all.

Therapy
Most (80.6%) patients used NSAIDs (alone = 17.2%; combination with other agents = 82.8%), and the majority (79.3%) reported an improvement in symptoms. However, 11 (37.9%) had a history of upper gastrointestinal symptoms suggestive of gastritis. Sulfasalazine was prescribed to 24 (66.7%) patients, although only 12 (50.0%) of these patients reported peripheral arthritis. Methotrexate was prescribed to 4 (11.1%) patients, and TNFi therapy to 5 (13.9%) patients. Only 8 (22.2%) patients practiced regular home-based exercise.

Functional impairment, health related quality of life and employment
The mean (SD) BASFI was 5.8 (2.6) and activity impairment according to the WPAI:SPH was 57.4%. All domains of the SF-36 were markedly impaired compared to healthy controls (Figure 1). The mean (SD) SF-36 physical composite score (PCS)
was 39.5 (18.9), with particularly low scores in role-physical, bodily pain and general health. The mean mental composite score (MCS) was 50.0 (18.5), with vitality and role emotional most affected.

Twenty-one (58.3%) patients were unemployed, and of these, 12 (57.1%) related unemployment to the impact of the disease on their ability to work. The scores obtained from WPAI:SHP for employed patients were as follows: 6.3% for absenteeism (percentage of work time missed related to the disease), 49.7% for presenteeism (percentage impairment whilst working related to the disease) and 45.7% for overall work impairment. The SF-36 scores were lower in the patients who could not work due to their disease, however the differences were not statistically significant. The role-emotional and mental health domains approached significance ($p=0.08$ and 0.06 respectively).

**Variables associated with high disease activity**

Comparing patients with high disease activity (BASDAI ≥ 4) with those with low disease activity (BASDAI < 4), there were no significant differences in demographic features (Table 1). High disease activity was associated with higher BASG scores ($p=0.003$), higher WPAI:SHP activity impairment scores ($p=0.004$), a BASFI that approached significance ($p=0.06$) and poorer SF-36 scores, particularly in the role-physical, bodily pain, and social functioning domains ($p=0.005, 0.001$ and $0.02$ respectively).

**Correlations**

There were statistically significant negative linear correlations between the BASDAI, BASFI, BAS-G and the certain domains of the SF-36 (Table 2). The strongest of these correlations were found between BASDAI and bodily pain, BASFI and bodily pain, and BASFI and general health. There was a strong positive linear correlation between the BASDAI and activity impairment according to the WPAI:SPH ($R=0.64; p=0.006$). Linear correlations were not demonstrated between age, symptoms duration, diagnostic delay and the BASDAI, BASFI or BASG, respectively.
**Discussion**

This study, the first to focus on HRQoL amongst axSpA patients in sub-Saharan Africa, demonstrates considerable disease activity, functional disability and poor physical and mental health scores accompanied by reduced productivity. As expected, disease activity was significantly associated with these impairments. Diagnosis was late in the disease course, radiographic changes were advanced, several patients had undergone hip arthroplasty and a high percentage of our patients were cigarette smokers. Thus, several factors associated with poor prognosis and radiographic progression of disease were present [15-17].

The patient characteristics were similar to those described in the literature from SA and elsewhere with regards to presenting symptoms, age of symptom onset, male predominance and HLA-B27 association [18]. Most patients were of mixed racial ancestry and only two patients were blacks Africans, perhaps reflecting a true low prevalence of axSpA in this population. Although there are reports from Africa of spondyloarthritides associated with HIV infection, no HIV infected individuals were identified in this study [19].

There was a marked delay between onset of symptoms and diagnosis of disease. This diagnostic delay has been recognised in other studies, where delays of 5 - 10 years are reported [17,20]. Recently, this delay has declined, likely due to the new ASAS classification criteria and the recognition of non-radiographic axSpA [21-22]. Since the introduction of TNFi in the treatment of axSpA, early diagnosis is becoming increasingly important, as its use has been shown to have a greater impact in patients with early disease [23]. It is therefore important for health care professionals to be aware of the characteristics of inflammatory back pain.

The optimal management of patients with axSpA is a combination of non-pharmacological and pharmacological treatment [24]. In our cohort, few patients made use of non-pharmacological modalities, and despite high disease activity, less than half of the patients used NSAIDs continuously. Very few patients were prescribed TNFi because of resource constraints, and concern of infection, particularly TB in this endemic area [25]. Indeed, a quarter of our patients reported a history of TB. There is
an urgent need for wider access to biologic therapies for these patients, but vigilance is required [26].

The worst preforming domains of the SF-36 were the physical domains of role-physical, bodily pain and general health, findings similar to those reported in a systematic review of HRQoL assessed in AS patients [4]. Besides poor performance in the physical domains, our patients had impairment in mental domains, in particular role-emotional and vitality. In keeping with this, depression and fatigue are emerging as major under-recognised burdens in SpA [27-28].

Functional impairment has a negative effect on employment and work performance. A systematic literature review concluded that work disability and sick leave in AS was substantial [2]. In our cohort, more than half of the unemployed patients related this to the impact of the disease on their ability to work, and of those who were employed, a significant impairment whilst working was demonstrated.

This study has limitations, including the small sample size, and missing data, in particular CRP level, HIV- and HLA-B27 status for some participants. We plan to enlarge this cohort and broaden our investigations with qualitative and interventional studies.

In conclusion, this study describes a cohort of SA patients with axSpA who have poor prognostic features, active disease, impaired function, poor HRQoL and work disability. Strategies to improve these outcomes might include better awareness and early referral of patients with inflammatory back pain, interventions to encourage smoking cessation, exercise, job retention and improved mental health together with improved access to biologic therapies.

Conflict of Interest Statement
The authors declare that there is no conflict of interest.

References


Table 1: Demographic and clinical features of 36 patients with Axial Spondyloarthritis, including subgroups with high disease activity (BASDAI score ≥ 4) compared to low disease activity (BASDAI score < 4)

<table>
<thead>
<tr>
<th></th>
<th>n=36</th>
<th>BASDAI ≥ 4; n=26</th>
<th>BASDAI &lt; 4; n=10</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - yr; mean (SD)</td>
<td>40.3 (13.3)</td>
<td>39.7 (13.4)</td>
<td>41.9 (13.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Age at symptom onset - yr; mean (SD)</td>
<td>24.1 (9.1)</td>
<td>23.7 (8.4)</td>
<td>25.3 (11.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Symptom duration - yr; mean (SD)</td>
<td>16.8 (11.2)</td>
<td>16.7 (12.3)</td>
<td>17.0 (7.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Diagnostic delay - yr; mean (SD)</td>
<td>8.7 (8.4)</td>
<td>7.9 (7.8)</td>
<td>11.1 (10.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Male - no. (%)</td>
<td>29 (80.6)</td>
<td>20 (76.9)</td>
<td>10 (90.9)</td>
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</tr>
<tr>
<td>Mixed Ancestry - no. (%)</td>
<td>25 (69.4)</td>
<td>20 (76.9)</td>
<td>5 (50.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Caucasian - no. (%)</td>
<td>9 (24.3)</td>
<td>4 (15.4)</td>
<td>5 (50.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Black - no. (%)</td>
<td>2 (5.6)</td>
<td>2 (7.7)</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Unemployed - no. (%)</td>
<td>21 (58.3)</td>
<td>14 (53.8)</td>
<td>7 (70.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Cigarette smoking ever - no. (%)</td>
<td>24 (66.7)</td>
<td>17 (65.4)</td>
<td>7 (70.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Pack years of smoking - yr; mean (SD)</td>
<td>14.9 (16.8)</td>
<td>9.6 (5.8)</td>
<td>27.8 (26.9)</td>
<td>ns</td>
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<tr>
<td>CRP - mg/l, mean (SD)</td>
<td>16.5 (18.2)</td>
<td>16.7 (19.2)</td>
<td>15.7 (17.6)</td>
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</tr>
<tr>
<td>BASDAI - mean (SD)</td>
<td>5.3 (2.1)</td>
<td>6.3 (1.3)</td>
<td>2.6 (1.1)</td>
<td>&lt;0.001</td>
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<tr>
<td>BASFI - mean (SD)</td>
<td>5.8 (2.6)</td>
<td>6.4 (2.1)</td>
<td>4.4 (3.4)</td>
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<tr>
<td>BASG - mean (SD)</td>
<td>6.4 (2.3)</td>
<td>7.3 (1.4)</td>
<td>4.2 (2.7)</td>
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</tr>
<tr>
<td>Physical functioning - mean (SD)</td>
<td>50.4 (24.9)</td>
<td>48.7 (21.8)</td>
<td>55.0 (32.6)</td>
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<tr>
<td>Role physical - mean (SD)</td>
<td>30.6 (39.7)</td>
<td>18.3 (32.1)</td>
<td>62.5 (41.2)</td>
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<tr>
<td>Bodily pain - mean (SD)</td>
<td>35.9 (21.8)</td>
<td>29.5 (16.4)</td>
<td>52.6 (25.8)</td>
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<tr>
<td>General health - mean (SD)</td>
<td>36.1 (15.9)</td>
<td>33.3 (13.2)</td>
<td>43.5 (20.5)</td>
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<tr>
<td>Vitality - mean (SD)</td>
<td>44.4 (21.2)</td>
<td>41.5 (21.0)</td>
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<td>Social functioning - mean (SD)</td>
<td>60.1 (21.3)</td>
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<td>Role emotional - mean (SD)</td>
<td>43.5 (43.5)</td>
<td>35.9 (42.1)</td>
<td>63.3 (42.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Mental health - mean (SD)</td>
<td>65.7 (19.5)</td>
<td>64.3 (19.4)</td>
<td>69.2 (20.3)</td>
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</tr>
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<td>PCS - mean (SD)</td>
<td>39.5 (18.9)</td>
<td>34.2 (14.3)</td>
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<tr>
<td>MCS - mean (SD)</td>
<td>50.0 (18.5)</td>
<td>46.1 (16.1)</td>
<td>60.1 (21.3)</td>
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<td>WPAI activity impairment - mean (SD)</td>
<td>57.4 (24.3)</td>
<td>66.8 (14.9)</td>
<td>27.5 (27.8)</td>
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</table>

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASG: Bath Ankylosing Spondylitis Global Score; CRP: C-reactive protein; ns: not significant; MCS: Mental Composite Score; PCS: Physical Composite Score; WPAI: Work Productivity and Activity Impairment.
Figure 1: Radar graph representing SF-36 subscales of Axial Spondyloarthritis patients and healthy controls

Fig. 1 A radar graph, or ‘spidergram,’ representing the various subscales of the SF-36 compared to healthy controls. There is marked limitation in both the physical and mental domains of patients with axSpA.
Table 2: Pearson correlation coefficients showing negative linear correlations between BASDAI, BASFI, BAS-G and domains of the SF-36

<table>
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<td>Bodily pain</td>
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<td>General health</td>
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Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BAS-G: Bath Ankylosing Spondylitis Global Score.
APPENDICES

A) INFORMED CONSENT FORM (ENGLISH)

Title:
Health related quality of life and work productivity amongst patients with axial spondyloarthritis living in the Western Cape

Investigators:
Dr. Robert Smith, Dr. Bridget Hodkinson and Dr. Trevor Gould.

Invitation:
You are invited to take part in a study being done by doctors from George Regional Hospital and Groote Schuur Hospital.

Background:
You have been chosen for this study because you are being treated for axial spondyloarthritis. Also known as ankylosing spondylitis, it is a troublesome disease that affects the spine and a number of other joints and organs in the body. Very little is known about the illness in South Africa and how well we are treating it with the medicine we have available.

Study procedure:
The study will be done when you come for your follow-up visit at the clinic. If you agree, we will first look your records to check your old results. You will then be asked to do 4 lists of questions that have been put together to measure how active your disease is and how badly it is affecting your life and work. You must try to answer the questions honestly. It will probably take 20 minutes of your time to do the questions.

Confidentiality of collected information:
Your privacy is very important to us and safety measures will be in place to protect this. Your information will be labeled with a code and stored in a safe place. Only doctors working on this study will be able to see your information. Your name will not appear in any reports on this study.
**Nature of participation:**
It is important to understand that whether you want to take part in this study is your own choice, and you may decide to change your mind and leave the study at any stage. This will not be held against you.

**Purpose:**
What we learn from the study may help us to better understand the disease in South Africa. It may also help us argue for better medicine to treat the disease.

**Remuneration:**
You will not receive any payment for taking part in this study.

**Questions:**
If you have any questions relating to the study please feel free to contact:

Dr. Robert Smith (Principal Researcher)
Telephone: (044) 802 4529; ext. 2534
Email: robert.smith@westerncape.gov.za

University of Cape Town, Faculty of Health Sciences and Human Research Ethics Committee can be contacted at (021) 406 6338, if participants have any questions regarding their rights and welfare as research participants.

By signing below, I agree that:
I have read the information presented in the consent form;
I have asked that anything that is unclear to me be explained, and that this was done to my satisfaction in a language I understand;
I have been given the necessary time to think about whether I would like to participate in this study;
I understand that participation is voluntary and consent may be withdrawn at any time.

________________________________________________________
Participant (print name) Signature Date
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<th><strong>Interviewers</strong> (print name)</th>
<th>Signature</th>
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<tr>
<td>If 'Yes' - Most recent CD4</td>
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<tr>
<td>Date (YY/MM/DD)</td>
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<td>If 'Yes' - estimated pack years</td>
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<tr>
<td><strong>Diagnosis</strong></td>
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Other Specify?

**Investigations**

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**Acute phase reactants:**

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<td></td>
<td>Value at diagnosis?</td>
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<tr>
<td></td>
<td>Most recent value?</td>
</tr>
<tr>
<td></td>
<td>Value at diagnosis?</td>
</tr>
</tbody>
</table>

**Full blood count**

| Most recent? (WCC / Hb / MCV / platelets) |  |
| At diagnosis? (WCC / Hb / MCV / platelets) |  |

**Radiology:**

| Sacroiliitis on plain film |  |
| Grade? |  |

| Sacroiliitis on MRI |  |
| Yes | No | Not done |

**Disease activity and functional impairment scores**

| BASDAI |  |
| BASFI |  |
| SF 36 |  |
| WPAI:SpA |  |
| BAS-G |  |

**Treatment**

| Home exercise | Yes | No |
| Physiotherapy | Yes | No |
| Analgesics | Yes | No |
| NSAIDs | Yes | No |

| Continuous? |  |
| Intermittent? |  |

| Response? | Yes | No |
| Related gastritis? | Yes | No |
| Anti-TNFs | Yes | No |
| Other | Yes | No |
C) BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX (BASDAI)

1. How would you describe the overall level of fatigue/tiredness you have experienced?
2. How would you describe the overall level of AS neck, back or hip pain you have had?
3. How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of discomfort you have had from the time you wake up?
6. How long does your morning stiffness last from the time you wake up?

(Calculation: Score of 1 - 10 (1 = none, 10 = severe) for all questions. The mean score of questions 5 and 6 is added to the scores from questions 1 to 4. This total is then divided by 5 to give the average.)
D) BATH ANKYLOSING SPONDYLITIS FUNCTIONAL INDEX (BASFI)

Please indicate your level of ability with each of the following activities during the past week.

1. Putting on your socks or tights without help or aids (e.g. sock aid).
2. Bending from the waist to pick up a pen from the floor without aid.
3. Reaching up to a high shelf without help or aids (e.g. helping hand).
4. Getting up from an armless chair without your hands or any other help.
5. Getting up off the floor without help from lying on your back.
6. Standing unsupported for 10 minutes without discomfort.
7. Climbing 12-15 steps without using a handrail or walking aid.
8. Looking over your shoulder without turning your body.
9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).
10. Doing a full days activities whether it be at home or at work.

(Calculation: The total is divided by 10 to give the average.)

E) BATH ANKYLOSING SPONDYLITIS GLOBAL SCORE (BAS-G)

F)

1. Please place a mark on the scale below to indicate the effect your disease has had on your well-being over the last week.
2. Please place a mark on the scale below to indicate the effect your disease has had on your well-being over the last six months.

(Calculation: The total is divided by 2 to give the average.)
G) WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE (WPAI:SHP)

The following questions ask about the effect of your ankylosing spondylitis on your ability to work and perform regular activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? If no, check “No” and skip to question 6.
   ___ No ___ Yes

The next questions refer to the past seven days, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your ankylosing spondylitis? Include hours you missed on sick days, times you went in late, left early, etc., because of your ankylosing spondylitis. Do not include time you missed to participate in this study.
   _____ hours

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
   _____ hours

4. During the past seven days, how many hours did you actually work? If “0,” write “0” and skip to question 6.
   _____ hours

5. During the past seven days, how much did your ankylosing spondylitis affect your productivity while you were working? Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If ankylosing spondylitis affected your work only a little, choose a low number. Choose a high number if ankylosing spondylitis affected your work a great deal.
6. During the past seven days, how much did your PROBLEM affect your ability to do your regular daily activities, other than work at a job? By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If PROBLEM affected your activities only a little, choose a low number. Choose a high number if PROBLEM affected your activities a great deal.

Ankylosing spondylitis had no effect on my work

Ankylosing spondylitis completely prevented me from working

Ankylosing spondylitis had no effect on my daily activities

Ankylosing spondylitis completely prevented me from doing my daily activities
H) MEDICAL SHORT FORM (SF)-36

Questions:

1. In general, would you say your health is?
2. Compared to one year ago, how would you rate your health in general now?
3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
   a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
   b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
   c. Lifting or carrying groceries
   d. Climbing several flights of stairs
   e. Climbing one flight of stairs
   f. Bending, kneeling, or stooping
   g. Walking more than a mile
   h. Walking several blocks
   i. Walking one block
   j. Bathing or dressing yourself
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
   a. Cut down the amount of time you spent on work or other activities.
   b. Accomplished less than you would like
   c. Were limited in the kind of work or other activities
   d. Had difficulty performing the work or other activities (for example, it took extra effort)
5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
   a. Cut down the amount of time you spent on work or other activities
   b. Accomplished less than you would like
   c. Didn't do work or other activities as carefully as usual
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

7. How much bodily pain have you had during the past 4 weeks?

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks
   a. Did you feel full of pep?
   b. Have you been a very nervous person?
   c. Have you felt so down in the dumps that nothing could cheer you up?
   d. Have you felt calm and peaceful?
   e. Did you have a lot of energy?
   f. Have you felt down hearted and blue?
   g. Did you feel worn out?
   h. Have you been a happy person?
   i. Did you feel tired?

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

11. How TRUE or FALSE is each of the following statements for you?
   a. I seem to get sick a little easier than other people
   b. I am as healthy as anybody I know
   c. I expect my health to get worse
   d. My health is excellent

Responses:
   1. Excellent, Very Good, Good, Fair, Poor
   2. Much better now than one year ago, Somewhat better now than one year ago, About the same as one year ago, Somewhat worse now than one year ago, Much worse than one year ago
   3. Yes, Limited a lot; Yes, Limited a little; No, Not limited at all
4. a-d. Yes, No
5. a-c. Yes, No
6. Not at all, Slightly, Moderately, Quite a bit, Extremely
7. None, Very mild, Mild, Moderate, Severe, Very severe
8. Not at all, A little bit, Moderately, Quite a bit, Extremely
9. All of the time, Most of the time, A good bit of the time, Some of the time, A little of the time, None of the time
10. All of the time, Most of the time, Some of the time, A little of the time, None of the time
11. Definitely true, Mostly true, Don't know, Mostly false, Definitely false

(Calculations according to: Ware, JE. et al. SF-36 Health Survey Manual Interpretations)
I) RHEUMATOLOGY INTERNATIONAL: INSTRUCTION FOR AUTHORS

Edited from original to include only instructions relevant to this manuscript. Full instructions are available at:


INSTRUCTIONS:
Original articles
Word limit 4000 words, 50 references, no more than 6 figures or tables.

Title Page
- The title page should include:
  - The name(s) of the author(s).
  - A concise and informative title.
  - The affiliation(s) and address(es) of the author(s).
  - The e-mail address, and telephone number(s) of the corresponding author.
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Abstract
Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

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Please provide 4 to 6 keywords which can be used for indexing purposes. The keywords should preferably be taken from the Medical Subject Headings (MeSH) thesaurus of the National Library of Medicine of the U.S., which reflect the essence of the submission.

Additional note on Abstract
Abstracts of studies must follow the structure: Introduction / Objective – Methods – Results – Conclusion. In addition, they must coherent and provide main results in numbers, not just p-values or interpretations.

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Abbreviations should be defined at first mention and used consistently thereafter.

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Acknowledgments
Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Scientific Style
Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention. We at Rheumatology International heartily encourage the authors to make sure that their manuscripts report the studies in the most appropriate form as recommended by the corresponding reporting guideline.

References
Citation
Reference citations in the text should be identified by numbers in square brackets.

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The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list. The entries in the list should be numbered consecutively. Always use the standard abbreviation of a journal’s name according to the ISSN List of Title Word Abbreviations. If you are unsure, please use the full journal title.

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- All tables are to be numbered using Arabic numerals.
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• Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
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If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that the independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study.

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J) ETHICS APPROVAL: HREC 070/2016

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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12 May 2016

HREC REF: 070/2016

Dr B Hodkinson
Rheumatology
J-Floor, OMB

Dear Dr Hodkinson

PROJECT TITLE: AXIAL SPONDYLOARTHRITIS IN THE WESTERN CAPE (MMED CANDIDATE - DR R SMITH)

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 9 May 2016.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th May 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

The HREC acknowledge that the student, Dr Robert Smith will also be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federa: Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH)
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