

Simon Jacques le Roux

Cigarette smoking amongst  
Rheumatoid Arthritis patients in a  
tertiary centre in South Africa

A research report submitted to the Faculty of Health  
Sciences, University of Cape Town, in partial fulfilment  
for the degree of Master of Medicine in Internal  
Medicine

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**Student number: LRXSIM004**

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I, Simon Jacques le Roux declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Internal Medicine at the University of Cape Town, South Africa. Neither the whole work or any part of it has been submitted before for any degree or examination at this or any other University. This work has not been reported or published prior to registration for the above mentioned degree.

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Simon Jacques le Roux

The 25 day of April , Cape Town, South Africa

## **Publications and presentations arising from thesis**

This work or parts thereof has been presented on the following platforms:

- South African Rheumatology Congress, held in Durban South Africa as provisional data in poster format – 26 – 29<sup>th</sup> May
- Abstract Submission European Alliance of Associations of Rheumatology (EULAR)

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All authors listed below meet the following criteria of the International Committee of Medical Journal Editors (ICMJE). We have itemised their contributions according to the ICMJE criteria below:

- SJ le Roux
  - Overall conception and design of the study, the acquisition of data at Groote Schuur Hospital, interpretation
  - Drafting and critical revising of the work
  - Final approval of the version to be published
  - Agrees to be accountable for all aspects, accuracy and integrity of the work
  
- B Hodgkinson
  - Overall conception and design of the study, the acquisition of data at Groote Schuur Hospital, interpretation
  - Drafting and critical revising of the work
  - Final approval of the version to be published
  - Agrees to be accountable for all aspects, accuracy and integrity of the work
  
- R van Zyl-Smit
  - Overall conception and design of the study
  - Critical revising of the work
  - Final approval of the version to be published
  - Agrees to be accountable for all aspects, accuracy and integrity of the work
  
- H Bagula
  - Statistical analysis
  - Final approval of the version to be published
  - Agrees to be accountable for all aspects, accuracy and integrity of the work

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## List of Abbreviations

<b>RA</b>	-	Rheumatoid arthritis
<b>DMARD</b>	-	Disease modifying anti rheumatic drug
<b>HLA – DR</b>	-	Human Leukocyte Antigen DR isotope
<b>EULAR</b>	-	European Alliance of Associations for Rheumatology
<b>ACR</b>	-	American College of Rheumatology
<b>PROM</b>	-	Patient reported outcome measures.
<b>VAS</b>	-	Visual Analogue scale
<b>HAQ – DI</b>	-	Health Assessment Questionnaire and Disability index
<b>HADS</b>	-	Hospital Anxiety and Depression Scale
<b>FACIT</b>	-	Functional assessment of Chronic illness therapy
<b>SES</b>	-	Socio-economic status
<b>BMI</b>	-	Body mass index
<b>RF</b>	-	Rheumatoid Factor

## Abstract

**Background:** Cigarette smoking is associated with worse outcomes amongst rheumatoid arthritis (RA) sufferers, with poorer disease control, increased extra-articular complications and comorbidities. There are currently no data from sub-Saharan Africa.

**Objective:** To describe the prevalence of cigarette smoking, and explore disease control, comorbidities, extra-articular disease, and attitudes of smokers to their habit amongst RA patients in an outpatient clinic at tertiary level public hospital in South Africa. Further, we asked patients about the impact of prohibition during the COVID pandemic.

**Methods:** A cross-sectional study of consenting adult outpatients with RA meeting the EULAR/ACR 2010 Classification Criteria. Demographic, clinical and patient-reported outcome measures (PROMs) together with a questionnaire about smoking and Fagerström test for nicotine dependence were collated.

**Results:** Of 632 patients (536 females), the mean (SD) age and disease duration were 55.4 (13.0) and 10.1 (9.3) years. The mean (SD) Clinical Disease Activity Index (CDAI) and HAQ-DI were 14.3 (11.8) and 1.5 (0.7). The cohort included 218 (34,5%) smokers, and 89 (14.1%) ex-smokers, and more males smoked ( $p=0,0002$ ). Compared to non- or ex-smokers, smokers had lower BMI (29.7 vs 32.9  $p= 0.01$ ), higher anxiety scores ( $p=0,048$ ) and incidence of COPD (8,26 % vs 2,66%,  $p< 0.005$ ). Smokers were more likely than non-smokers to have a positive Rheumatoid Factor (80,3% vs 69,8%,  $p=0.006$ ). There were no significant differences in age of RA onset, disease duration, SES, number of comorbidities, CDAI nor its individual components, extra-articular diseases nor in HAQ-DI, FACIT, depression nor pain scores. Of 160 patients who completed the smoking questionnaire, only 83 (49,5%) believed smoking worsened their arthritis, yet 119 (71,6%) reported receiving smoking cessation advice at the RA clinic. Participants' most common reasons for smoking were emotional support (45.8%), nicotine craving (30.5%) and pain control (25,2%). The Fagerström score revealed mild, moderate and severe nicotine dependence in 67.5%, 24.4%, and 7.5% respectively. Although 50.1% felt that living with RA made quitting difficult, 86.9% had considered quitting, and almost half (45.6%) had previously quit for more than 3 months.

### **Conclusion:**

In this cohort of RA patients, a third actively smoke. Smoking is a modifiable risk factor, although half of the smokers reported that their RA made quitting difficult despite only 7.5% having severe nicotine addiction. Adequate disease control along with behavioural support should be the basis of engaging around tobacco cessation.

# Publication ready manuscript

Dr Simon Jacques le Roux  
Department Internal Medicine, University of Cape Town  
J Floor, Old Main Building, Groote Schuur Hospital  
Main road  
Observatory  
Cape Town  
South Africa  
7925

## **Cigarette smoking amongst Rheumatoid Arthritis patients in a tertiary centre in South Africa**

SJ le Roux<sup>1</sup>, H Bagula<sup>1</sup>, R van Zyl Smit<sup>2</sup> and B Hodkinson<sup>3</sup>

1. Internal Medicine registrar
2. Professor and second chair, Division of Pulmonology, Department Internal Medicine
3. Professor and Head of Division of Rheumatology, Department of Internal Medicine

Correspondence to Prof B Hodkinson ([drbridget@gmail.com](mailto:drbridget@gmail.com))

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## Background

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory joint disease requiring lifelong treatment to prevent joint destruction with irreversible functional disability, as well as extra articular manifestations of the disease. Disease modifying antirheumatic drugs (DMARDs) control inflammation and prevent these complications.(1, 2)

Cigarette smoking is now well recognised as a major risk factor for the development of rheumatoid factor, and the subsequent development of RA. In one subset grouping of RA patients with anti-citrullinated antibody positive arthritis, a combination of the environmental risk factor of smoking and a genetic susceptibility of HLA - DR shared epitope showed a significant increased relative risk for developing RA. Amongst cigarette smokers, persons with a single copy of the risk gene showed a relative risk of 6.5 and those with double copies a relative risk of 21. (3, 4)

Once RA is established, cigarette smokers have increased joint inflammation with higher swollen joint counts and elevated inflammatory markers, radiological progression, a higher incidence of extraarticular manifestation including nodules and interstitial lung disease, together with comorbidities such as an increased rate of infections, cardiovascular events and osteoporosis.(5) Active smoking can result in a reduced response to treatment, in particular methotrexate and tumour necrosis factor inhibitors with variable outcomes in current smokers on disease control, joint destruction, inflammatory markers and pain control.(5-8)

In South Africa the prevalence of smoking has shown a steady decline over the years as a result of many governmental health intervention strategies. This is against the trend in other low to middle income countries which have seen an increase over time. (9) The highest prevalence of smoking in South Africa is in the Western Cape and Northern Cape, and this has contributed to a high burden of both communicable and non-communicable diseases. (9)

The prevalence of smoking amongst RA patients in the Western Cape, including knowledge about smoking and joint disease and patient attitudes to quitting is unknown. Smoking has a multifaceted negative impact on RA patients, documenting and treating smoking habits and nicotine dependence together with co-morbidities in this population group plays an important role in long term disease management.(10, 11) We therefore undertook this cross sectional study of RA patients attending an academic state-sector hospital to gain insight into the prevalence of cigarette smoking, as well as improve our understanding of patient beliefs and readiness to quit.

## Patients and Methods:

### *Study design:*

A cross-sectional study recruiting patients with a diagnosis of RA attending the arthritis outpatient clinics at a tertiary academic hospital in the Western Cape, South Africa. Over a one year period (11/02/2021-23/08/2022), adult patients ( $\geq 18$  years) meeting the EULAR/ACR 2010 RA Classification Criteria(12) were invited to participate.

### *Data collection:*

Clinicodemographic particulars including age, gender, features of RA (seropositivity, duration of illness, therapy and current disease activity as measured by the Clinical Disease Activity Index)(13), were captured together with comorbid conditions (hypertension, diabetes, chronic obstructive pulmonary disease, obesity), extra-articular manifestations (interstitial lung disease, nodulosis, scleritis) and anthropomorphic details. Patient-reported outcome measures (PROMs) endorsed by the 2010 Outcome Measures in Rheumatology Meeting were recorded.(14) These included the visual analog scale (VAS) for pain and global assessment and EuroQol (EQ-5D), Health Assessment Questionnaire-Disability Index (HAQ-DI), Hospital Anxiety and Depression Score (HADS) and FACIT Fatigue Score. (15-19)

A poor socio-economic setting (SES) was defined using a pooled index, if any of the following were present: highest level of education as primary school or less; more than 7 persons living in the household; clothes washing done by hand (i.e. no access to domestic washing machine).(20)

Participants completed a smoking related questionnaire detailing smoking history (past/current), age of initiation, pack year history, current cigarette consumption, attitude to quitting and previous quitting attempts. Patients were also asked if they felt that smoking worsened their RA, if their arthritis doctors had advised quitting and if the COVID-19 lockdown had affected their smoking habits. Patients' reasons for smoking, and their impressions of the benefits of quitting were explored through multiple-choice questions where one or more answer options could be selected, with space for comments or details. Participants who identified as current smokers completed the Fagerström test to assess their level of nicotine dependence, and were asked about their interest in smoking cessation, with an offer for referral to the Groote Schuur Hospital smoking Cessation Clinic.(21)

### *Statistical Analysis:*

Numerical variables were presented as mean and standard deviation, categorical variables were reported as frequencies and proportions. T test was used to test for differences in numerical variables and chi squared test was used to test for differences between categorical variables. Spearman rank correlation was used to assess for correlation between numerical variables. Stata 10 software (StataCorp, USA) and Microsoft excel was used. A p value of less than 0.05 was considered significant.

*Ethics Approval:*

Approval was granted from the joint Groote Schuur Hospital and University of Cape Town Faculty of Health Sciences Research Ethics Committee (HREC 179/2021), and all participants signed informed consent prior to their inclusion in the study.

## Results:

Of 632 participants (536 females), the mean (SD) age and disease duration were 55.4 (13.0) and 10.1 (9.3) years respectively. (Table 1) Over a third (n=218, 34.5%) self-identified as current smokers, with 89 (14.1%) ex-smokers. A poor SES was noted in 67.0% of participants. Comparing smokers to non-smokers, smokers were more likely to be male, and have a significantly lower body mass index. Smokers were more likely to be rheumatoid factor positive, and were more likely to have rheumatoid nodules, although this was not statistically significant. There were no differences in age of onset, level of education and family history. (Table 1)

Table 1: The characteristics of rheumatoid arthritis participants described as mean (standard deviation) or numbers (proportions).

		All patients n= 632		Smokers n = 218		Non-smokers n= 414		p-value
<b>Males</b>	n (%)	96	(15,2)	49	(22,5)	47	(11,4)	<b>0.0002</b>
<b>Age enrolment (years)</b>	mean (SD)	55,4	(13)	54,1	(11,6)	56,1	(13,7)	ns
<b>Disease Duration (years)</b>	mean (SD)	10,1	(9,3)	9,4	(8,5)	10,4	(9,7)	ns
<b>BMI (Kg/m<sup>2</sup>)</b>	mean (SD)	31,5	(8)	29,7	(7,4)	32,9	(9,6)	<b>&lt;0.001</b>
<b>Poor SES</b>	n (%)	405	(70)	146	(67)	259	(62,6)	ns
<b>Comorbidities ( 2 or more)</b>	n (%)	468	(74)	154	(70,6)	314	(75,8)	ns
<b>CDAI</b>	mean (SD)	14,3	(11,8)	14,3	(12,6)	14,2	(11,4)	ns
<b>-Tender Joint Count</b>	mean (SD)	3,15	(4,49)	3,08	(4,55)	3,18	(4,47)	ns
<b>-Swollen Joint Count</b>	mean (SD)	3,06	(4,44)	3,28	(5,02)	2,94	(4,10)	ns
<b>-Physician Global Assessment</b>	mean (SD)	3,30	(2,74)	3,19	(2,71)	3,35	(2,76)	ns
<b>-Patient Global Assessment</b>	mean (SD)	4,83	(2,70)	4,90	(2,78)	4,79	(2,66)	ns
<b>CDAI low activity</b>	n (%)	309	(48,9)	111	(50,9)	198	(47,8)	ns
<b>CDAI moderate activity</b>	n (%)	185	(29,3)	62	(28,4)	123	(29,7)	ns
<b>CDAI high activity</b>	n (%)	134	(21,2)	44	(20,9)	90	(21,7)	ns
<b>RF positive</b>	n (%)	464	(73,4)	175	(80,3)	289	(69,8)	<b>0.006</b>
<b>Nodules</b>	n (%)	144	(22,8)	59	(27)	85	(20,5)	ns
<b>Total HAQ – DI</b>	mean (SD)	1,5	(0,7)	1,5	(0,7)	1,5	(0,7)	ns
<b>Pain Severity Score</b>	mean (SD)	4,8	(2,00)	4,9	(2,0)	4,8	(2,0)	ns
<b>Pain interference score</b>	mean (SD)	4,4	(2,4)	4,4	2,5	4,4	(2,4)	ns
<b>Anxiety Score</b>	mean (SD)	8,3	(4,8)	8,8	(4,7)	8,0	(4,8)	<b>0.049</b>
<b>Depression score</b>	mean (SD)	9,1	(6,1)	9,5	(6,3)	8,9	(4,8)	ns
<b>FACIT Score</b>	mean (SD)	28,3	(13,3)	27,5	(12,9)	28,8	(13,4)	ns
<b>Eq5d level sum score</b>	mean (SD)	9,1	(2,2)	9,2	(2,5)	9,1	(2,0)	ns
<b>-Mobility</b>	mean (SD)	1,69	(0,52)	1,70	(0,51)	1,68	(0,52)	ns
<b>-Self Care</b>	mean (SD)	1,77	(0,66)	1,80	(0,64)	1,75	(0,67)	ns
<b>-Usual Activities</b>	mean (SD)	1,80	(0,49)	1,86	(0,50)	1,77	(0,47)	<b>0.05</b>
<b>-Pain and Discomfort</b>	mean (SD)	2,36	(0,59)	2,37	(0,60)	2,35	(0,59)	ns
<b>-Anxiety and Depression</b>	mean (SD)	1,70	(0,60)	1,77	(0,64)	1,66	<b>(0,58)</b>	<b>0.04</b>

BMI: body mass index, SES: Socioeconomic Status, HAQ-DI: health assessment questionnaire disability index, FACIT: functional assessment of chronic illness therapy, CDAI: clinical disease activity index. RF : Rheumatoid Factor

Comparing the disease activity and PROMs of smokers and non-smokers, smokers showed significantly worse anxiety scores, and more impairment on the EQ5d domains of usual activities and anxiety and depression, with no statistical difference between the two groups for CDAI score and its components, complications of RA, HAQ- DI or HADs depression scores. Smokers were significantly more likely to have COPD than non-smokers, and tended to have more comorbidities although this did not reach statistical significance. The main comorbidities were hypertension (58.7% of all patients), diabetes mellitus (27.9%), dyslipidaemia (25.3%) and obesity (7% ).

More than half the patients (56 %) reported starting smoking at an age of 18 years or younger. The total number of cigarettes smoked per day was reported as less than ten in 72,8% of individuals. The major reasons participants identified for ongoing smoking was emotional support (45.8%), nicotine craving (30.5%) and pain control (25,2%). Less commonly listed reasons included social reasons (22.9.0%), boredom (20.0%) and coping strategy (17.6%). Many (50,6%) reported that living with RA makes it difficult to quit smoking. Only 48.0 % patients were aware that smoking worsened arthritis, yet 74.4% reported receiving advice to quit smoking from their arthritis doctors. Patients who smoked for reported pain control had higher pain severity scores 5.91 (1.6) vs 4.65 (2.0),  $p<0.001$ . Those smoking for emotional support had higher anxiety scores 10.61 (4.94) vs 7.90 (4.37),  $p<0.001$ .

When asked to list the benefits of smoking cessation, the most common responses were: lower risk of heart attack (74.8%), cancer (59.5%) and emphysema (54.0 %). Half of the smokers felt that quitting would lead to better control of arthritis (49.7%), others listed financial savings (47.9%), better fitness (37.4%), no longer smelling of smoke (32.5%) and approval from partner or family members (31.2%) as advantages of quitting. A small percentage (16.8%) reported being “desperate to quit”, the majority ambivalent or not interested: “maybe give it a try” (44.2%) “not right now” 32.6%.

The majority of actives smokers (67.5%) had mild nicotine dependence per the Fagerström test, a quarter (24.4%) moderate and only 7.5 % severe dependence. The Fagerström score positively correlated with both depression and anxiety scores:  $r\ 0.28$  ( $p<0,005$ ) and  $r\ 0.20$  ( $p=0.02$ ) respectively.

## Discussion

In this cross-sectional study of RA patients attending a tertiary referral centre, over a third of participants were smokers, with a further 14.1% previous smokers. This level of smoking is high in comparison to the national prevalence of 17.6% but similar to regional numbers, where the smoking prevalence in the Western Cape is 32.9%.<sup>(9)</sup> Elsewhere, the prevalence amongst RA patients has wide regional variability and ranges from 0.9% [Morocco] to 48% [Austria].<sup>(22-24)</sup>.

In our study, we found that more males smoked, in keeping with national demographic trends and smokers had lower BMI.<sup>(9, 25)</sup> Seropositivity, nodules and anxiety were more prevalent in smokers, which has been reported elsewhere.<sup>(26, 27)</sup> We found no significant difference between other PROM's. An association between smoking, pain, anxiety and depression has been well described. Current tobacco smoking worsens pain and early stages of nicotine withdrawal amplifies pain. Smoking has been associated with other chronic pain syndromes. Smokers have worse pain treatment outcomes. Anxiety and depression are more prevalent amongst smokers relative to non-smokers and in patients experiencing chronic pain. A complex bi-directional relationship ensues with pain and smoking associated or worsening anxiety/depression and the effects these disorders have on pain or pain management, smoking habits, and smoking cessation.<sup>(7, 28, 29)</sup>

Our participants reported emotional support and pain control as major reasons for continuing their smoking habit. This subgroup had higher pain severity and anxiety scores reflecting the challenges of living with RA, pain and anxiety and perhaps demonstrating that cigarette smoking is felt to ameliorate these problems. Improved control of RA disease, better nonpharmacological and pharmacological pain management together with attention to mental health care may improve PROMs in conjunction with smoking cessation programmes.<sup>(30, 31)</sup>

Smoking is a modifiable risk factor and contributes to cardiovascular risk, together with other smoking associated diseases. <sup>(32)</sup> The comorbidities of non-communicable and lifestyle diseases are prevalent in our patients with the vast majority, 74.1% having two or more comorbidities, and hypertension, dyslipidaemia, diabetes, and obesity were amongst the more common comorbidities. Each of these individually contribute towards a significant cardiovascular risk profile in RA patients.<sup>(33, 34)</sup> Smokers have lower BMIs due to appetite suppression, metabolic effects on lipid and glucose pathways and sympathetic activation. This does not however offset the cardiovascular risks of smoking. <sup>(35, 36)</sup>

Of concern is that less than half of participants believed that smoking worsened their arthritis, although most reported having received smoking cessation advice from their arthritis clinic team. This is an area for improvement and should be ongoing at every clinic visit. Encouragingly, the minority of patients have severe nicotine dependence, with most patients having mild dependence. This has been reported at our local smoking cessation clinic with low levels of nicotine dependence but high levels of depression in that clinic.<sup>(37)</sup> This along with the long time to return to non-smoker risk level, highlights the importance

of early and repeated interventions for smoking cessation for potential benefits in management of that subgroup. (38)

The costly nature of pharmacological therapies available for smoking cessation in low to middle income countries limits availability. From this study majority of patients are not interested or ambivalent to smoking cessation, despite low nicotine dependence. Simple and affordable strategies like reading material, education and brief interventions are likely needed to increase the interest in quitting with readily available support for those that are actively interested in quitting. Addressing the underlying level of disease control and associated anxiety/ depression in parallel with smoking cessation advice is likely to yield the best results, given the high prevalence of 'self-medication with tobacco'.

This is a single centre study in the Western Cape with high smoking prevalence which may limit its generalisability to other RA centres. As participation was voluntary, smoking may be under reported but this would no likely impact on those who did complete the smoking questions and related PROMs. A portion of this study was impacted by COVID – 19 regulations which included a brief period of tobacco regulation and lock downs. These regulations might have also had some impact on anxiety and depression scores during this period. Other forms of nicotine delivery e.g., chewing tobacco, vaping nor cannabis or other recreational drugs were not evaluated in this research project.

In conclusion, the prevalence of smoking amongst RA patients in Cape Town is as high as in the local population, many using tobacco as a way of self-medicating. Many smokers with RA were unaware of the direct negative effects on their joint disease despite knowledge of risk for cardiovascular, cancer and respiratory disease. It is critical to interrupt the cycle of pain and inflammation induced smoking with further smoking induced pain and inflammation. A multidisciplinary approach addressing, anxiety/depression, joint pain and reduced quality of life along with smoking specific behavioural modification and nicotine replacement therapy in those that need is required.

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# UNIVERSITY OF CAPE TOWN



**Bridget Hodkinson**

MBBCh, PhD, FCP (SA), Cert Rheum SA

J47-24 Old Main Building, Groote Schuur Hospital  
Anzio Rd, Observatory 7925  
Cape Town South Africa  
Tel +27 (0)21 404 2131  
Fax +27 (0)21 448 3253  
Mobile +27 (0)82 395 0503  
Email: [drbridget@gmail.com](mailto:drbridget@gmail.com)

To Postgraduate Committee

Supervisor's declaration for MMed dissertation Dr Simon Jacques le Roux

"Cigarette smoking amongst Rheumatoid Arthritis patients in a tertiary center in South Africa"

**Please find this thesis in publication-ready format, and note that I consider this thesis to be meeting all requirements to be included in the dissertation, namely:**

The journal to whom this manuscript has been submitted (Clinical Rheumatology) is accredited and:

- The candidate is the first author on the paper
- The candidate contributed the most to the paper
- The candidate developed the protocol and wrote the paper under supervision
- The candidate was involved in the analysis, presentation and interpretation of results
- The other authors and their contributions to the paper are stated

A handwritten signature in black ink, appearing to read 'Bridget Hodkinson'.

**Bridget Hodkinson**

**Professor and Head  
Rheumatology, Department of Medicine  
Groote Schuur Hospital  
Faculty of Health Sciences, University of Cape Town**

## Appendix A:

DATE of entry: \_\_\_\_/\_\_\_\_/\_\_\_\_

Contact number : \_\_\_\_\_

SEX:  M  F

ETHNIC ORIGIN:  B  C  A  W

SMOKER  Y  N  EX

PACK YEARS: \_\_\_\_\_

HIGHEST LEVEL OF EDUCATION  PRIMARY  SECONDARY  TERTIARY

WORK (current or last job) \_\_\_\_\_

WORK STATUS  EMP  UNEM  Disability grant  Old age pension **Stopped work d/t rheum illness?**  Y  N

YEAR OF Rheum Diagnosis: \_\_\_\_\_ At GSH Rheum since \_\_\_\_\_

### Rheumatology Diagnosis

- ANCA vasculitis       Ankylosing spondylitis       Gout
- Anti-phospholipid syndrome     Juvenile idiopathic arthritis
- Dermatomyositis/ polymyositis/ inflammatory muscle disease       Lupus
- Mixed connective tissue disease       Polymyalgia rheumatica
- Psoriatic arthritis       Rheumatoid arthritis
- Other inflammatory arthritis       Other spondyloarthritis

Sarcoidosis

*Sticker* or

NAME: \_\_\_\_\_

HOSPITAL NO: \_\_\_\_\_

Date of Birth \_\_\_\_\_

Postal code \_\_\_\_\_

Systemic sclerosis
   
  Sjogren's syndrome  
 Undifferentiated connective tissue disease Other
   
  \_\_\_\_\_

**COMORBIDITIES (cross or leave blank):**

HT	DM	Dyslipidaemia	Renal dysfunction	COPD	IHD or CCF	Obesity
HYPOTHYROID	HYPERTHYROI	NAS	STROK	PERIPH VASCULAR	FMS	
TB	HIV	Hep B	Hep C	DEPRESSION	Valvular heart dis	Inflam bowel disease
MALIGNANCY IF y details..						

Other \_\_\_\_\_

3. Are you on any of the following medication?

Prednisone
   
  Chloroquine
   
  Methotrexate
   
  Sulfasalazine  
 Leflunomide
   
  MMF
   
  Azathioprine
   
  Sildenafil  
 Cyclophosphamide
   
  Cyclosporin
   
  Biologics

**DATE:**

**Complications of RA**

nodule	scleriti	Pyoderma gangrenosum	ILD
myelopathy	scleriti	OSTEOPOROSI	CQ maculopathy

**MEDICATION**
 MTX
   
  CQ
   
  SASP
   
  LEF
   
  RITUX
   
  TNFi

Highest PRED dose in last 12 months	PRED dose now
-------------------------------------	---------------

**WEIGHT (kg)**\_\_\_\_\_ **HEIGHT (cm)**\_\_\_\_\_

**SWOLLEN JOINT COUNT**

**TENDER**

**JOINT COUNT**

**PHYSICIAN GLOBAL ASSESSMENT**

**PATIENT GLOBAL ASSESSMENT**

**PATIENT GLOBAL ASSESSMENT**

**HAQ**

Changes to therapy:

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**How bad has your PAIN over the last week?**

*No pain    mild pain    moderate pain    severe pain    unbearable pain*

<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	2.5	5	7.5 10
---	---	---	---	---	-----	---	--------

**How has your ARTHRITIS been in the last week?**

*Very Good    Good    Fair    Poor    Very poor*

<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	<input style="width: 40px; height: 20px;" type="checkbox"/>	2.5	5	7.5 10
---	---	---	---	---	-----	---	--------

**HEALTH ASSESSMENT QUESTIONNAIRE**

**We are interested in learning how your illness affects your ability to function in daily life.**

**Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:**

**DRESSING & GROOMING**

**Are you able to:**

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
Dress yourself, including shoelaces and buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**ARISING**

**Are you able to:**

Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**EATING**

**Are you able to:**

Cut your own meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**WALKING**

**Are you able to:**

Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Please check any AIDS OR DEVICES that you usually use for any of the above activities:**

<input type="checkbox"/> Devices used for Dressing (button hook, zipper pull, etc.)	<input type="checkbox"/> Built up or special utensils	<input type="checkbox"/> Crutches
<input type="checkbox"/> Special or built up chair	<input type="checkbox"/> Cane	<input type="checkbox"/> Wheelchair
	<input type="checkbox"/> Walker	

**Please check any categories for which you usually need HELP FROM ANOTHER PERSON:**

<input type="checkbox"/> Dressing and grooming	<input type="checkbox"/> Arising	<input type="checkbox"/> Eating	<input type="checkbox"/> Walking
--	----------------------------------	---------------------------------	----------------------------------

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
<b><u>HYGIENE</u></b>				
<b>Are you able to:</b>				
Wash and dry your body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Take a tub bath?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get on and off the toilet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<b><u>REACH</u></b>				
<b>Are you able to:</b>				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bend down to pick up clothing from the floor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<b><u>GRIP</u></b>				
<b>Are you able to:</b>				
Open car doors?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open previously opened jars?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turn faucets on and off?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<b><u>ACTIVITIES</u></b>				
<b>Are you able to:</b>				
Run errands and shop?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of a car?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do chores such as vacuuming or yard work?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Please check any AIDS OR DEVICES that you usually use for any of the above activities:**

<input type="checkbox"/> Raised toilet seat	<input type="checkbox"/> Bathtub bar	<input type="checkbox"/> Long-handled appliances for reach
<input type="checkbox"/> Bathtub seat	<input type="checkbox"/> Long-handled appliances in bathroom	<input type="checkbox"/> Jar opener (for jars previously opened)

**Please check any categories for which you usually need HELP FROM ANOTHER PERSON:**

<input type="checkbox"/> Hygiene	<input type="checkbox"/> Reach	<input type="checkbox"/> Gripping and opening things	<input type="checkbox"/> Errands and chores
----------------------------------	--------------------------------	--	---

**Your ACTIVITIES:** To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## Rheumatology Smoking Review

Dear patient

We would like to ask you some questions about cigarette smoking, your reasons for smoking and your interest in quitting smoking. Your answers will help us understand your habit and your attitudes to this habit. Please answer each question honestly – you will not be judged for any of your answers. Please feel free to discuss these questions or your answers with any of the doctors or sisters at the arthritis clinic, or with the lead investigator, Prof Bridget Hodkinson.

1) Are you a cigarette smoker?

Y  N  Used to smoke  (which year did you quit \_\_\_\_\_)

2) How old were you when you started smoking regularly?

3) How many cigarettes do you smoke on most days?

2-3  3-  10  11-20  more than 20

4) What do you feel is the major reason you smoke? (you may choose more than 1 answer)

Pain  control  Emotional Support (eg   
anxiety, stress  or depression)   
Coping strategy because of living  circumstances   
I keep company with smokers (at home or  work)   
Nicotine      
craving/dependence/addiction  Boredom   
Socializing   
Other (Please explain)

5) Do you think that living  with rheumatoid arthritis makes it more difficult for you to  quit  smoking? Y  N

6) Have you ever thought about stopping smoking?

Y  N

7) Have you ever quit smoking for more than 3 months in the past?

Y  N

8) Can you think of any advantages/benefits of quitting smoking? (you may choose more than 1 answer)

Lower risk of cancer  risk  Lower risk of heart   
attack or stroke   
Lower risk of emphysema or lung  disease   
control of  arthritis  Financial  Better  fitness   
Won't smell  of smoke   
Partner/family want me to  quit   
Other (Please explain)

---

---

9) Do you believe that smoking cigarettes may worsen your arthritis?

Yes  Not   sure  No

10) Have you ever received advice to stop smoking from your arthritis doctors?

Yes  Not  sure  No

11) Has COVID -19 and lockdown in 2020 affected the number of cigarettes you smoke?

Quit during lockdown  Reduced smoking  No  
affect  Reduced or quit during lockdown but back up  now

12) How motivated are you to quit smoking?

Don't want to quit  Not right now  Maybe give it a try   
Desperate to stop

13) How can we help?

Offer more information for me to  read  Smoking   
cessation clinic referral (E16)  
Individual counselling  sessions  Group   
counselling sessions

This is a questionnaire to assess how dependant on cigarette smoking you are at the moment:

Fagerström test

Please answer each question....

- | 1. How soon after you wake up do you smoke your first cigarette?  | Score    |
|---|----------|
| <u>After 60 min</u> <input type="checkbox"/>  | <u>0</u> |
| <u>31 – 60 min</u> <input type="checkbox"/>   | <u>1</u> |
| <u>6 – 30 minutes</u> <input type="checkbox"/>  | <u>2</u> |
| <u>Within 5 minutes</u> <input type="checkbox"/>  | <u>3</u> |
| 2. Do you find it difficult to refrain from smoking in places where it is forbidden?                    |          |
| <u>No</u> <input type="checkbox"/>  | <u>0</u> |
| <u>Yes</u> <input type="checkbox"/>   | <u>0</u> |
| 3. Which cigarette would you hate most to give up?  |          |
| <u>The first in the morning</u> <input type="checkbox"/>  | <u>1</u> |
| <u>Any other</u> <input type="checkbox"/>   | <u>0</u> |
| 4. How many cigarettes per day do you smoke?  |          |
| <u>10 or less</u> <input type="checkbox"/>  | <u>0</u> |
| <u>11 to 20</u> <input type="checkbox"/>  | <u>1</u> |
| <u>21 to 30</u> <input type="checkbox"/>  | <u>2</u> |
| <u>31 or more</u> <input type="checkbox"/>  | <u>3</u> |
| 5. Do you smoke more frequently during the first hours after awakening than during the rest of the day? |          |
| <u>No</u> <input type="checkbox"/>  | <u>0</u> |
| <u>Yes</u> <input type="checkbox"/>   | <u>1</u> |
| 6. Do you smoke even if you are so ill that you are in bed most of the day?                             |          |
| <u>No</u> <input type="checkbox"/>  | <u>0</u> |
| <u>Yes</u> <input type="checkbox"/>   | <u>1</u> |

Total Score

0-2 Very low dependence  
3-4 Low dependence

5 medium dependence  
6-7 High dependence

8-10 very high dependence

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**SELF-CARE**

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN / DISCOMFORT**

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**ANXIETY / DEPRESSION**

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	Not at all	A little bit	Some- what	Quite a bit	Very much
I feel fatigued.	0	1	2	3	4
I feel weak all over.	0	1	2	3	4
I feel listless (“washed out”).	0	1	2	3	4
I feel tired.	0	1	2	3	4
I have trouble <u>starting</u> things because I am tired.	0	1	2	3	4
I have trouble <u>finishing</u> things because I am tired.	0	1	2	3	4
I have energy.	0	1	2	3	4
I am able to do my usual activities.	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat.	0	1	2	3	4
I need help doing my usual activities.	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do.	0	1	2	3	4
I have to limit my social activity because I am tired.	0	1	2	3	4

### Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.  
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		<b>I feel tense or 'wound up':</b>			<b>I feel as if I am slowed down:</b>
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		<b>I still enjoy the things I used to enjoy:</b>			<b>I get a sort of frightened feeling like 'butterflies' in the stomach:</b>
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		<b>I get a sort of frightened feeling as if something awful is about to happen:</b>			<b>I have lost interest in my appearance:</b>
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		<b>I can laugh and see the funny side of things:</b>			<b>I feel restless as I have to be on the move:</b>
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		<b>Worrying thoughts go through my mind:</b>			<b>I look forward with enjoyment to things:</b>
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		<b>I feel cheerful:</b>			<b>I get sudden feelings of panic:</b>
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		<b>I can sit at ease and feel relaxed:</b>			<b>I can enjoy a good book or radio or TV program:</b>
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

**Scoring:**

Total score: Depression (D) \_\_\_\_\_ Anxiety (A) \_\_\_\_\_

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

## Appendix B

### PATIENT INFORMATION:

#### **Rheumatology UCT Smoking Prevalence Study**

#### Dear patient

I am Professor Bridget Hodkinson and would like to invite you to take part in our Rheumatology UCT smoking prevalence study. We would like to collect information about your rheumatology illness and smoking habits so that we can learn more about our patients, and so that we can develop studies in the future or offer help should you decide to quit smoking.

#### **What is involved?**

Your doctor will record details about you (your age, gender and postal code), and about your rheumatological problem (diagnosis, date of diagnosis and medications you are using) and an additional section for Smokers. The collected information would then be registered on a computer database. This database will not entail any extra visits over and above normal care. You will not be receiving any experimental therapies. There are no risks, nor are there any direct benefits to you if you agree to join the study. There may be benefit to society in the long term as we improve our understanding of rheumatic diseases and develop strategies and studies to improve the lives of our patients.

#### **What if I do not wish to take part in this study?**

All registries and studies are always completely voluntary. If you do not wish to take part this will not affect the treatment you receive. All the information collected will be handled in a strictly confidential manner and the results will only be used for research purposes. You can withdraw from this database at any time.

#### **Other information**

All your written and computer records will be kept strictly confidential at all times. Data Protection Act regulations have been complied with to ensure confidentiality. We plan to store this database for 5 years. The database team reserves the right to withdraw you from the database at any time.

**IF YOU HAVE ANY FURTHER QUESTIONS ABOUT THE DATABASE, PLEASE CONTACT:**

Principal Investigator: Prof Bridget Hodkinson telephone:021 404 2131

Ethics Committee Chairman Prof Blockman telephone 021 650 5057

INFORMED CONSENT

1. I have read the patient information sheet regarding the above study and have had the opportunity to discuss the details with \_\_\_\_\_ and to ask questions. I understand fully what is to be done.
2. I have agreed to take part in the study as it has been explained to me, but I understand that I am completely free to withdraw from the study or any part of the study at any time I wish, without prejudice to my further treatment.
3. I understand that this study is designed to promote medical knowledge and may not benefit me personally.
4. I understand that the results of the study may be published if a research project is done, but my personal results will remain confidential, and my name will not be disclosed in any report. I understand that my family doctor will be notified of my participation in this study and that any results, which might be relevant to my medical care, will be forwarded onto my family doctor. I hereby fully and freely consent to participate in the study, which has been fully explained to me.

Signature of patient, \_\_\_\_\_

Name of patient (Print) \_\_\_\_\_ Date \_\_\_\_\_

I confirm that I have explained to the volunteer named above, the nature and purpose of the tests to be undertaken.

Signature                  Rheumatologist                  or                  Rheumatology                  Nurse

\_\_\_\_\_

Name \_\_\_\_\_ Date \_\_\_\_\_



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



Room G50- Old Main Building  
Groote Schuur Hospital  
Observatory 7925  
Telephone [021] 406 6492  
Email: hrec-submissions@uct.ac.za  
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 May 2021

**HREC REF: 179/2021**

**Prof B Hodkinson**  
Division of Rheumatology  
FHS  
Email: [Drbridget@gmail.com](mailto:Drbridget@gmail.com)  
Student: [Jacquesleroux86@gmail.com](mailto:Jacquesleroux86@gmail.com)

Dear Prof Hodkinson

**PROJECT TITLE: CIGARETTE SMOKING AMONGST RHEUMATOID ARTHRITIS PATIENTS IN A TERTIARY CENTER IN SOUTH AFRICA (MMED DEGREE – DR SIMON JACQUES LE ROUX)**

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

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

**This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.**

**Approval is granted for one year until the 30 May 2022.**

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](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

***The HREC acknowledge that the student: - Dr Simon J le Roux will also be involved in this study.***

**Please quote the HREC REF 179/2021 in all your correspondence.**

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

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

Yours sincerely

Signed by candidate

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE**

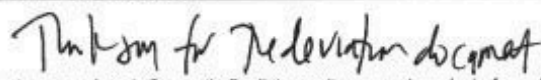
HREC/REF 179/2021sa



**FHS016: Annual Progress Report / Renewal**

<b>HREC office use only (FWA00001637; IRB00001938)</b>			
<b>This serves as notification of annual approval, including any documentation described below.</b>			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30/11/23
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signed by candidate		Date Signed 3/11/22

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to [hrec-enquiries@uct.ac.za](mailto:hrec-enquiries@uct.ac.za).  
 Please clarify your plan for research-related activities during COVID-19 lockdown.  
 Please use the latest form found on our website:  
<http://www.health.uct.ac.za/fhs/research/humanethics/forms>

Comments to PI from the HREC

Data collection completed. Currently finalising write up and analysis for submission.

Signed by candidate

**Principal Investigator to complete the following:**

**1. Protocol information**

Date (when submitting this form)	17/10/2022		
HREC REF Number	179/2021	Current Ethics Approval was granted until	30/05/2023
Protocol title	Cigarette Smoking amongst Rheumatoid Arthritis Patients in a Tertiary Center in South Africa		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof Bridget Hodkinson		



# Appendix D:

## Instructions for Authors

### Instructions for Authors

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*Clinical Rheumatology* endorses complete and transparent reporting of biomedical and clinical research. Depending on the study, we recommended the authors to adhere to the relevant [EQUATOR Network](#) reporting guidelines when preparing their manuscript.

#### Types of papers

- **Original Research articles:** word limit 4000 words, 45 references, no more than 6 figures/tables; abstracts must be structured as specified below. After the abstract, include key-points (min. of 1, max. of 4) presented in brief sentences, highlighting the contributions of the paper.

Please note: **It is mandatory that abstracts for Original Research articles adopt the below structure (150-250 words):**• Introduction / objectives – specify the context of the problem (optional), the research aim, question or purpose, and the tested hypothesis. • Method – specify the design of the study, selection criteria of patients, main outcome variable and statistical approach used to test the primary hypothesis. • Results – summarise the main results, present the results that support the hypothesis stated in Introduction providing results in numbers, not just p-values or interpretations, and other relevant results (optional). • Conclusions – summarise what the findings might imply, and the implications and recommendations for future research; conclusions should be coherent with the objectives and the results presented in the abstract.

- **Review articles:** Provide accessible, authoritative, and balanced overviews of a field or topic. Abstract (unstructured, 150-250 words, please avoid using abbreviations and references); 4-6 keywords (please note that the word count refers to individual MeSH words representing the main content of the article); up to 4 key-points; up to 100 references; up to 5 Tables/figures, not including supplementary material. Word limit: 5,000 words.
- **Brief report** 2000 word limit, 25 references, no more than four figures; include key points (minimum of 1, maximum of 4) presented in short sentences, highlighting the contributions of the article. Each manuscript must be formatted as an original article, including a structured abstract.

- **Clinical Image:** Clinical Images are a brief clinical report describing a unique image. All Clinical Images must have patient consent for publication, and the copyright form must be sent with your submission to Clinical Rheumatology, including:• Title page• Structured text including two sections: Presentation (case narrative); Discussion (brief, concise messages).• References (up to 5)• Figure (up to 1, not including supplementary material). Make sure that the figure complies with the image quality standards described in the Clinical Rheumatology instructions for authors section (artwork).• Word count: Up to 300. Provide a figure footnote that is not redundant with the main text.
- **Letters of Biomedical and Clinical Research:** word limit 650 words, 10 references, 2 tables or figures and a discussion; summaries and supplementary material should not be included. Should present advances in highly focused, original clinical and biomedical research that is easily replicable.
- **Perspectives in Rheumatology:** word limit 3500 words, 40 references, no more than 3 figures. Should share a clinical, methodological, scientific, or ethical point of view regarding provocative or hot topics emerging in the clinical practice of rheumatology. Unstructured abstract.
- **Case Based Review:** a case report of extreme clinical interest incorporating a mini review in an area of new knowledge. Word limit 3500 words, 50 references, no more than 5 figures.
- **Letters to editor:** up to 600 words
- **Editorial:** up to 1500 words

#### Title Page

##### **Title Page**

Please make sure your title page contains the following information.

##### **Title**

The title should be concise and informative.

##### **Author information**

- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
- If available, the 16-digit [ORCID](#) of the author(s)

If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Large Language Models (LLMs), such as [ChatGPT](#), do not currently satisfy our [authorship criteria](#). Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.

#### **Abstract**

Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

*For life science journals only (when applicable)*

- Trial registration number and date of registration for prospectively registered trials
- Trial registration number and date of registration, followed by "retrospectively registered", for retrospectively registered trials

#### **Keywords**

Please provide 4 to 6 keywords which can be used for indexing purposes.

#### **Statements and Declarations**

The following statements should be included under the heading "Statements and Declarations" for inclusion in the published paper. Please note that submissions that do not include relevant declarations will be returned as incomplete.

- **Competing Interests:** Authors are required to disclose financial or non-financial interests that are directly or indirectly related to the work submitted for publication. Please refer to "Competing Interests and Funding" below for more information on how to complete this section.

Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs.

#### **Specific Remark for Original Research articles**

**It is mandatory that abstracts for Original Research articles adopt the below structure:**

- Introduction / objectives – specify the context of the problem (optional), the research aim, question or purpose, and the tested hypothesis.
- Method – specify the design of the study, selection criteria of patients, main outcome variable and statistical approach used to test the primary hypothesis.
- Results – summarise the main results, present the results that support the hypothesis stated in Introduction providing results in numbers, not just p-values or interpretations, and other relevant results (optional).
- Conclusions – summarise what the findings might imply, and the implications and recommendations for future research; conclusions should be coherent with the objectives and the results presented in the abstract.

Full Instructions available at Link

<https://www.springer.com/journal/10067/submission-guidelines#Instructions%20for%20Authors>