Range and consistency of outcome measures reported in randomised trials in dermatomyositis: a systematic review

A.H. Kelly[1-3], D. Singh-Grewal[1,2], D. Sumpton[2,4,5], G. Hasset[6,7], K.E. Manera[2,4], A. Tong[2,4]

[1]Department of Paediatric Rheumatology, The Children's Hospital Network, Sydney, NSW; [2]Sydney School of Public Health, The University of Sydney, NSW; [3]Department of Medicine, Campbelltown Hospital, Sydney, NSW; [4]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW; [5]Rheumatology Department, Concord Repatriation General Hospital, Concord, NSW; [6]Department of Rheumatology, Liverpool Hospital, Liverpool, NSW; [7]South Western Sydney Clinical School, University of New South Wales, Sydney, NSW, Australia.

Abstract

Objective

Dermatomyositis (DM) and juvenile dermatomyositis (JDM) are idiopathic inflammatory myopathies, which can be resistant and unresponsive to initial treatments, leading to severe complications and impaired quality of life. There are few randomised trials in dermatomyositis and the outcomes reported may not be consistent, which can limit decision-making. The aim of this study is to assess the scope and consistency of outcomes reported in randomised trials in dermatomyositis.

Methods

MEDLINE, Embase, PsycINFO and clinicaltrials.gov were searched from 1993-2020 for randomised trials in children and adults with dermatomyositis. The frequency and characteristics of the outcomes reported were analysed and classified.

Results

20 trials were included. Across these trials, a total of 743 outcome measures were reported, which were grouped into 34 outcome domains; of which 17 were clinical, 13 were surrogate/biochemical, and 4 were patient-reported outcomes. The top five most frequently reported outcome domains were muscle inflammation (15 trials, 46 outcome measures), physical function (14 trials, 16 outcome measures), muscle strength (13 trials, 30 outcome measures), global health (12 trials, 33 outcome measures) and immunologic marker (11 trials, 91 outcomes).

Conclusion

The majority of outcomes reported in trials in people with dermatomyositis and JDM are clinical and surrogate outcomes rather than patient-reported outcomes. The outcomes reported are very inconsistent across trials, with wide heterogeneity in the measures used. Standardised reporting of critically important outcomes is needed to strengthen the value of trials for decision-making.

Key words

dermatomyositis, juvenile dermatomyositis, outcome measures, outcome domains

Amy Helen Kelly, MD, FRACP
Davinder Singh-Grewal, MD, PhD, FRACP
Daniel Sumpton, MD, PhD, FRACP
Geraldine Hasset, MD, PhD, FRACP
Karine E. Manera, PhD
Allison Tong, PhD

Please address correspondence to:
Amy H. Kelly,
Department of Medicine,
Campbelltown Hospital,
Therry Road,
Campbelltown,
NSW 2560, Australia.
E-mail: amy.kelly@health.nsw.gov.au

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Introduction

Dermatomyositis (DM) and juvenile dermatomyositis (JDM) are rare connective tissue diseases that make up the majority of the idiopathic inflammatory myopathies (1). They can present with a range of symptoms including skin rash, poikiloderma, muscle weakness and elevated muscle enzymes (1). Both DM and JDM may also cause significant end-organ damage, which can be life-threatening. DM has also been associated with depression, anxiety and fatigue, with patients reporting worse quality of life compared to healthy individuals (2). Despite a lack of evidence for their use and significant side effects, glucocorticosteroids remain the mainstay of first line treatments (3). Given the proportion of patients whose disease remains refractory to steroid treatment, new, targeted treatments are being proposed to treat these diseases (3).

There are few randomised control trials for interventions for DM and JDM. Of the trials that exist, outcome measures reported often have limited relevance to patients and their caregivers, with few patient-reported outcome measures (PROMs) used (4). With the development of new treatments there is a critical need for consistent reporting of relevant outcome measures to ensure comparability across studies and improve the interpretation of the evidence base for interventions (5). Efforts have been made by the International Myositis Assessment and Clinical Studies Group (IMACS) and Paediatric Rheumatology International Trials Organisation (PRINTO) in 2011 to standardise reporting of outcome measures in DM and JDM (6-9). However, there has not been detailed assessment of the outcomes and measures reported in trials in dermatomyositis and JDM. OMERACT clearly stipulates the development of outcome measure sets should start with a review of existing measures used in the literature (10).

The aim of this study was to review, determine the scope and consistency of outcome measures reported in randomised trials for dermatomyositis and juvenile dermatomyositis, to inform strategies for further development of outcome measures that are important to patients, caregivers, clinicians and policy makers (11).

Methods

Search and study selection

We searched MEDLINE, Embase, PsycINFO and clinicaltrials.gov up to 30th May 2020 for randomised trials in children and adults with dermatomyositis/juvenile dermatomyositis (see Supplementary index). Citations were limited to those in the English language and had to include more than 50% participants with a diagnosis of DM and/or JDM in the intervention group (Fig. 1). We used searched terms related to dermatomyositis and juvenile dermatomyositis (Suppl. Index). Where applicable, PRISMA guidelines (2009) were followed within the scope of a systematic review providing a descriptive summary of the type of outcomes reported in trials (12). Co-authors (AT and DS) verified the search strategies and search results.

Data extraction

We extracted the following characteristics from each trial: year published, participating countries, study duration, intervention type, number of participants, number of male/female participants and all outcomes reported. Outcome measures were defined as any measures reported separately from any trial arm (13). We extracted details of the outcome measures including specific metric and time point of measurement (the time frame from trial commencement to when the outcome was measured) (13).

Analysis

All outcomes were extracted by the first author (AHK) and classified into domains. The extracted outcome measures and domain classifications were checked by a second reviewer (DS). A third reviewer, (AT) further checked the domain classifications until consensus was reached. The outcome measures identified as core set measures were classified according to published domain names by IMACS/PRINTO wherever possible (4). Appropriate and descriptive domain classifications were developed where there was no existing

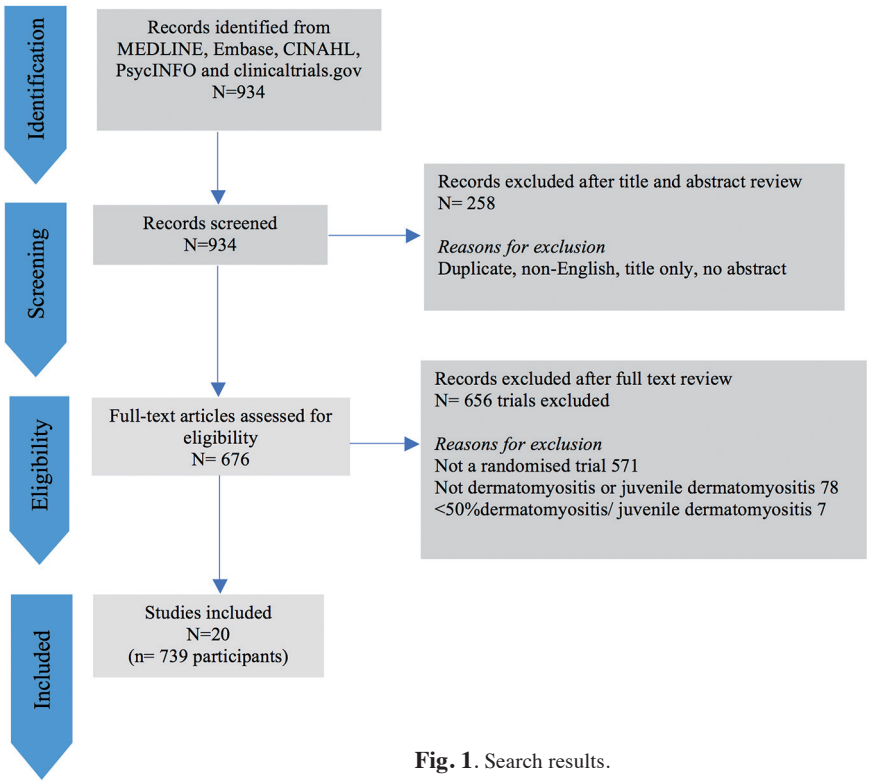

Fig. 1. Search results.

domain name for the outcome measures reported (Suppl. index).

All outcome domains were further classified into surrogate (*e.g.* biochemical markers, imaging or measures used as a substitute for a clinical outcome) (14), clinical (composite scores that included clinical evaluation, or medical outcome of a treatment or disease) and patient-reported (outcome measures reported by patients or caregivers; including quality of life or symptoms) (15). The number of trials that reported each outcome domain was then recorded.

We then conducted a detailed analysis of the muscle strength domain and deconstructed the components of the composite scores that were classified within the global health domain. For the purpose of this review, Visual Analogue Scales (VAS) were considered as their own individual composite score comprising of one component.

Results

Trial characteristics

From 934 citations (Fig. 1), we included 20 randomised control trials published between the years 1993 and 2019 (Table I). Three trials included children. Thirteen (65%) trials were of pharmacological interventions. The number of participants ranged from 14 to 200, with the majority of participants being female. The trial duration ranged from 4 to 130 weeks. The number of outcome measures reported by each trial ranged from 3 to 49.

Outcome domains

There were a total of 743 different outcome measures reported across all 20 trials. These were grouped into 34 outcome domains which were identified and classified into clinical (17 outcomes), surrogate (13 outcomes) and patient-reported outcome domains (4 outcomes) (Fig. 2). The top ten most frequently reported outcomes domains were muscle inflammation (15 trials), physical function (14 trials), muscle strength (13 trials), global health (12 trials), immunologic markers (11 trials), haematologic (9 trials), cardiovascular (8 trials), inflammation (5 trials), adverse event not specified (5 trials), skin (5 trials) and treatment efficacy (5 trials). The number of times an outcome domain was reported across all the trials ranged from 1–90. The outcome measures used for each of the top five outcome domains are described in the following.

Outcome measures

– Muscle inflammation

Within the muscle inflammation domain there was a total of 11 different measures reported across 15 trials. The majority of measures (n=7) were reported without units of measurement. The timepoints measurements were made at ranged from 1 to 96 weeks. The most commonly reported outcome was creatinine kinase, further examples of measures in this domain include AST, muscle MRI (T2 STIR) signal and other novel markers of muscle inflammation as described within a specific trial.

– Physical function

Within the physical function domain there were 9 different measures reported across 14 trials, over timepoints ranging from 1 to 130 weeks. The most frequently reported outcome measure was the Health Assessment Questionnaire (HAQ) which was reported across six trials. The next most reported measure was Activity of Daily Living scale, reported across three trials. Five of the 14 trials reported measures that were not reported in any other trials, these measures included; the McMaster Toronto Arthritis Patient preference disability questionnaire, the Physical Activity Enjoyment scale, Convery Assessment scale, the CMAS and the 6 minutes walking distance (6-MWD) test.

– Global health

Within the Global Health Domain there were 15 composite scores identified, with 75 individual components of all the composites (Fig. 4). Physician global activity was the most frequently reported composite score across the trials (n=7). There were 42 different components that were reported in only one trial. The five most frequent components used in the composite measures included physician-assessed Visual Analogue Scales (VAS) (7 trials), patient-reported VAS (6 trials), CPK (6 trials), myositis treatment (5 trials) and other muscle enzymes (5 trials). For the purpose of this review Visual Analogue Scales were considered as their own individual composite score comprising of one component.

Table I. Characteristics of included trials (n=20).

Trial	ID	Country	Disease	Females	Males	Number of participants	Trial duration	Intervention	Comparator	Outcome	Number of outcome measures reported
1	Amato 2011 (25)	USA	DM	10	6	16	52 weeks	Etanercept	placebo (prednisone)	no major safety concerns, evidence of a steroid sparing effect.	22
2	Munters 2013 (26)	Sweden	DM and PM	16	5	21	12 weeks	exercise	No exercise control	endurance exercise maybe beneficial	10
3	Munters 2013 (27)	Sweden	DM and PM	15	2	17	12 weeks	exercise	No exercise control	endurance exercise maybe beneficial	14
4	Alexanderson 2014 (28)	Sweden	DM and PM	14	5	19	24 weeks	exercise	exercise	safety of resistive exercise, but no difference between goups	6
5	Chung 2007 (29)	United Kingdom/Sweden	DM and PM	31	6	37	24 weeks	oral creatine	placebo	benefit	15
6	Dalakas 1993 (30)	USA	DM	N/A	N/A	15	12 weeks	IVIg	placebo	benefit	13
7	Guo 2014 (31)	USA	DM and PM	N/A	N/A	48	49 weeks	Sifalimumab	placebo	benefit	24
8	Habers 2016 (32)	Netherlands	JDM	N/A	N/A	26	36 weeks	exercise	no exercise (waiting)	benefit	25
9	Ito/Ibi 2011 (33)	Japan	DM/mitochondrial myopathy	N/A	N/A	22	8 weeks	hydrogen enriched water	placebo	benefit	17
10	Miller 1992 (34)	USA	PM and DM	28	11	39	4 weeks	plasma exchange and leukapheresis	placebo	no benefit	9
11	Miyasaka 2012 (35)	Japan	DM and PM	20	6	26	8 weeks	IVIg	placebo	no benefit	3
12	Oddis 2013 (36)	USA	DM, PM and	146	54	200	8 weeks	Rituximab	placebo	benefit	11
13	Ruperto 2016 (37)	Europe	JDM	82	47	129	96 weeks	Prednisone and cyclosporin or prednisone and methotrexate	prednisone	benefit	19
14	Solis 2016 (38)	Brazil	JDM	10	5	15	20 weeks	Creatine	placebo	no benefit	35
15	Vencoskv 2000 (39)	Czech Republic	PM and DM	23	13	36	12 weeks	Cyclosporine and prednisone	methotrexate and prednisone	benefit	10
16	Wiesinger 1998 (40)	Austria	PM and DM	9	5	14	6 weeks	exercise	control	benefit	4
17	Higgs 2014 (41)	USA	PM and DM	29	10	39	24.5 weeks	Sifalimumab	placebo	possible benefit	32
18	Tjarnlund 2015 (42)	Europe and USA	PM and DM	13	7	20	24 weeks	Abatacept	placebo (delayed start)	possible benefit	22
19	Idera Pharmaceuticals 2019 (43)	United States, Hungary and United Kingdom	DM	7	23	30	28 weeks	IMO-8400	placebo	N/A	41
20	Novartis Pharmaceuticals 2019 (44)	United States, Czech Republic and Japan	DM and PM	4	13	17	130 weeks	BAF 312	placebo/ BAF312	no safety concern	23

– Muscle strength

Within this domain a total of 19 outcomes were reported. Manual Muscle testing-8 (MMT-8) was the most commonly reported outcome reported in 5 trials, followed by MMT (Medical Research Council extended 0–15 scale) in 3 trials and MMT-8 (0–80 scale) in 2 trials (Fig. 3). The remaining 16 outcome measures were all only reported in one trial each. The timepoints at which each outcome was measured ranged from 3–27 weeks. The majority of outcomes (n=11) were measured at 12 weeks.

– Immunologic markers

Outcome measures classified into the immunologic domain included surrogate biomarkers such as ANA, ENA and other autoantibodies. Within this domain, there were 69 different measures reported across 11 trials. Immunologic measures were by far the most frequently reported when compared to other surrogate markers, including haematologic (n=9), other measures of inflammation (n=7) and metabolic (n=3).

Discussion

Even within the small number of randomised trials in children and adults with DM, the outcomes reported are varied and inconsistent, with a range of different measures used to report the same outcome. Across the 20 trials, there were 34 outcome domains, consisting of 743 different outcome measures. The majority of outcome domains

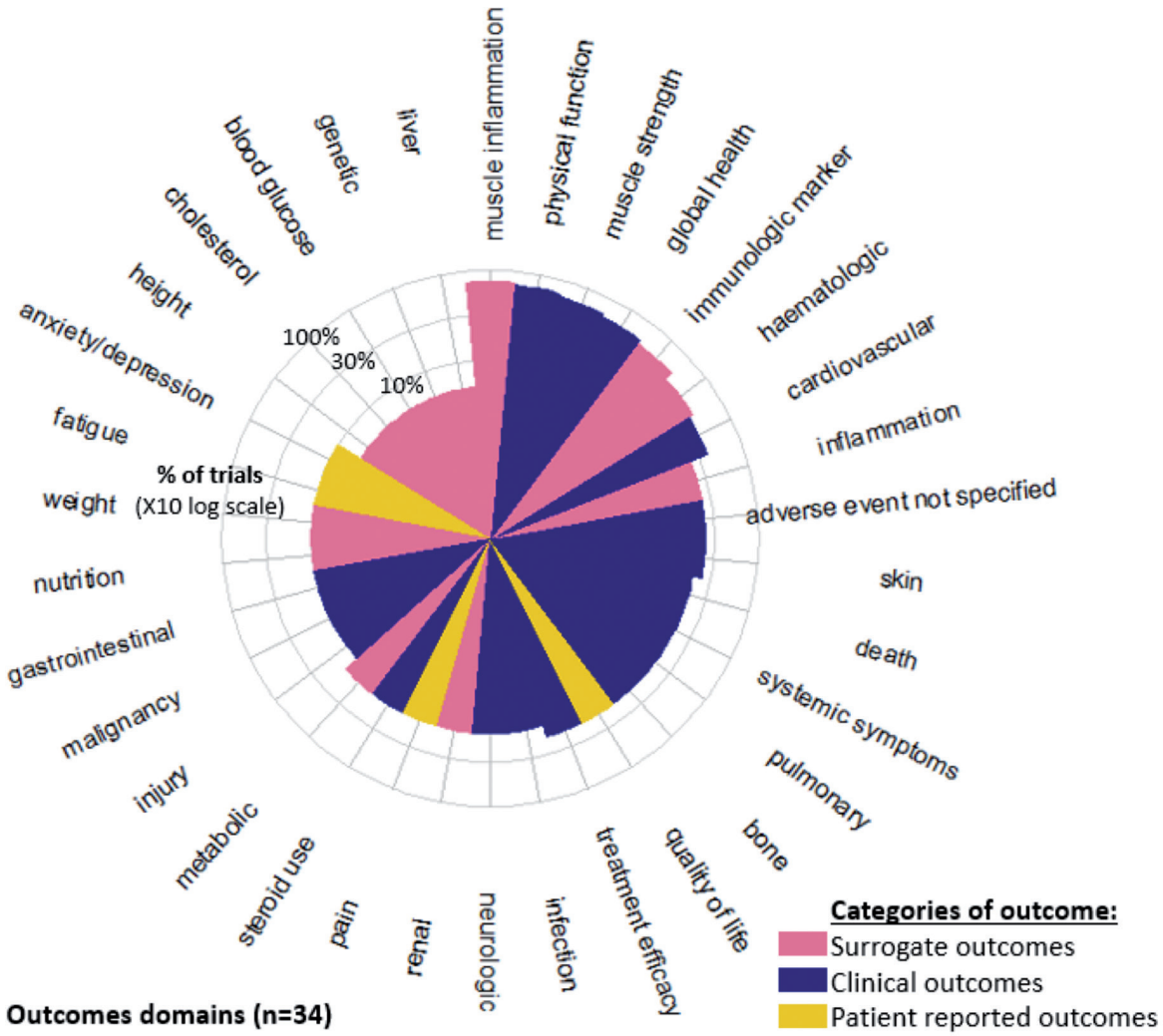

Fig. 2. Number of trials reporting each outcome domain (total 20 trials) (total 34 outcome domains).

were surrogate and clinical endpoints. Only four outcome domains (pain, anxiety/depression, fatigue and quality of life), included patient-reported outcome measures. The top five most frequently reported outcome domains were muscle inflammation (16 trials, 46 outcome measures), physical function (13 trials,16 outcome measures), muscle strength (13 trials, 30 outcome measures), global health (12 trials, 33 outcome measures) and immunologic markers (11 trials, 91 outcomes).

The global health domain (Fig. 4) included 15 composite scores where a number of these scores reported the same components. These overlapping components detail specific disease manifestations, which to complete, require a high degree of experience, clinical knowledge and are vulnerable to different interpretation between investigators (4). They may also be time consuming to complete. For example, the MITAX (a measure of the physicians intention to treat) and MYOACT (a measure of disease activity within the last 4 weeks) are two overlapping tools, differing by only one component (16) (Fig. 4). Both include information relating to the extent of involvement in the constitutional, articular, cardiac, pulmonary, gastrointestinal, cutaneous and skeletal muscle organ/systems (16), totalling 29 and 30 components respectively. The utility of the clinical meaning of a composite score that differs by one component, we would argue, is limited. Complex composite scores have been criticised as potentiating the misinterpretation of the magnitude of the effect of an intervention (17). Complex composite scores may also be difficult to utilise in the busy clinical setting.

Improvements in consistency of outcomes reported by adopting core outcome sets has been demonstrated in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (14). However, IMACS and PRINTO have developed core outcome measures that include clinical and surrogate measures (4) and there are currently only two recommended and defined as patient-reported outcome measures, Short Form36 (SF36) for adult patients with IIM and the Child Health Questionnaire–Parent Form 50 (CHQ–PF50) for patients with juvenile dermatomyositis (4). Neither of these have been validated in patients with IIMS (4) and measure patient reported physical function only. We identified only four outcome

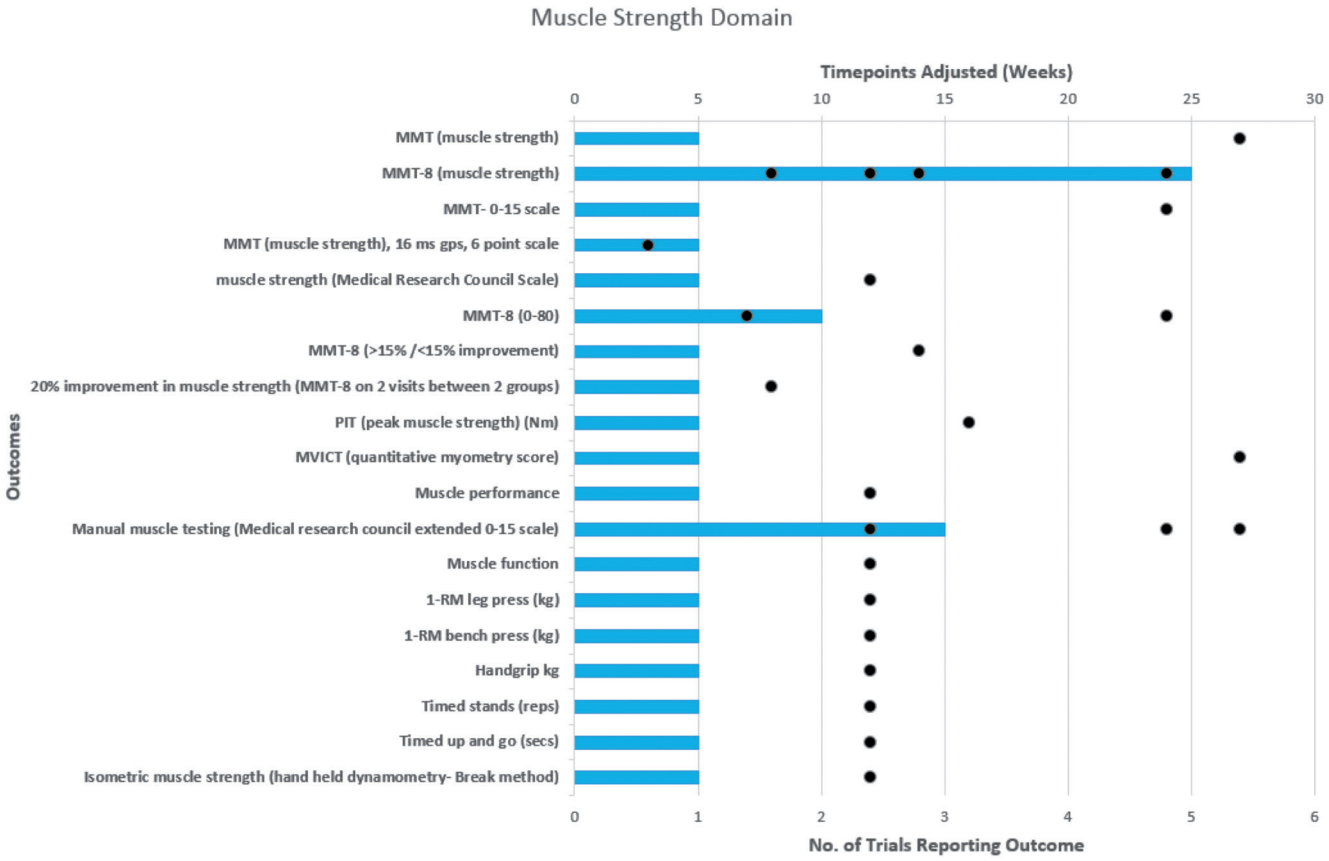

Fig. 3. Number of outcome measures in muscle strength domain, their timepoints and the number of trials reporting that outcome, noting the number of muscle groups or scale reported.

domains (Fig. 2) that described patient reported outcome measures, illustrating that there has been limited inclusion of patient reported outcome measures within dermatomyositis and juvenile dermatomyositis trials to date.

There is strong evidence to support the inclusion of the patient's perspective in determining disease activity (18). Tory *et al*. (18) found patient reported outcome measures in JDM were associated with greater discordance between the patient's perception of their disease and their treating physician, concluding that patients/families may place a greater emphasis on patient reported outcomes (18). In adult DM, poorer quality of life scores are associated with worse muscle strength (18). Patient-reported outcomes are vital to inform physicians assessments of disease activity, as the patient experience is recognised as central to achieving high quality, high value care (19). Without including patient reported outcomes, trials are potentially missing a vital component of the patient experience of their disease.

To better capture the patient's perspective, the OMERACT Myositis Special Interest Group identified five themes as being essential to include in myositis-specific PROMs; symptoms, activity/participation, strategies, knowledge of disease, self-management and emotional factors (4). Outcome measures that reflect how patients feel or function were underreported in the twenty trials we identified, with only four trials reporting quality of life; three trials reporting pain, two trials reporting fatigue, and two reporting anxiety/depression. The development of validated PROMs, inclusive of the patient's perspective (symptoms, activity/participation, strategies, knowledge of disease, self-management and emotional factors) in dermatomyositis and JDM is urgent and the paucity of PROMs in this review demonstrates that the choice of outcomes reported has not always been those that are most relevant to patients (13). Patient reported outcome measures have demonstrated similar reliability in trials compared to other surrogate measures, such as diastolic blood pressure and blood glucose levels in (20).

One unpublished, qualitative study found that caregivers value knowledge of surrogate measures of muscle inflammation, as they provided an easy measure for them to understand their own child's response to treatment (21). Creatinine kinase can be used as a measure of disease activity and damage assessment and is included in the IMACS core set measures for DM and JDM (4). However, in our study, there were 11 different measures of muscle inflammation reported across 16 trials. The effectiveness of surrogate markers is lost where too many are used, or their relationship to response to the intervention is obscure (11).

Randomised clinical trials should report consensus determined outcome measures to better gauge the impact of treatment interventions (6). With the development of new therapeutic interventions, trials will need to report replicable, meaningful outcome measures so that interventions can be

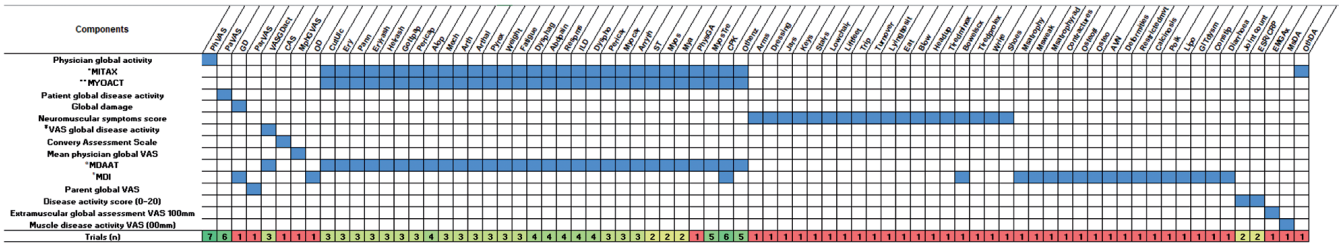

Fig. 4. Composite matrix of Global Health Domain measures showing breakdown of composite scores (far left column) into their components (top row, see Supplementary index). The bottom row represents the number of trials (n) that report each component.
*Myositis Intention to Treat Activity Index (MITAX);
**Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT);
ɣVisual Analogue Scale (VAS);
αMyositis Disease Activity Assessment Score (MDAAT);
Myositis Damage Index (MDI).

compared across trials (11). The ability for clinicians to apply research findings to everyday practice is limited if outcome measures reported are varied, inconsistent(15) or lacking important clinical information. We note that skin is an important element (often), in the presentation of DM and JDM, however, outcome measures reporting skin disease, such as the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), a validated tool to assess cutaneous manifestations in DM (22), were not universally reported across all trials (Fig. 2). A validated skin outcome measure should be considered as an important outcome measure to be reported across DM/JDM trials.

Our study showed that historically there is great variation and inconsistency in how outcomes are reported across DM and JDM. At every level, including the domain, outcome reported, timepoint and metric of measurement there was a lack of uniformity in reporting. Within the physical function domain, for example, 5 of the 14 trials reported measures that were not reported in any other trial. Previous studies in nephrology and cardiovascular disease have reported similar problems (15). Even amongst similar outcome measures, the way in which they are measured and reported varies across trials. The muscle strength domain (Fig. 3) reported 19 different measures, all measuring muscle strength, with varying groups of muscles being tested, using different scales (Suppl. Table S3). The timepoints over which these outcomes were measured varied from 5 weeks to 27 weeks. Manual Muscle Testing is purported to be a surrogate of muscle function (23) (and recently proposed as a validated, core outcome measure, by IMACS/PRINTO) (4) is one example where there were nine different metrics reported across the trials that we identified. It has been reported in other diseases that reporting inconsistent outcome measures can result in reporting bias(15, 24), whereby trialists selectively report outcomes that show an effect. We acknowledge that efforts have been made to improve the reporting of these measures. However, in the future it will be vital for trials to include standardised, validated measures.

Our findings provide systematic and detailed evidence of the inconsistencies in the reporting of outcome measures. However, there are some potential limitations. Only 20 randomised trials were included reporting predominantly on drug interventions. Inevitably because of the rarity of DM and JDM, trials may include other inflammatory myopathies which may necessitate reporting additional outcome measures. We acknowledge that there may be differences in the outcomes reported in early-stage trials, where surrogate markers may be preferentially reported. However, we decided it was not possible to exclude these trials given the small number of trials identified. Being limited to only 20 trials, we were not able to apply a meaningful, in-depth analysis of the uptake of the published core outcome measures sets. Our review was also limited to including trials that reported in English and all the trials identified were from high income countries, which may imply publication bias.

There is wide heterogeneity and lack of consistency in the reporting of outcome measures across trials in DM and JDM. The findings highlight the need to revise and implement core measures set and draws attention to improving the use of patient-reported outcome measures. Rare diseases such as DM and JDM with already few randomised trials in the literature, offer an opportunity to develop cohesive, uniform and most importantly patient relevant outcome measures that can be reported across all future trials and ultimately improve patient outcomes.

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