Demographic and Clinical characteristics of children with Juvenile Dermatomyositis in Cape Town

by

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OKNLAW001

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Declaration

I, Dr. Lawrence Owino Okong’o, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Study rationale: Juvenile dermatomyositis (JDM) is a rare idiopathic inflammatory myopathy of childhood with an incidence of 1.9-3.2 per million. The aetiology of JDM is uncertain but may result from immune dysregulation triggered by environmental factors in genetically susceptible children. The demographic and clinical characteristics of JDM may thus differ by race and geographic regions. Few studies have described the characteristics of JDM patients from Africa. There is need for further studies for better understanding of the epidemiology, clinical characteristics and outcome of patients with JDM from the continent.

Methods: We conducted a retrospective observational study to determine clinical characteristics and outcomes of patients satisfying the Bohan and Peter criteria for probable JDM seen between 2004-2013 in Red Cross, Groote Schuur and Tygerberg hospitals in Cape Town. Data was analyzed using R version 3.1.0 (2014-04-10).

Results: Twenty five cases were identified: 16 female and 9 male. Thirteen (52%) of the cases were of indigenous African, eleven (44%) mixed and one (4%) European ancestry. The median ages at disease onset and diagnosis were 6.75 (range 2.0-9.7) and 7.9 (range 3.4-9.75) years respectively. Muscle weakness and characteristic cutaneous manifestations occurred in all the 25 patients while 24 had elevated muscle enzymes. All the patients received corticosteroids, seventeen (73.9%) received methotrexate and four received rituximab. Eleven patients had calcinosis during the disease course [median follow up period of 50 (range 0.5-159) months]. The mortality was 2/25 (8%) while only 40% of the patients had clinically inactive disease by PRINTO criteria. There was no difference in racial distribution (p-value
= 1), age at disease onset (p-value = 0.87) and disease duration prior to treatment
initiation (p-value = 0.75) between patients who had clinically active and inactive
disease.

Discussion: The demographic characteristics of children with JDM were similar to
that from most other regions of the world with female predominance and similar age
at onset. The median delay in diagnosis (4 months) was not longer than that reported
in most other studies. However, some children had prolonged delay of up to 7 years
due to misdiagnosis that denied them appropriate treatment in a timely manner.

Majority (60%) of the patients also remained with clinically active disease, which put
them at risk of further disease complications including calcinosis. Even though the
mortality rate was low (8%) this was still more than double that reported in most
recent large studies especially from the resource rich countries.

Conclusions: Long term follow up of JDM patients is advisable since majority of
patients seem to have clinically active disease many years after disease onset despite
treatment. Formulation and use of appropriate treatment guidelines and protocols
may aid in the early diagnosis and appropriate management for optimum outcomes.
Acknowledgements

Thanks to Prof. Jo Wilmshurst, Dr. Alvin Ndondo and other staff in the department of paediatric neurology at the Red Cross War Memorial Children’s Hospital who were involved in the management of most of the cases and who documented the clinical findings that were our most important source documents. Special thanks to Prof. Jo Wilmshurst for contributing to the conceptualization of the study, identifying and providing data on the cases and reviewing the protocol and final dissertation.

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The African Paediatrics Fellowship Program (APFP) for sponsoring and facilitating Dr. Lawrence Okong’o fellowship. The study was done as part fulfilment for the MPhil degree at the end of the fellowship.
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<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
</tr>
<tr>
<td>CMAS</td>
<td>Childhood Myositis Assessment Scale</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CT Scan</td>
<td>Computerised Tomography Scan</td>
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<tr>
<td>CK</td>
<td>Creatine Kinase</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
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<tr>
<td>GSH</td>
<td>Groote Schuur Hospital</td>
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<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
</tr>
<tr>
<td>IMACS</td>
<td>International Myositis And Clinical Studies</td>
</tr>
<tr>
<td>IVIG</td>
<td>Intra-Venous Immune Globulin</td>
</tr>
<tr>
<td>JDM</td>
<td>Juvenile Dermatomyositis</td>
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<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MAA</td>
<td>Myositis Associated Antibodies</td>
</tr>
<tr>
<td>MDI</td>
<td>Myositis Damage Index</td>
</tr>
<tr>
<td>MHC</td>
<td>Major Histocompatibility Complex</td>
</tr>
<tr>
<td>MMT</td>
<td>Manual Muscle Testing</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MSA</td>
<td>Myositis Specific Antibodies</td>
</tr>
<tr>
<td>PRINTO</td>
<td>Paediatric Rheumatology International Trials Organization</td>
</tr>
<tr>
<td>RCWMCH</td>
<td>Red Cross War Memorial Children’s Hospital.</td>
</tr>
<tr>
<td>TBH</td>
<td>Tygerberg Hospital</td>
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<tr>
<td>vWF</td>
<td>Von Willebrand Factor</td>
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Section I: Dissertation (publication format)
1 Chapter 1: Introduction

1.1 Context

1.1.1 Historical perspective

Juvenile dermatomyositis (JDM) is an immune mediated vasculopathic disease of childhood characterized by inflammation of the striated muscles, skin and internal organs. The descriptions of patients presenting with muscle damage and skin lesions were first given by Wagner in 1863[1]. Hans Unverritch later described a case of a man who presented with systemic symptoms, muscle weakness, periorbital discolorations and degenerative muscle changes on histology. This patient later died of respiratory failure. In 1891, Unverritch reported a second case and used for the first time, the term dermatomyositis to describe these cases.

1.1.2 Aetiopathogenesis of juvenile dermatomyositis

JDM probably arises as a result of immune dysregulation in genetically susceptible individuals following exposure to some as yet incompletely described environmental triggers. The role of genetic factors in the aetiology and pathogenesis of JDM has been backed by reports of familial clustering of JDM with other autoimmune diseases such as SLE, rheumatoid arthritis and type-1 Diabetes [2].

Several HLA haplotypes such as HLA DRB1*0301, DQA1*0301, HLA-DQA1*0501 and HLA-B8 occur more frequently in patients with JDM than in the general population and may thus confer risk for JDM. Conversely, HLA DQA1*0201 and DQA1*0101 alleles have been associated with lower risk of JDM in Caucasians [3,4]. Other gene loci that appear to confer risk of JDM include genes for the inflammatory cytokines TNFα, IL-1α and IL-1β; as well as the lymphocyte
signaling gene PTPN22. The TNF308A and IL1 polymorphisms are associated with higher risk of ulcerative disease and calcifications in JDM patients [4,5].

Environmental exposures such as infections, exposure to sunlight, vaccination and drugs have been reported as possible triggers [5-7] that may induce or worsen symptoms of JDM. Seasonal clustering of cases of JDM has further added to the speculation about the role of infections in the pathogenesis of JDM [8].

JDM is associated with a broad range of immune aberrations involving autoantibody production; complement mediated endothelial damage; aberrations in innate immunity and T-cell dysfunction. Increased levels of inflammatory cytokines including type I interferon stimulate up-regulation of MHC I expression on muscle. Expression of MHC I in myofibrils is associated with development of myositis with perivascular inflammatory cell (T cells, B cells, Macrophages and plasmacytoid dendritic cell) infiltration of muscle fibres [6].

Autoantibodies are identifiable in most cases of JDM. These can be classified either as myositis specific antibodies (MSA) or myositis associated antibodies (MAA). The MAA also occur in autoimmune diseases other than JDM. The MSAs include: anti Jo-1, anti-SRP and anti-Mi2. The more recently described MSAs such as anti-TIF1 (anti p155/140) and anti-NXP (anti p140) are more prevalent in JDM than the previously described autoantibodies and occur in upto 40% of JDM patients [4,9]. These newer MSAs are also associated with specific disease phenotypes with anti-p140 being associated with calcinosis.
1.1.3 Demographic characteristics

Dermatomyositis affects people of all ages though two peaks at onset have been described: 5-14 years and 45-64 years. The bimodal distribution demonstrates the uniqueness of the childhood [Juvenile Dermatomyositis (JDM)] form as a distinct disease from the adult form. JDM is the most common of the idiopathic inflammatory myopathies of childhood with incidence of 1.9-3.2 per a million [8,10].

Data from large patient registries indicate that the average age of onset of JDM is seven years (ranges from 5.7-8.7 years) with greater incidence in girls than boys (ratio of 1.9-4.2:1)[11-14]. However, regional differences exist and studies from India and Saudi Arabia have reported higher incidence rates in male children [15,16]. JDM occurs in all regions of the world though some studies suggest that there could be differences in incidence rates among different racial groups. Mendez et al found a lower incidence rate among children of Hispanic ancestry compared to those of African and Caucasian ancestry in the USA [10]. Racial differences have been noted in the incidence rates of certain disease manifestations with much higher incidence of calcinosis among children of African ancestry compared to other racial groups [12,17,18].

1.1.4 Clinical characteristics, investigations and diagnosis

JDM is a multisystem disease and manifests with symptoms in the skin, muscles as well as other organs including the lungs, gut, joints, heart and kidneys. Even though there are no validated criteria for the diagnosis and classification of JDM, the Bohan and Peter criteria which were initially proposed in 1975 for the diagnosis of inflammatory myositis in adults [19,20] are often applied for this purpose. The Bohan and Peter criteria are a set of five clinical and laboratory features that include characteristic cutaneous features, proximal muscle weakness, raised muscle enzymes,
characteristic muscle biopsy and suggestive electromyographic (EMG) findings. Presence of the characteristic cutaneous features with three of the other four criteria is necessary for a diagnosis of definite JDM while presence of the characteristic rash with two other features denotes Probable JDM.

However, in current paediatric practice, muscle biopsy and EMG are rarely performed due to their invasive nature. Instead, Magnetic Resonance Imaging (MRI) of muscle has gained popularity and has been proposed as a non-invasive alternative to muscle biopsy and EMG for assessing muscle inflammation [21,22]. Further, whole body muscle MRI has been found to perform well in identifying areas of muscle inflammation, identifying areas of active inflammation to biopsy and in quantifying the inflammatory burden in JDM [23].

Other non-invasive modalities for the evaluation of muscle inflammation for diagnosing dermatomyositis that have been explored include PET scans [24,25], Ultrasound Scan (MSUS)[ 26,27], and Scintigraphy (bone scans) [ 28-30]. Even though MRI is increasingly being used in the diagnosis and monitoring of JDM, it is still relatively expensive and inaccessible in most resource limited settings like Sub-Saharan Africa. Ultrasound is cheaper and more widely available compared to MRI. Further, MSUS is not associated with exposure to radiation just like with MRI. Bone scans are another alternative that is cheaper than MRI and may be less affected by operator (subjective) factors compared to MSUS.

1.1.5 Management

Steroids have been used empirically as the mainstay and first line of management of JDM even though there had been no Randomized Controlled Trials (RCTs) supporting their use and efficacy until recently. A multinational prospective cohort
study on the treatment modalities employed by clinicians confirmed steroids as being the most common drugs used in JDM treatment [33]. In addition to steroids, immunosuppressive and immune modulating drugs such as methotrexate, intravenous immunoglobulin (IVIG), azathioprine, cyclosporine, mycophenolate mofetil and cyclophosphamide have traditionally been used to induce remission in severe disease and as steroid sparing agents.

In response to the lack of evidence based standardized guidelines, the Childhood Arthritis & Rheumatology Research Alliance (CARRA) proposed consensus treatment guidelines for the management of moderately severe JDM [31,32]. Three consensus treatment guidelines were proposed: Prednisone and methotrexate, Prednisone with methotrexate and pulse methyl prednisone; and Prednisone, methotrexate, pulse methyl prednisone and Intravenous Immunoglobulin. Ruperto et al [33] recently published the results of their RCT which showed that combination of prednisone with methotrexate or with cyclosporine was more effective than prednisone alone in the management of JDM. Further, the prednisone methotrexate combination had less adverse effects than the prednisone cyclosporine combination.

Few studies have looked at the efficacy of biological agents in JDM and therefore there are currently insufficient data to recommend use of biologic agents for the treatment of JDM. Oddis et al conducted an RCT on the efficacy of rituximab in refractory adult and Juvenile Dermatomyositis and noted that rituximab was efficacious in management of refractory JDM to achieve the IMACS definition of improvement [34]. A small study looking at the efficacy of infliximab for the treatment of refractory JDM in 5 patients demonstrated clinical benefit in muscle strength, patient global wellbeing, physician global assessment of improvement and even calcinosis in all the patients [35]. However, some studies have reported
unfavourable results with use of anti-TNF biologics in dermatomyositis and inflammatory myositis [36]. Generally, caution is advised in the use of anti-TNF biologics due to reports of TNF inhibitor induced dermatomyositis in patients receiving adalimumab and eternacept for the treatment of arthritis [37,38].

1.1.6 Treatment Outcome

The outcome of JDM has markedly improved over the years. In the years before the introduction of steroids for the treatment of JDM (before 1960s), the mortality rates were about 30% and a further 30% of the patients survived with major sequelae [14]. With the use of modern diagnostic and therapeutic strategies, JDM mortality rate has reduced to less than 5% [14,39-41]. Despite the improvement in mortality rates among JDM patients, disease and treatment related damage such as calcinosis, interstitial lung disease, residual muscle weakness, lipodystrophy and steroid toxicity remain major challenges and significantly affect the quality of life of affected individuals.

However, data on the characteristics and treatment outcome of JDM patients from Africa is scarce and only one study has been published that specifically described a series of JDM patients from the continent [12]. In that study, a higher rate of calcinosis and vasculitis compared to that from other regions was reported suggesting that the clinical manifestations and outcome of JDM in African patients could be different. There is need of further studies for a better understanding of the epidemiology, clinical manifestations and treatment outcomes of JDM in patients from Africa. We therefore carried out a study to review and describe the clinical features and treatment outcomes of JDM patients from Cape Town, South Africa.
1.2 Ethical considerations

The study was approved by the Human Research Ethics Committees (HREC) of the Universities of Cape Town (HREC/REF: 062/2014, appendix 5) and Stellenbosch (Ref: S14/04/080, appendix 6). Permission to carry out the study and access patient records was sought from the respective hospital administrators. Consent from patients or their parents was not obtained since this was a retrospective case note review and did not involve direct patient contact. Patient confidentiality was observed and information collected was kept anonymous. The study was conducted in observance of the principles of Helsinki (2008) and Good Clinical Practice (GCP).

1.3 Author guidelines Paediatric rheumatology journal

The manuscript will be submitted to the journal Paediatric Rheumatology for publication. Paediatric Rheumatology is the official journal of the Paediatric Rheumatology European Society (PReS) and the premier journal specifically dedicated to paediatric rheumatology. It is an online open access journal and thus shall provide the maximum reach among the paediatric rheumatology community and to any other interested scientist, clinician or researcher. The journal does not limit the length of the manuscripts submitted for publication though authors are encouraged to be concise. The journal is listed in the citation index of the Institute for Scientific Information (ISI) and is accredited by the South African Department of Education.

The full author guidelines for paediatric rheumatology journal is included as appendix 7. The author instructions can be accessed at “http://www.ped-rheum.com/authors/instructions.”
1.4 References


[17] Chickermane PR, Mankad D, Khubchandani RP. Disease patterns of juvenile dermatomyositis from Western India. Indian Pediatr 2013 Oct 8;50(10):961-963.


Chapter 2: Publication-ready manuscript
Characteristics and outcome of children with Juvenile Dermatomyositis in Cape Town: A cross-sectional study.

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2.1 Abstract

**Background:** Juvenile dermatomyositis (JDM) is a rare idiopathic inflammatory myopathy of childhood with an incidence of 1.9-3.2 per million. The aetiology of JDM is uncertain but may result from immune dysregulation triggered by environmental factors in genetically susceptible children. The demographic and clinical characteristics of JDM may thus differ by race and geographic regions. Few studies have described the characteristics of JDM patients from Africa. There is need for further studies for better understanding of the epidemiology, clinical characteristics and outcome of patients with JDM from the continent.

**Methods:** We conducted a retrospective observational study to determine clinical characteristics and outcomes of patients satisfying the Bohan and Peter criteria for probable JDM seen between 2004-2013 in Red Cross, Groote Schuur and Tygerberg hospitals in Cape Town. Data was analyzed using R version 3.1.0 (2014-04-10).

**Results:** Twenty five cases were identified: 16 female and 9 male. Thirteen (52%) of the cases were of indigenous African, eleven (44%) mixed and one (4%) European ancestry. The median ages at disease onset and diagnosis were 6.75 (range 2.0-9.7) and 7.9 (range 3.4-9.75) years respectively. Muscle weakness and characteristic cutaneous manifestations occurred in all the 25 patients while 24 had elevated muscle enzymes. All the patients received corticosteroids, seventeen (73.9%) received methotrexate and four received rituximab. Eleven patients had calcinosis during the disease course [median follow up period of 50 (range 0.5-159) months]. The mortality was 2/25 (8%) while only 40% of the patients had clinically inactive disease by PRINTO criteria. There was no difference in racial distribution (p-value = 1), age at disease onset (p-value = 0.87) and disease duration prior to treatment...
initiation (p-value = 0.75) between patients who had clinically active and inactive disease.

**Conclusion:** The demographic characteristics of children with JDM were similar to that from most other regions of the world with female predominance and similar age at onset. However, majority of the patients remained with clinically active disease, which put them at risk of further disease complications including calcinosis. Long term follow up of JDM patients and use of appropriate treatment guidelines and protocols may guide appropriate management for optimum outcomes.

**Keywords**

Juvenile dermatomyositis, JDM, Outcome, Africa.
2.2 Background

Juvenile dermatomyositis (JDM) is an immune mediated vasculopathic disease of childhood characterized by inflammation of the striated muscles, skin and internal organs. The most common clinical manifestations are proximal muscle weakness and characteristic cutaneous lesions such as heliotrope rash, Gottron’s papules and calcinosis. However, disease manifestations may occur in the lungs, heart, gastrointestinal tract and other organs. The pathogenesis of JDM is not fully understood but environmental factors are thought to trigger the disease in genetically predisposed children [1-4].

JDM is most commonly diagnosed and classified using the Bohan and Peter criteria published in 1975 [5,6]. Though initially proposed for use in adults, these criteria are also widely used for diagnosis of myositis in the paediatric age group. The criteria include presence of a characteristic rash, symmetrical proximal muscle weakness, elevated muscle enzymes in serum, electromyographic changes and muscle biopsy features of inflammatory myositis. The presence of the skin manifestations is mandatory for diagnosis while presence of three of the other features is necessary for classification as definite JDM and of two other features as probable JDM. Presence of characteristic skin lesions without apparent muscle involvement may be seen in about 1.0% of cases and is referred to as amyopathic dermatomyositis [7].

Data from multicenter patient registries indicate that the average age of onset of JDM is seven years with greater incidence in girls than boys (ratio of 2:1) [8-11]. However, regional differences exist and studies from India and Saudi Arabia have reported higher incidence rates in male children [12,13]. JDM occurs in all regions of the world though some studies suggest that there could be differences in incidence rates among different racial groups. Mendez et al reported a lower incidence rate
among children of Hispanic ancestry compared to those of African and Caucasian ancestry in the USA [14]. Racial differences have also been noted in the incidence rates of certain disease manifestations with much higher incidence of calcinosis being reported among children of African ancestry compared to other racial groups [9,15,16].

The reported treatment outcome of JDM has improved over the years. The mortality rate has significantly reduced from more than 30% before routine use of steroids [17], to less than 5% reported in most recent studies [11,18-20]. Despite the improvement in mortality rates among JDM patients, disease and treatment related damage remains a major challenge and significantly affect the quality of life of affected individuals. However, data on the characteristics and treatment outcome of JDM patients from Africa is scarce and only one study has been published that specifically described a series of JDM patients from the continent [9]. In that study, a higher rate of calcinosis and vasculitis compared to that from other regions was reported suggesting that the clinical manifestations and outcome of JDM in African patients could be different.

There is need of further studies for a better understanding of the epidemiology and treatment outcomes of JDM in patients from Africa. We therefore carried out a study to review and describe the clinical features and treatment outcomes of patients seen with JDM from Cape Town, South Africa.
2.3 Methods

2.3.1 Study design, study setting and patients

We carried out a retrospective folder review of JDM patients seen between January 2004 and December 2013 in three tertiary care hospitals [Tygerberg, Groote Schuur and Red Cross War Memorial Children’s Hospital] in Cape Town, South Africa. These three hospitals are the main tertiary referral hospitals for the Western Cape Province and also serve the surrounding regions of the Eastern and Northern Cape provinces of South Africa. Patients from this catchment area diagnosed with JDM were likely to have been referred to one of these centres for evaluation and treatment. The approximate population in the primary catchment area was 4.6 Million in 2004 and 6.1 million in mid-2014 with children (people aged <15 years) constituting 35% and 26.5% of the population respectively [21]. The province populace is composed of people of diverse ancestral backgrounds with the most populous groups being, in descending order, people of mixed, indigenous African and European ancestries [21].

Only patients who were seen between January 2004 and December 2013 and satisfied the Bohan and Peter criteria for classification as probable JDM were included. Data was extracted from the patient records as at the last review prior to 31st December 2014 to allow for a follow up period of one year for each patient. Data was abstracted onto case record forms (CRF) and later transcribed onto an excel spreadsheet. Information collected included: demographics, clinical and laboratory features, radiological investigation results, treatment given and treatment outcomes.

The primary outcome variable was disease activity at last review. Patients were classified as having clinically active disease or inactive disease. A modification of the PRINTO criteria for inactive disease [22] was used. The PRINTO criteria include CK<150 U/L, CMAS>48, MMT>78 and Physician global (VAS) <0.2. Patients
satisfying any three of these criteria are classified as having clinically inactive disease. We used a modification of these criteria due to difficulties with direct comparisons since this was a retrospective study and data on some of the PRINTO criteria items was not available. Therefore for this study we modified the criteria as follows (modification in brackets):

- CK<150 U/L (No modification),

- CMAS>48 (No modification),

- MMT>78 (or documented full muscle strength using any muscle strength assessment scale by the attending physician) and

- Physician global (VAS) <0.2 (or documentation of absence of symptoms and signs of active disease by the clinician).

Patients were classified as having inactive disease if they satisfied any three of these criteria.

Secondary outcome measure was damage defined as persistent changes in anatomy, physiology or function present for at least 6 months at the last review (IMACS definitions of damage and specific damage items) [23,24]. Damage was assessed as being present or absent by systems and patients classified as either exhibiting damage (any) or none at last follow up.

2.3.2 Data analysis

Data was analysed using R i386 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) software. Median and interquartile ranges were used for descriptive statistics for quantitative variables (non-normally distributed data). Frequencies were computed for qualitative variables. Non-parametric tests (Wilcoxon rank sum tests)
were used for comparison of medians across groups. For comparison between categorical variables, cross-tabulation was used with formulation of Fisher’s exact (chi square) statistic. The two sided p-values <0.05 were considered to be statistically significant.

The study was approved by the human research ethics committees of Cape Town (HREC/REF: 062/2014) and Stellenbosch universities (S14/04/080).
2.4 Results

2.4.1 Patient characteristics

Twenty seven cases with a diagnosis of JDM seen between 2004 and 2013 were identified. Two had amyopathic JDM and were excluded as they did not meet the inclusion criteria of probable JDM. Of the other twenty five, twelve satisfied the criteria for definite JDM. Six of the probable JDM cases were reclassified as definite JDM when muscle MRI findings were considered. Thus in total, eighteen (72%) were classified as definite and seven (28%) probable JDM. Sixteen of the patients were female (F:M 1.8:1). Thirteen (52%) of the cases were of indigenous African, eleven (44%) mixed and one (4%) European ancestry. The median age at disease onset was 6.75 (range 2.0-9.7) years and at diagnosis 7.9 (range 3.4-9.75) years. The median duration from symptom onset to diagnosis was 4 (range 0.5-84) months. One patient was retrospectively diagnosed with JDM after a period of 84 months having previously been labelled as discoid lupus. The median duration of follow up was 50 (range 0.5-159) months. Some of the findings are presented graphically in figure 1.

Figure 1: Box and whisker plot illustrating delay in diagnosis (months). The median period from disease onset to diagnosis (delay) was 4 (range 0.5-84) months with maximum of 84 months for a patient initially diagnosed as discoid lupus before the final diagnosis of JDM was made seven years later.
2.4.2 Diagnostic features and characteristics

Muscle weakness and characteristic cutaneous manifestations were documented in all the 25 patients with heliotrope rash occurring in 20 and Gottron’s papules in 19 patients. Muscle enzymes were elevated in all but one patient. This patient however, had suggestive muscle biopsy changes and satisfied the criteria for classification as probable JDM. Creatine phosphokinase (CK) was elevated in 22 of 24 cases. The two patients with normal CK had elevated AST and ALT and in addition one had elevated aldolase and the other had elevated lactose dehydrogenase (LDH). Aldolase was only determined in five patients and was elevated in three of them. Figure 2 summarizes results of the diagnostic procedures and criteria.

**Figure 2: Bar graph illustrating results of diagnostic investigations**

**Present:** features supportive of myositis; **Absent:** not supportive of myositis; **Not available:** Not done or results not accessible. Muscle enzymes were elevated in 24 of the 25 patients. Biopsy was done in 12 and showed features consistent with JDM in 11. Other investigations done were EMG in 5 and MRI in 9 patients.

Muscle biopsy was performed in twelve (48%) of the patients and showed characteristic features including perifascicular atrophy, fibre degeneration and regeneration and perivascular inflammation consistent with JDM in 11 (91.7%) of the cases. Figure 3 demonstrates some of the characteristic muscle biopsy changes of perifascicular atrophy (3a and b) and perivascular inflammation (3c and d) seen in one of our patients. Five of the patients had documented EMG results showing features consistent with myositis.
**Figure 3a-d clockwise from top.** Haematoxyllin and Eosin sections showing (a & b) perifascicular fibre atrophy (b high power); and c & d perivascular inflammation (c high power). Note the atrophic myofibres at the periphery of the fascicles (a & b) and the abundant perivascular mononuclear inflammatory cell infiltrates (c & d). These features are typical of dermatomyositis with accompanying vasculitis.

Muscle MRI for initial diagnostic work-up was done in nine patients and demonstrated active inflammation in eight of the patients. **Figure 4** shows the characteristic diffuse edema on MRI of the thigh muscles of one of the patients. All the patients in whom MRI was done were diagnosed in the latter half of the period under review (2009-2013).

**Figure 4:** Saggital (STIR) and Coronal MRI images showing diffuse edema in the thigh muscles characteristic of JDM.

### 2.4.3 Clinical characteristics

There was no documented family history of neuromuscular or autoimmune diseases among the cases. However, history of preceding infection was reported in 6 cases: upper respiratory tract infection (URTI) in 4 cases and dental or skin abscesses in 2 cases with a median time to onset of JDM symptoms of 1 month. One patient had a traumatic event (sexual abuse) one month prior to onset of JDM symptoms.

Pulmonary involvement was reported in four patients and two of them died; one with suspected severe interstitial lung disease and the other with pulmonary hemorrhage
and sepsis. The third patient had clinical as well as HRCT features of interstitial lung
disease (ILD) and restrictive pattern on pulmonary function tests (PFTs). One other
patient had deranged spirometry results, which normalized with treatment. In total,
PFT results were available for six patients (done after mean of 4.4 years from
diagnosis) and only two of the patients had deranged lung function parameters
(restrictive pattern).

Cardiovascular involvement was observed in one patient who presented with
generalized oedema and heart failure. Echocardiography showed mildly dilated
chambers with reduced ejection fractions of <55%. Echocardiography however, was
not routinely done to document baseline state or monitor cardiac function of JDM
patients in the three centres. Neurological manifestations were seen in two cases; one
had convulsions thought to be due to cerebral vasculitis and the other had localized
sensory neuropathy.

Cutaneous and musculoskeletal manifestations were the most common and are
summarized together with other clinical features in Table 1. Of note, three patients
had calcinosis at diagnosis, 8 others developed calcinosis and three had resolution of
calcinosis during follow up. Figure 5 shows a radiograph of one of the patients
showing tumoural and planar calcinosis in the forearm. There was no statistically
significant difference in the age at onset, age at diagnosis and duration of follow up
among patients who developed calcinosis and those who did not have calcinosis. The
median time to diagnosis from symptom onset was longer in children who had
calcinosis (6 months) than in those who did not have calcinosis (3 months). The
difference was however not statistically significant (p = 0.13). In addition, even
though there was a tendency towards a higher prevalence of calcinosis among
indigenous African children (8/13) compared to children of other racial backgrounds (3/12), the difference was not statistically significant (p=0.11).

Figure 5: Forearm radiograph showing mixed tumoural and planar calcinosis in one of the JDM patients.

2.4.4 Laboratory investigations

Autoantibodies [Myositis associated (MAA) and myositis specific antibodies (MSA)] were only tested in a few patients. Among the MSAs, only anti-Jo1 was tested and was negative in all the six patients tested. ANA results were available in 19 patients and was low positive in seven (three had Hep-2 titres of 40, 40 and 100; and four had composite ANA ratio of 8, 2.2 4.6 and 32 U/L). The results of the laboratory investigations are summarized in table 2.

2.4.5 Treatment

Information on treatment was available for 23 of the 25 patients. We could not locate treatment records in two cases. The most common drugs used were oral prednisone (100%), methotrexate (74%), intravenous methylprednisolone (39%) and intravenous immunoglobulin (IVIG). Prednisone alone was used in five patients, prednisone and methotrexate without another agent in nine patients and various other drugs were added as second line drugs to the main treatment modality (prednisone and methotrexate) in poor responders as summarized in figure 6 below.

Figure 6: Treatment modalities in Cape Town JDM patients. All the patients received corticosteroids during the course of their treatment. Biologics were used in
6 patients (rituximab in 5 and infliximab in 1). **Abbreviations:** - Cyclophos: cyclophosphamide; Medrol: intravenous methylprednisolone; Pred: Prednisone

**PredMTX:** Prednisone and methotrexate; IVIG: Intravenous immunoglobulin.

### 2.4.6 Treatment outcome: diseases activity, mortality and damage

Of the 25 patients, 10 were still in care, 8 were discharged, 2 transferred to other centres, 3 were lost to follow up and 2 patients died. Ten (40%) of the patients had clinically inactive disease. Patients who had clinically inactive disease had significantly lower CK levels (mean 105.5 U/L) than those with clinically active disease at their last review (mean CK 203.5 U/L) \( p=0.02 \). There was no statistically significant difference in the median duration of follow up \( p = 0.28 \), age of onset, race, diagnostic delay, disease category (probable or definite) and disease type (chronic/polycyclic or monocyclic) between those who had clinically inactive and active disease.

The mortality rate was 2/25 (8%) over a median follow-up period of 50 months. Death resulted from respiratory failure in the setting of global weakness (and possible interstitial lung disease) in one patient and from sepsis, GI bleed and pulmonary hemorrhage (at autopsy) in the other.

Overall, 18 (72%) of the patients had some documented damage though a full damage assessment was hampered by missing data occasioned by the retrospective nature of the study. The most common systems in which disease damage was reported were: endocrine (9 cases), skin (8 cases), musculoskeletal (7 cases) and respiratory (3 cases) systems. Endocrine damage was mainly as a result of growth failure (figure 7) though one patient developed diabetes mellitus and another,
adrenal insufficiency. Growth failure occurred in a high proportion of patients (36%). Growth failure was defined by the IMACS criteria as presence of two of the following three features:

a. Less than 3 percentile height for age.
b. Growth velocity over 6 months less than 3 percentile for age.
c. Crossing at least 2 centiles (5%, 10%, 25%, 50%, 75%, 95%) on growth chart.

Musculoskeletal damage included one patient who had osteoporosis with vertebral fracture that was demonstrated using bone scans (scintigraphy). One patient, who had suffered from suppurative otitis media during follow up, developed sensorineural hearing loss. Three patients had calcinosis at diagnosis, 8 developed calcinosis and three had resolution of the calcinosis during follow up.

**Figure 7**: growth chart for one of the patients with growth failure. Note stature for age line crosses from above 50\(^{th}\) centile to below 3\(^{rd}\) centile and remains below 3\(^{rd}\) centile line for >3 years.
2.5 Discussion

A better understanding of the epidemiology and clinical outcomes of JDM has been enhanced by the establishment of multicenter and multinational collaborations such as the paediatric rheumatology international trials organization (PRINTO) and international myositis assessment and clinical studies group (IMACS). However, data from Africa has been scarce and the epidemiology of JDM from the continent has been based on extrapolation of data collected from other populations and regions. The mean age at disease onset in most of these registries has been reported to be about seven years with a female predominance of about 2:1 [10,11,20]. The median age of onset (6.75 years) and gender composition (female: male 1.9:1) among the JDM patients in our series was similar to that of most studies from other regions.

In the current study, we also found a relatively high rate of calcinosis (44% of the cases). Even though children of indigenous African ancestry appeared to have a higher prevalence of calcinosis (61.5%) compared to patients of other ancestral background (25%), the difference was not statistically significant (p=0.11). Higher rates of dystrophic calcinosis have been reported among indigenous African compared to JDM patients of other ancestral backgrounds [16]. It is not clear why indigenous African patients appear to have higher risk of calcinosis. Certain immune phenotypes have been associated with higher risk of occurrence of calcinosis. It is not known if black African children have higher prevalence of these immune phenotypes thus putting them at greater risk for calcinosis. The immune phenotype was not determined for our patients and published studies are not available on the comparative prevalence of autoantibody and other associated risk factor profiles among indigenous African compared to children of other ancestral backgrounds.
Increased risk of calcinosis and other disease damage could also be related to poor access to care with subsequent inappropriate and delay in instituting treatment. Delay in diagnosis may be the consequence of lack of access to clinicians skilled in diagnosing and managing dermatomyositis and similar conditions; and lack of access to diagnostic facilities such as EMG and muscle biopsy. However, there was no significant difference in the delay in making a diagnosis between the patients of indigenous African and patients of other ancestral origins (p = 0.27).

As the search for better and more acceptable diagnostic procedures and tools continues, MRI is gradually being used in the three centres instead of or in addition to EMG and muscle biopsy for diagnosis of JDM. Eleven muscle MRIs were done as part of the diagnostic evaluation of children; all in the latter half of the period under review. Thus MRI seems to have gained prominence as a diagnostic tool for JDM consistent with findings from other studies [19,25,26]. However, in Africa and many other resource constrained economies, MRI may not be available in many centres and even where it is available, long waiting times, technical issues with reporting and cost implications may prove prohibitive. Thus additional diagnostic modalities such as muscle ultrasound and Bone scintigraphy that may provide cheaper and more convenient alternatives for demonstrating evidence of muscle inflammation may be welcome [27-29].

The mortality rate (8%, 1 death per 52 patient years) in our series appears higher than the 2-4% reported in most recent studies from other regions [11,18-20]. This finding was consistent with that by Faller et al [9] who reported a mortality of 9.5% (1 death per 27.3 patient years) among indigenous African children with JDM from Johannesburg, South Africa. These two studies were small and it’s not possible to draw generalizable conclusions. They however provide some insight into possible
treatment outcomes of JDM in Africa. Two deaths were reported in our study as well as in the study by Faller et al and all the four deaths resulted from respiratory (involvement) disease which has been identified as an early disease feature predictive of mortality [18].

Juvenile dermatomyositis is a chronic disease and many patients may never achieve a clinically inactive disease state. After a median follow up time of 50 months, only ten (40 %) of the 25 patients had clinically inactive disease (PRINTO criteria) at their last follow up. Sanner et al studied the long-term outcome of JDM and after 16.8 years, 59% of the patients still had clinically active disease [30]. Other authors have similarly reported a relatively high level of disease activity, with only 33% among a cohort of 39 JDM patients being disease free at last review over a ten year period [31]. It is thus clear that most children with JDM have long-term inflammation and disease activity that linger long after initiation of treatment.

Formulation of appropriate guidelines and standard of care protocols to guide short-term and long-term management of JDM could enable appropriate timely interventions for better treatment outcomes.
2.6 Conclusion

The demographic characteristics of JDM patients from Cape Town (median disease onset age of 6.75 years and Female to male ration of 1.9:1) was similar to that reported from most regions of the world. It is probable that there was unnecessary delay in the diagnosis of cases. One patient was diagnosed retrospectively seven years after disease onset. There was however a relatively high rate of calcinosis (44%) and mortality (8%).

Further, there was persistent clinically active disease in a large proportion of this cohort (60%), putting them at risk of further disease complications. This could be a reflection of inadequate or less aggressive treatment. The study adds to the available literature on JDM in Africa and demonstrates a need for a defined standard of care package to ensure adequate access to skilled multidisciplinary teams, essential diagnostic facilities and therapeutic resources for better treatment outcomes.

The study limitations included missing values and the relatively small number of cases identified. Establishment of a prospective cohort in future could be useful in providing better quality data for better outcome assessments in line with currently accepted international guidelines.
2.7 List of abbreviations

AST  Aspartate transaminase
CMAS  Childhood Myositis Assessment Scale
CRP  C-Reactive Protein
CT Scan  Computerised Tomography Scan
CK  Creatine Kinase
EMG  Electromyography
ESR  Erythrocyte Sedimentation Rate
IMACS  International Myositis And Clinical Studies
IVIG  Intra-Venous Immune Globulin
JDM  Juvenile Dermatomyositis
LDH  Lactate Dehydrogenase
MAA  Myositis Associated Antibodies
MDI  Myositis Damage Index
MMT  Manual Muscle Testing
MRI  Magnetic Resonance Imaging
MSA  Myositis Specific Antibodies
PRINTO  Paediatric Rheumatology International Trials Organization
vWF  Von Willebrand Factor
2.8 Competing interests

We declare that there are no financial competing interests. This study was undertaken as a thesis component of an MPhil (Paediatric Rheumatology) degree for Lawrence Owino Okong’o.
2.9 Authors' contributions

LO drafted the protocol, analysed the data and drafted the manuscript. ME provided the data on the cases from one of the three centres and reviewed the protocol and manuscript. JW participated in the design of the study, provided data on the cases from one of the three study centres and reviewed the protocol and manuscript. CS conceived of the study, and participated in its design and coordination, helped to draft the manuscript and provided general supervision.

All authors read and approved the final manuscript.
2.10 Acknowledgements

Special thanks to Dr. Alvin Ndondo and other members of paediatric rheumatology team at the Red Cross War Memorial Children’s Hospital who managed most of the cases and documented the findings that formed our most important source documents for the study.

Members of the Radiology departments in the three hospitals for availing the radiology images and reports for the study.

Anita Brinks, the head of nuclear medicine at the Red Cross War Memorial Children’s Hospital for helping with case identification and availing the bone scan images and reports for the study.

Other members of the paediatric rheumatology teams including Dr. Nicky Brice and Dr. Kate Webb who were involved in managing the patients and documented the findings that have formed part of the study source documents.

The African Paediatrics Fellowship Program (APFP) for sponsoring and facilitating Dr. Lawrence Okong’o fellowship. The study was done as part fulfilment for the MPhil degree at the end of the fellowship.
2.11 References


[12] Chickermane PR, Mankad D, Khubchandani RP. Disease patterns of juvenile dermatomyositis from Western India. Indian Pediatr 2013 Oct 8;50(10):961-963.


2.12 Tables and figures

Table 1: Disease manifestations and organ damage among the JDM cases

<table>
<thead>
<tr>
<th></th>
<th>Cumulative clinical manifestations (%)</th>
<th>Clinical manifestations at last review</th>
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<tr>
<td><strong>Skin</strong></td>
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</tr>
<tr>
<td>Calcinosis, scarring, atrophy</td>
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<td>8 (32)</td>
</tr>
<tr>
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<td>9 (36)</td>
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<td><strong>Nervous system</strong></td>
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Table 2: Laboratory investigation results

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<td>Anti-RNP</td>
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<td>vWF activity</td>
<td>77 (62-112%)</td>
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Table 3: Determinants of disease activity

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<td>6/9</td>
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<td>CK (Median)</td>
<td>105.5</td>
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†Fisher exact ‡ Wilcoxon rank sum test
Figure 1: Box and whisker plot illustrating age of patients (years) and delay in diagnosis (months). The median age at onset was 6.75 years and at diagnosis 7.9 years. The median period from disease onset to diagnosis (delay) was 4 months with maximum of 84 months (the extreme outlier) for a patient initially diagnosed as discoid lupus before the final diagnosis was made.
Figure 2: Bar graph illustrating results of diagnostic investigations

**Present:** features supportive of myositis; **Absent:** not supportive of myositis; **Not available:** Not done or results not accessible. Muscle enzymes were elevated in 24 of the 25 patients. Biopsy was done in 12 and showed features consistent with JDM in 11. Other investigations done were EMG in 5 and MRI in 9 patients.
Figure 3a-3d clockwise from the top. Haematoxyllin and Eosin sections showing (a & b) perifascicular fibre atrophy (b high power); and c & d perivascular inflammation (c high power). Note the atrophic myofibres at the periphery of the fascicles (a & b) and the abundant perivascular mononuclear inflammatory cell infiltrates (c & d). These features are typical of dermatomyositis with the accompanying vasculitis.
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**Abbreviations.** Cyclophos: cyclophosphamide; Medrol: intravenous methylprednisolone; Pred: Prednisone PredMTX: Prednisone and methotrexate; IVIG: Intravenous immunoglobulin.
**Figure 7:** growth chart for one of the patients with growth failure. Note stature for age line crosses from above 50th centile to below 3rd centile and remains below 3rd centile line for >3 years.

*Graph produced by replotting the child growth indices on the WHO AnthroPlus v1.0.4 software ([http://www.who.int/growthref/tools/en/](http://www.who.int/growthref/tools/en/)).*
2.13 Appendices

2.13.1 Appendix 1: Case record form

Section A: Demographic data and disease classification

<table>
<thead>
<tr>
<th>Sex</th>
<th>1. Male</th>
<th>2. Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>1. Indigenous African</td>
<td>2. European Caucasian</td>
</tr>
<tr>
<td>3. Cape coloured</td>
<td>4. Other</td>
<td></td>
</tr>
<tr>
<td>Residential address</td>
<td>Province/Municipality:………………………………..</td>
<td></td>
</tr>
<tr>
<td>Date of onset</td>
<td>Date of first visit</td>
<td>Date of diagnosis</td>
</tr>
</tbody>
</table>

Outcome: 1. Ongoing care | 2. Discharged | 3. Lost to follow up | 4. Death | Last Date of Visit |

Family history of autoimmune disease (1= Yes; 2= No; 3= Unknown) | If Yes, Specify disease and relationship |

**Diagnostic criteria**

0 = Not present  1 = Present  NA = Cannot be assessed

1. Heliotrope rash OR Gottron's papules/sign
2. Proximal Muscle Weakness
3. Muscle Biopsy Changes
4. Electromyographic changes
5. Muscle MRI changes
6. Elevated Muscle Enzymes


**Comorbid conditions (specify)**

Section B: Clinical manifestations

A modified Myositis Disease Activity Assessment Tool (MDAAT) shall be used to document the clinical features that were present at diagnosis (or first visit) and cumulatively up to the last documented visit.

<table>
<thead>
<tr>
<th>Constitutional Activity</th>
<th>NA = Cannot be assessed 0 = Not present 1 = Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At diagnosis Cumulatively</td>
</tr>
<tr>
<td>Pyrexia (fever &gt; 38°C Celsius)</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Fatigue, malaise, lethargy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cutaneous Activity</th>
<th>NA = Can’t be assessed 0 = Not present 1 = Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At diagnosis Cumulatively</td>
</tr>
<tr>
<td>Cutaneous ulceration</td>
<td></td>
</tr>
<tr>
<td>Manifestation</td>
<td>Time from remission</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 25. Relapses

<table>
<thead>
<tr>
<th>Core set</th>
<th>Diagnosis</th>
<th>Review 1</th>
<th>Review 2</th>
<th>Other reviews</th>
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</thead>
<tbody>
<tr>
<td>CMAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMT8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS Physician</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS Patient global</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Section C: Drugs and other therapeutic modalities

<table>
<thead>
<tr>
<th>Drug/Modality</th>
<th>At diagnosis</th>
<th>during disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose and Duration</td>
<td>Dose and Duration</td>
</tr>
<tr>
<td>1. Prednisone (Medrol I.V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Prednisone (Oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Methotrexate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Chloroquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Mycophenolate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Ciclosporin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Azathioprim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Cyclophosphamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Infliximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Immunoglobulin (IVIG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Physiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Other</td>
<td></td>
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</table>

### Section D: Diagnostic work up

#### Laboratory work up

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range</th>
<th>Value at assessment</th>
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<tr>
<td></td>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>ESR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dsDNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Ro/SSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-La/SSB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-RNP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Scl 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PMScl</td>
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<td></td>
</tr>
<tr>
<td>Anti-Jo1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pANCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cANCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldolase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results of Radiological and other Diagnostic investigations

<table>
<thead>
<tr>
<th>Modality</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
</tr>
<tr>
<td>1. Muscle MRI</td>
<td></td>
</tr>
<tr>
<td>2. Chest CT</td>
<td></td>
</tr>
<tr>
<td>3. Barium swallow</td>
<td></td>
</tr>
<tr>
<td>4. Muscle biopsy</td>
<td></td>
</tr>
<tr>
<td>5. EMG</td>
<td></td>
</tr>
<tr>
<td>6. Spectroscopy</td>
<td></td>
</tr>
<tr>
<td>7. Nailfold Capillaroscopy</td>
<td></td>
</tr>
<tr>
<td>8. ECG</td>
<td></td>
</tr>
<tr>
<td>9. Echocardiogram</td>
<td></td>
</tr>
<tr>
<td>10. FEV1</td>
<td></td>
</tr>
<tr>
<td>12. FVC</td>
<td></td>
</tr>
<tr>
<td>13. DLCO</td>
<td></td>
</tr>
<tr>
<td>14. Ophthalmology</td>
<td></td>
</tr>
</tbody>
</table>

Section E: Damage Assessment

A modified Myositis Damage Index (MDI) tool shall be used to document organ damage cumulatively over the entire period of care till the last documented visit. The items are scored as present (1), absent (0) or Cannot be assessed (NA).

<table>
<thead>
<tr>
<th>MUSCLE DAMAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA = Cannot be assessed</td>
</tr>
<tr>
<td>0 = Not present</td>
</tr>
<tr>
<td>1 = Present</td>
</tr>
</tbody>
</table>

1. Muscle atrophy (clinical) 0 1 NA
2. Muscle weakness not attributable to active muscle disease 0 1 NA
3. Muscle dysfunction: decrease in aerobic exercise capacity 0 1 NA
4. Muscle atrophy assessed by radiographic methods 0 1 NA
5. Low serum creatinine (Value ..................) 0 1 NA

<table>
<thead>
<tr>
<th>SKELETAL DAMAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA = Cannot be assessed</td>
</tr>
<tr>
<td>0 = Not present</td>
</tr>
<tr>
<td>1 = Present</td>
</tr>
</tbody>
</table>

6. Joint contractures 0 1 NA
7. Osteoporosis with fracture / vertebral collapse 0 1 NA
8. Avascular necrosis 0 1 NA
9. Deforming arthropathy (excluding contractures) 0 1 NA
10. Osteoporosis without clinical fracture, 0 1 NA
11. Limitation of motion (Passive Joint ROM in degrees):
   a. Elbow extension (degrees): R______L______ 0 1 NA
   b. Hip flexion (degrees): R______L______ 0 1 NA
   c. Knee extension (degrees): R______L______ 0 1 NA
d. Ankle dorsiflexion (degrees)  R______L_______ 0  1  NA

**CUTANEOUS DAMAGE**  NA = Cannot be assessed  0 = Not present  1 = Present

12. Calciosis:  0  1  NA
   a. Calciosis, superficial plaques or nodules  0  1  NA
   b. Calciosis, tumoral  0  1  NA
   c. Calciosis, planar  0  1  NA
   d. Calciosis, exoskeleton/calciñosis universalis  0  1  NA

13. Alopecia  0  1  NA
14. Cutaneous scarring or atrophy  0  1  NA
15. Poikiloderma  0  1  NA
16. Lipodystrophy  0  1  NA

**GASTROINTESTINAL (GI) DAMAGE**

17. Dysphagia  0  1  NA
18. GI dysmotility, constipation, diarrhea or abdominal pain  0  1  NA
19. Infarction or resection of bowel or other GI  0  1  NA
20. Steatosis  0  1  NA

**PULMONARY DAMAGE**  NA = Cannot be assessed  0 = Not present  1= Present

21. Dysphonia  0  1  NA
22. Impaired lung function due to respiratory muscle damage  0  1  NA
23. Pulmonary fibrosis  0  1  NA
24. Pulmonary hypertension  0  1  NA
25. Diminished lung function:
   a. DL-CO/Va (Carbon monoxide diffusing capacity corrected for alveolar volume)
      (% Predicted =_________%)  0  1  NA
   b. FEV1 (% predicted =_________%)  0  1  NA

**CARDIOVASCULAR DAMAGE**  NA=Can’t be assessed 0=Not present 1=Present

26. Hypertension requiring treatment > 6 months  0  1  NA
27. Ventricular dysfunction / cardiomyopathy  0  1  NA

**PERIPHERAL VASCULAR DAMAGE**

30. Tissue or pulp loss  0  1  NA
31. Digit or limb loss or resection  0  1  NA
32. Venous or arterial thrombosis with swelling, ulceration or venous stasis
<table>
<thead>
<tr>
<th><strong>ENDOCRINE DAMAGE</strong></th>
<th>NA = Cannot be assessed</th>
<th>0 = Not present</th>
<th>1 = Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>34. Growth failure</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>35. Delay in development of secondary sexual characteristics</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>36. Hirsutism or Hypertrichosis</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>37. Irregular menses</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>38. Primary or Secondary Amenorrhea</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>39. Diabetes</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>40. Hyperlipidemia (regardless of treatment)</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>41. Infertility (female or male)</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>42. Sexual dysfunction</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>OCULAR DAMAGE</strong></th>
<th>NA = Cannot be assessed</th>
<th>0 = Not present</th>
<th>1 = Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>43. Cataract resulting in visual loss</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>44. Visual loss, other, not secondary to cataracts</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>INFECTION</strong></th>
<th>NA = Cannot be assessed</th>
<th>0 = Not present</th>
<th>1 = Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>45. Chronic infections:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46. Multiple infections Specify:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MALIGNANCY</strong></th>
<th>NA = Cannot be assessed</th>
<th>0 = Not present</th>
<th>1 = Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Any form of cancer, Specify type, grade and stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>OTHER DAMAGE, specify</strong></th>
<th>NA = Cannot be assessed</th>
<th>0 = Not present</th>
<th>1 = Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>48. Death: Cause and date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49. Other (specify):</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
2.13.2 Appendix 2: Confidential log of JDM study patients.

<table>
<thead>
<tr>
<th>Participant ID</th>
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</tr>
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<tbody>
<tr>
<td>JDM1</td>
<td></td>
</tr>
<tr>
<td>JDM2</td>
<td></td>
</tr>
<tr>
<td>JDM3</td>
<td></td>
</tr>
<tr>
<td>JDM4</td>
<td></td>
</tr>
<tr>
<td>JDM5</td>
<td></td>
</tr>
<tr>
<td>JDM6</td>
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<tr>
<td>JDM7</td>
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<td>JDM9</td>
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<td>JDM10</td>
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<td>JDM27</td>
<td></td>
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<tr>
<td>JDM28</td>
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</tbody>
</table>
2.13.3 Appendix 3: Budget

The principal investigator shall do the data collection and analysis.

The budget is self-funded.

<table>
<thead>
<tr>
<th>ITEM</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone, cell phone &amp; fax</td>
<td>R – 100</td>
</tr>
<tr>
<td>Internet &amp; email</td>
<td>R – 0</td>
</tr>
<tr>
<td>Office supplies</td>
<td>R – 100</td>
</tr>
<tr>
<td>Courier &amp; postage</td>
<td>R – 200</td>
</tr>
<tr>
<td>Printing &amp; copying</td>
<td>R – 200</td>
</tr>
<tr>
<td>Ethics committee fee</td>
<td>R – 0</td>
</tr>
<tr>
<td>Transport</td>
<td>R – 300</td>
</tr>
<tr>
<td><strong>Total direct costs</strong></td>
<td>R – 900</td>
</tr>
<tr>
<td><strong>Indirect costs (12%)</strong></td>
<td>R – 108</td>
</tr>
<tr>
<td><strong>GRAND TOTAL</strong></td>
<td>R – 1008</td>
</tr>
</tbody>
</table>
### 2.13.4 Appendix 4: Timelines

<table>
<thead>
<tr>
<th>Activity</th>
<th>Proposed Start Date</th>
<th>Proposed end date</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Proposal submission for review and ethical approval</td>
<td>December 2013</td>
<td>April 2014</td>
</tr>
<tr>
<td>3. Data collection</td>
<td>April 2014</td>
<td>May 2014</td>
</tr>
<tr>
<td>4. Dissertation write up</td>
<td>October 2014</td>
<td>February 2015</td>
</tr>
<tr>
<td>6. Submission of articles for publication</td>
<td>April 2014</td>
<td>August 2014</td>
</tr>
</tbody>
</table>
2.13.5 Appendix 5: Ethics committee approval University of Cape Town

14 March 2014

HREC/REF: 062/2014

Dr C Scott
Paediatric Rheumatology
Room 5.16-ICH Building
Red Cross War Memorial Children’s Hospital
Rondebosch

Dear Dr Scott

Project Title: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CHILDREN WITH JUVENILE DERMATOMYOSITIS IN CAPE TOWN-Mphil Dr L Okongo

Thank you for your letter dated 03rd March 2014, addressing the issues raised by the Human Research Ethics Committee.

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 28 March 2015.

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.

We acknowledge that the following student: Dr L O Okongo is also involved in this study.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:062/2014
2.13.6 Appendix 6: Ethics committee approval University of Stellenbosch

Ethics Letter

24 Jun 2014

Ethics Reference #: S10/04/080
Clinical Trial Reference #: 
Title: Demographic and clinical characteristics of children with juvenile dermatomyositis in Cape Town.

Dear Dr Lawrence Owino Okongo,

We acknowledge receipt of documents pertaining to the above study and the approval letter from the UCT Human Research Ethics Committee, for this project.

The approval of the UCT HREC is recognised by the Stellenbosch University Health Research Ethics Committee for this particular project. However please continue to keep us informed of the progress of the project, by submitting annual progress reports.

Please note that research that will be conducted at any tertiary academic institution also requires approval from the relevant hospital manager.

If you have any queries or need further assistance, please contact the HREC Office 0219889156.

Sincerely,

REC Coordinator
Franklin Weber
Health Research Ethics Committee 1
Appendix 7: Paediatric rheumatology

Instructions for authors

Presubmission enquiries: If you wish to make a presubmission enquiry about the suitability of your manuscript, please email the editors who will respond to your enquiry as soon as possible.

Submission process: Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Please note that Pediatric Rheumatology levies an article-processing charge on all accepted Research Articles; if the submitting author's institution is a BioMed Central member the cost of the article-processing charge may be covered by the membership (see About page for detail). Please note that the membership is only automatically recognised on submission if the submitting author is based at the member institution.

To facilitate rapid publication and to minimize administrative costs, Pediatric Rheumatology prefers online submission. Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

See below for examples of word processor and graphics file formats that can be accepted for the main manuscript document by the online submission system.

Additional files of any type, such as movies, animations, or original data files, can also be submitted as part of the manuscript.
During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the 'About Pediatric Rheumatology' page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the Editor-in-Chief and/or Editorial Board members.

Assistance with the process of manuscript preparation and submission is available from BioMed Central customer support team. We also provide a collection of links to useful tools and resources for scientific authors on our Useful Tools page.

**File formats**

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- Portable document format (PDF)
- TeX/LaTeX (use BioMed Central's TeX template)
- DeVice Independent format (DVI)
TeX/LaTeX users: Please use BioMed Central's TeX template and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF. For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

**Preparing main manuscript text**

General guidelines of the journal's style and language are given below.

**Overview of manuscript sections for Research Articles**

Manuscripts for Research Articles submitted to Pediatric Rheumatology should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Methods
The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, SwissProt:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).

You can download a template (Mac and Windows compatible; Microsoft Word 98/2000) for your article.
For reporting standards please see the information in the About section.

Title page

The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: Background, the context and purpose of the study; Methods, how the study was performed and statistical tests used; Results, the main findings; Conclusions, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. Trial registration, if your research reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. Trial registration: Current Controlled Trials ISRCTN73824458). Please note that there should be no
space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the **CONSORT extension for abstracts**.

**Keywords**

Three to ten keywords representing the main content of the article.

**Background**

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

**Methods**

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'.

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For further details of the journal's data-release policy, see the policy section in 'About this journal'.

Results and discussion

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Competing interests
A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

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Financial competing interests

- In the past three years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.

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• Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

Authors' contributions

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

According to ICMJE guidelines, An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Acknowledgements

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The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

**Endnotes**

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

**References**

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive
referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author.

Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first six before adding 'et al.'.

Any in press articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office. An Endnote style file is available.

Examples of the Pediatric Rheumatology reference style are shown below. Please ensure that the reference style is followed precisely; if the references are not in the correct style they may have to be retyped and carefully proofread.

All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, in the following format: The Mouse Tumor Biology Database [http://tumor.informatics.jax.org/mtbwi/index.do]. If an author or group of authors
can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

**Examples of the Pediatric Rheumatology reference style**

*Article within a journal*


*Article within a journal (no page numbers)*


*Article within a journal by DOI*


*Article within a journal supplement*


*Book chapter, or an article within a book*


*OnlineFirst chapter in a series (without a volume designation but with a DOI)*

Complete book, authored


Online document


Online database


Supplementary material/private homepage


University site


FTP site


Organization site

Preparing illustrations and figures

Illustrations should be provided as separate files, not embedded in the text file. Each figure should include a single illustration and should fit on a single page in portrait format. If a figure consists of separate parts, it is important that a single composite illustration file be submitted which contains all parts of the figure. There is no charge for the use of color figures.

Please read our figure preparation guidelines for detailed instructions on maximising the quality of your figures.

Formats

The following file formats can be accepted:

- PDF (preferred format for diagrams)
- DOCX/DOC (single page only)
- PPTX/PPT (single slide only)
- EPS
- PNG (preferred format for photos or images)
- TIFF
- JPEG
- BMP

Figure legends

The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure, the following information should be provided: Figure number (in sequence, using Arabic numerals
- i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words); detailed legend, up to 300 words.

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If you wish to do so, you may submit an image which, in the event of publication, will be used to create a cover page for the PDF version of your article. The cover page will also display the journal logo, article title and citation details. The image may either be a figure from your manuscript or another relevant image. You must have permission from the copyright to reproduce the image. Images that do not meet our requirements will not be used.

Images must be 300dpi and 155mm square (1831 x 1831 pixels for a raster image).

Allowable formats - EPS, PDF (for line drawings), PNG, TIFF (for photographs and screen dumps), JPEG, BMP, DOC, PPT, CDX, TGF (ISIS/Draw).

Preparing tables

Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be concise. Tables should always be cited in text in consecutive numerical order.
Smaller tables considered to be integral to the manuscript can be pasted into the end of the document text file, in A4 portrait or landscape format. These will be typeset and displayed in the final published form of the article. Such tables should be formatted using the 'Table object' in a word processing program to ensure that columns of data are kept aligned when the file is sent electronically for review; this will not always be the case if columns are generated by simply using tabs to separate text. Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. Commas should not be used to indicate numerical values. Color and shading may not be used; parts of the table can be highlighted using symbols or bold text, the meaning of which should be explained in a table legend. Tables should not be embedded as figures or spreadsheet files.

Larger datasets or tables too wide for a landscape page can be uploaded separately as additional files. Additional files will not be displayed in the final, laid-out PDF of the article, but a link will be provided to the files as supplied by the author.

Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). As with all files, please use the standard file extensions.

**Preparing additional files**

Although *Pediatric Rheumatology* does not restrict the length and quantity of data included in an article, we encourage authors to provide datasets, tables, movies, or other information as additional files.

Please note: All Additional files will be published along with the article. Do not include files such as patient consent forms, certificates of language editing, or
revised versions of the main manuscript document with tracked changes. Such files should be sent by email to PRjournal@nationwidechildrens.org, quoting the Manuscript ID number.

Results that would otherwise be indicated as "data not shown" can and should be included as additional files. Since many weblinks and URLs rapidly become broken, *Pediatric Rheumatology* requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission.

Additional files can be in any format, and will be downloadable from the final published article as supplied by the author. We recommend CSV rather than PDF for tabular data.

Certain supported files formats are recognized and can be displayed to the user in the browser. These include most movie formats (for users with the Quicktime plugin), mini-websites prepared according to our guidelines, chemical structure files (MOL, PDB), geographic data files (KML).

If additional material is provided, please list the following information in a separate section of the manuscript text:

- File name (e.g. Additional file 1)
- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
• Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

Additional file formats

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

• Additional documentation
  o PDF (Adobe Acrobat)

• Animations
  o SWF (Shockwave Flash)

• Movies
  o MP4 (MPEG 4)
  o MOV (Quicktime)

• Tabular data
  o XLS, XLSX (Excel Spreadsheet)
  o CSV (Comma separated values)

As with figure files, files should be given the standard file extensions.

Mini-websites
Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article. In order to do this, please follow these instructions:

1. Create a folder containing a starting file called index.html (or index.htm) in the root.
2. Put all files necessary for viewing the mini-website within the folder, or sub-folders.
3. Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.
4. Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.
5. Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

Style and language

General

Currently, Pediatric Rheumatology can only accept manuscripts written in English. Spelling should be US English or British English, but not a mixture.
There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise.

*Pediatric Rheumatology* will not edit submitted manuscripts for style or language; reviewers may advise rejection of a manuscript if it is compromised by grammatical errors. Authors are advised to write clearly and simply, and to have their article checked by colleagues before submission. In-house copyediting will be minimal. Non-native speakers of English may choose to make use of a copyediting service.

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The abstract is one of the most important parts of a manuscript. For guidance, please visit our page on [Writing titles and abstracts for scientific articles](#).

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For more detailed guidance on preparing a manuscript and writing in English, please visit the [BioMed Central author academy](#).

**Abbreviations**

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

**Typography**

- Please use double line spacing.
- Type the text unjustified, without hyphenating words at line breaks.
• Use hard returns only to end headings and paragraphs, not to rearrange lines.

• Capitalize only the first word, and proper nouns, in the title.

• All pages should be numbered.

• Use the *Pediatric Rheumatology* reference format.

• Footnotes are not allowed, but endnotes are permitted.

• Please do not format the text in multiple columns.

• Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. **Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.**

**Units**

SI units should be used throughout (liter and molar are permitted, however).