Correspondence on 'Current myositis clinical trials and tribulations' by Saygin *et al*

We read the viewpoint titled 'current myositis clinical trials and tribulations' with great interest.[1] We congratulate the authors for addressing critical patient-centred and science-forward concerns in idiopathic inflammatory myopathies (IIMs) clinical trials. These valuable insights highlight current pitfalls and the need for more effective engagement of patients, physicians and trial methodology experts in the development of clinical trial designs for complex rare diseases. Lengthy placebo arms, trial recruitment and equity/diversity challenges, outdated classification criteria, and outcome measures that insufficiently demonstrate therapeutic responsiveness in large subsets of patients, such as skin-predominant involvement, cripple the current landscape of IIM trials, levying a toll on a rare diseases' premium resource: patient life-years.

The authors substantiate this by citing 10 competing IIM trials currently recruiting 1427 patients (inclusion body myositis trials excluded), a considerable number for a rare disease. Such recruitment challenges, given the scarcity of approved treatments, pose a discouraging strain on successful clinical trial completion that the IIM community cannot afford. Thus, to sustain ongoing research in IIMs, the need for effective, efficient and patient-centred alternatives, sanctioned by diverse expertise (including patient advisors), including trial designs accommodating sample size reduction, robust patient participation and establishment of optimal outcome measures, is indisputable.

Saygin *et al*[1] describe two worthy design alternatives for consideration, namely adaptive and platform clinical trials. The IIM expert community will also likely support additional trial design strategies with advantages in myositis and rare diseases in general such as:[2 3]

1. Delayed-start arms, such as in the phase 2 MYOJAK (NCT04208464, testing baricitinib, a JAK 1/2 inhibitor) and ARTEMIS (NCT01315938, testing abatacept, a CTLA-4 analogue that blocks the costimulatory signal mediated by the CD28-CD80/86 pathway) IIM clinical trials, randomise subjects to a briefer placebo-controlled phase either at the beginning or at the end of the trial. All subjects receive treatment which incentivises patient participation. Further, the design facilitates disease progression assessment in the delayed-start arm and possibly detects disease worsening in the withdrawal phase of the immediate-start arm; although it may not fully account for potential carry-over effects from the initial phase to the subsequent phase.
2. Randomised withdrawal trials minimise exposure time to ineffective treatments while ensuring that every participant receives treatment. The design initiates with an open-label phase, with subjects subsequently randomised to treatment-continuation or placebo arms. While there is a potential risk for overestimation of the treatment effect, this model provides multiple comparative views of efficacy, both of the potential response of the entire cohort in the open-label phase and the potential for worsening upon withdrawal compared with potential ongoing response in the continued treatment arm.
3. Pragmatic trials: The intervention in pragmatic trials, also known as 'real-world trials', is integrated into the healthcare system workflow, and data from routine electronic healthcare records are used. Subsequently, if such interventions are successful, they can be more easily translated into clinical practice. Pragmatic trials require broad stakeholder engagement and more flexibility in the administration of the trial.
4. Cross-over trials, used previously in the phase 2 PRESIDIO (NCT04033926; testing KZR-616, a first-in-class selective inhibitor of the immunoproteasome) and phase 3 ustekinumab (IL-12 and IL-23 antagonist) (NCT03981744) IIM trials, randomise the sequence of initiating active treatment versus placebo delivery. This design allows subjects to serve as their own controls, thus reducing sample size requirement and encourages patient participation by ensuring that every patient ultimately receives treatment. At the same time, cross-over trials may require a longer duration for a participant to complete both arms with the potential for unblinding, and the carryover effect has to be taken into consideration, especially with drugs with long-lasting effect.
5. Bayesian statistical modelling provides a formal framework for combining relevant available evidence. Prior data reflect disease knowledge known before the trial and can incorporate information from previous or ongoing trials, published studies and other real-world data. While current data collected during the clinical trial suggest the likelihood of the treatment effect. Prior and current data can be combined to generate updated estimates of the treatment effect, which are then used to quantify results and infer conclusions.
6. Finally, in the appropriate context, N-of-1 trials could be considered: these are randomised, placebo-controlled, double-blind trials on a single patient with multiple cross-over.[4] N-of-1 trials should follow the same scientific rigour as traditional parallel trials and use the same outcome measures. They are the closest to the concept of personalised medicine and would allow evaluating the efficacy of expensive drugs on an individual level and limit patients' time on suboptimal treatment. Challenges are related to generalisability, complexity of the analysis, and approval by regulatory authorities.

It is also important to consider innovative trials for the paediatric and adolescent population with juvenile myositis (JM), an often-overlooked vulnerable group. Currently, there are a limited number of approved medications to treat JM adding to the burden these families carry. Legislation exists to promote paediatric trials in Europe and USA. Large networks (eg, Myositis International Health and Research Collaborative Alliance (MIHRA), Global Myositis Network, and Childhood Arthritis and Rheumatology Research Alliance) should be leveraged to collaboratively conduct trials or extrapolation studies in children to facilitate expedited safety and efficacy data as well as enhance approval and availability of appropriate medications for JM.[5] Moreover, strong research collaborations among healthcare professionals caring for patients with juvenile and adult onset myositis will allow for 'age-inclusive' trials in IIM. This approach is crucial to enable faster results for children and young people, as opposed to waiting for 'child-specific' trials after drugs have been granted a license in adults, or disadvantaging younger children by drugs only being available in postpubertal children.

While there are currently no established biomarkers that can predict how effective treatments will be in IIM, there is hope that in the future reliable biomarkers will demonstrate subtle changes that help detect treatment responses.[2 6] Similarly, growing interest in the reliability, discrimination and sensitivity to change of imaging modalities suggests benefits that go beyond these being 'objective measures'.[7 8] Measurement performance might even be enhanced when combined with other methods to detect changes in disease activity and treatment response. Furthermore, determining the minimal clinically significant change of a biomarker and its correlation with improvement in function is of critical importance. Nevertheless, individually, these potential advancements remain only a strand in the equation to discern treatment responses, while

incorporating the patient perspective with validated patient-reported outcome measures (PROMs), as mentioned by Saygin *et al*, remains central to the understanding of treatment efficacy and drug tolerance.[1] Importantly, these PROMs should be age-appropriate and codeveloped with patients and carers.

Lastly, Saygin *et al*[1] discuss decentralised alternatives to trial implementation that promote diversity, equity and improvement of recruitment. In addition to navigating variations of local laws, drug supply chains and language barriers common to international studies, it is imperative to consider the important role that regulatory entities play in helping to mitigate challenges and facilitate global clinical trial success. Particularly in the case of rare diseases, involving regulatory entities in very early conversations with researchers and patients is critical such as the University of Birmingham's recently developed Rare Diseases Translational Acceleration Programme (RD-TAP).[9] RD-TAP is part of the wider UK Rare Diseases Framework and Rare Diseases Action Plan, and exemplifies the implementation of integrated phase clinical trial designs and overcoming regulatory barriers through local agreements between National Health Service hospitals. More initiatives that support regional, national and international networks are being ignited worldwide in an attempt to narrow the gap between researchers, patients and government entities, and influence government policies through regulatory science.[10]

At a global level, one of these initiatives was the recent establishment of MIHRA (https://mihrafoundation.org/; @MIHRAfoundation), a newly formed purpose built non-profit charitable multidisciplinary research organisation, created to address research challenges in rare diseases. The vision of MIHRA is 'to create a world where we can cure myositis together' with 'Clinical Trial Readiness' and 'Global Equity and Engagement' being two of its driving organisational cores. MIHRA works to address issues of reliability and feasibility of trial design, outcome measures and recruitment potential to accelerate the conduct of global patient-centric trials, while prioritising inclusivity across demographic, geographical and professional backgrounds.[10]

The future in myositis-related disorders holds promise if the approach to clinical trial design secures true and extensive expertise. Through initiating and sustaining a critical, discerning and diverse expert contribution, which is interdisciplinary and interspecialty, we can then collectively use resources and advocate wisely and bravely to 'cure myositis together'.

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