Challenges in international investigator-led rare disease clinical trials and the case for optimism in inclusion body myositis

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Abstract

Objective

This paper aims to provide insight into the challenges and opportunities of conducting an investigator-led, international, multicentre clinical trial for Inclusion Body Myositis (IBM), a rare inflammatory myopathy.

Methods

An international, multicentre, randomised, controlled trial of a repurposed drug (sirolimus) was initiated based on promising results from a mono-centric pilot study. The progress of the trial was analysed to identify key challenges encountered and solutions developed.

Results

This large, collaborative study has presented a mosaic of challenges and opportunities, many ubiquitous with investigator-led trials. Key challenges have included securing adequate funding, coordinating manufacture of placebo, negotiating international contracts, managing limited study budgets and delays linked to the COVID-19 pandemic. Alongside these challenges, the study team have found opportunities for creative and effective solutions, including the flexibility of building study databases, optimising digital data capture and harnessing patient involvement.

Conclusion

Instrumental to the progress of the trial has been the collaboration between site teams, patient partnership and adaptability.

Key words

clinical trials, inclusion body myositis, international, investigator-initiated

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Competing interests: see page 314.

Introduction

Inclusion body myositis (IBM) is a relentlessly progressive and disabling inflammatory muscle disease without any effective disease-modifying therapies (1, 2). Due to the rarity of this orphan disease, there are significant challenges obtaining funding for novel therapies or interventions. Ideally, particularly in rare diseases, if a therapy is showing promise in pilot cohorts or early phase clinical trials, the ability to rapidly design and deliver conclusive phase 2b/3 trials at multiple sites across the globe would be extremely advantageous to the whole community, both clinicians and patients.

Even for industry-sponsored trials there are challenges associated with rare disease research and accessing patient cohorts. However, for multicentre, international, investigator-initiated trials, the challenges can be nearly insurmountable. Alternative trial designs, such as multi-arm platform trials are recommended in rare disease, but the costs of these trials are significant and often require involvement from several industry partners (3, 4). In addition, these trials require a strong network of like-minded, collaborative clinicians and clinical trial centres across the world. Such networks provide global access for patients, facilitate recruitment, guarantee adequate patient selection and rapid translation of results and allow investigators and subject-matter experts to refine trial design and outcome measures (5).

There are significant challenges in establishing such a network, with funding as a major hurdle, particularly the ability to share grant funding across international borders but also within the European Union (EU). Contractual complexities between countries/regions can stifle collaborative intent, particularly when in-kind support is required and little or no income for the trial will be received. Adding to these hurdles are the peculiarities around the national and local regulatory environment for investigational studies to navigate. Provision of drug and over encapsulation with matching placebo are costly and require investing into the cost of compliance with local authorities' rules and regulation. Moreover, legal issues around data governance and data sharing also provide further hurdles that require tenacity and willingness to solve. These trials require significant commitment and investment from investigators and sites just to get to start-up and continually coordinate progress across different time zones. The in-kind support required from investigators and study teams for these trials can be burdensome; with most study staff funded by industry-sponsored trials or other project grants, time spent on 'un-funded' studies cannot always be prioritised. These studies can only move forward due to the unwavering commitment of investigators to conduct trials of promising drugs that may have the potential to improve the lives of people with rare diseases. In our case, this investigative team is focused on innovation in IBM.

Sirolimus trial

In IBM, there have been only 4 international multicentre clinical trials in the last decade, (bimagrumab, arimoclomol, ABC008, and sirolimus) (6, 7), with only one (sirolimus) an investigator-initiated academic study. The phase 2/3 study of arimoclomol in Inclusion Body Myositis NCT02753530 was an international investigator-initiated academic study initially funded by the FDA Office of Orphan Products Development. It was initially supported by the drug company with provision of drug and placebo. Later, it was further supported by Orphazyme A/S to fund costly mechanisms for regulatory compliance. The investigator-led 'Sirolimus in IBM' study was conceived at the Global Conference of Myositis (GCOM) in Berlin in 2018, after the initial results of a proof-of-concept monocentric controlled phase 2 study of 44 French IBM patients were presented (8). This phase 2 study utilised a re-purposed drug, sirolimus, aiming to slow or stabilise disease progression. Although the primary outcome was not met, a number of secondary outcome measures suggested a positive impact on disease progression and warranted further exploration in a larger multicentre study. The manufacturers of

sirolimus (Pfizer) were unable to support an international, multicentre Phase IIb/III trial, however agreed to provide drug for an investigator-led trial unconditionally and free of charge. From that initial discussion in 2018, many further meetings were held to establish a project team, agree on the trial protocol and site selections to form the basis of grant applications. There were the usual challenges of clinical trial design in terms of agreeing to the primary outcome measure, secondary outcome measures, calculation of sample size and determining clinically-significant change, trial duration, data capture, and security and safety/monitoring of patients; however with the benefit of the direct involvement of international IBM clinicians, clinical trial site staff, patients and expert allied health colleagues in the protocol design, this study is currently ongoing.

Table I. Factors considered when selecting outcome measures.

Validated, with normative data available
Repeatable, with low inter-rater variability
Relatively easy to access and perform (cost, available translations, practicality)
Clinically significant
Sensitive to change
Applicable to early disease/late disease/different phenotypes
Meaningful to patients (functional measures)
Acceptable to Regulators
Lessons from other trials and experts
Inclusion of broad range of secondary outcomes
Area for continued improvement in IBM

Factors considered when selecting outcome measures

Awareness of IBM natural history, data-driven selection of robust outcome tools, and appropriate design of patient inclusion and exclusion criteria were critically important to optimise the probability to detect a positive signal.

The primary objective of the trial was carefully considered. Where some past trials in IBM have sought to improve strength and/or function, the primary objective of the sirolimus trial was deliberately established as 'slowing or stabilising' of disease. The involvement of patients in the trial design and grant submissions confirmed that this was a meaningful outcome for patients. A challenge for IBM clinical trials is the limited outcome measures validated in IBM that are sensitive to change across patient subgroups. The optimal primary outcome measure in IBM is still not clear, with the inclusion body myositis functional rating scale (IBMFRS) currently accepted by the IBM community as the best one at this time, however the variability of IBM phenotypes may impact its sensitivity to change. US regulators view the IBMFRS as relevant to IBM (Type C FDA Regulatory Meeting, personal communication MMD). Well after the selection of the IBMFRS as the primary outcome measure, two publications have reported on its reliability, content validity, responsiveness and meaningful decline (9, 10). Lastly, the 272nd ENMC international workshop convened international experts who recommended utilising the IBMFRS as the primary outcome in long lasting randomised controlled efficacy studies over 1.5-2 years (11).

Measuring muscle strength with both manual and quantitative muscle testing are commonly done in clinical practice. This tracks IBM progression, particularly quadriceps strength, but this outcome does not always correlate with function and therefore is perhaps less meaningful for patients and regulators. The 6-minute walk test has long been used in neuromuscular clinical trials, but is affected by factors other than IBM, such as fatigue, arthritis, pain and recent injuries from falls to name but a few, so it is probably not reliable as a primary outcome measure in IBM clinical trials. Modified Timed-Up-and-Go (mTUG) is a good test of a patient's ability to rise from a chair and walk a short distance and is a good test of lower limb function and to some extent of the arms to push up from a chair, but patients with IBM lose this ability before they lose the ability to ambulate and therefore will not be sensitive to change or even able to be performed in moderate-to-severe disease. A lack of robust, validated outcome measures for upper limb function, specifically hand function and swallowing, limit inclusion of patients where these domains are the most severely affected. Within the sirolimus in IBM trial, to ensure the best chance of a conclusive trial result, inclusion and exclusion criteria included minimum physical requirements for strength/function to increase the probability that change could be measured. In particular, we established a range of distance covered on the 6-minute walk test which we believe select out the too strong and too weak IBM patients who would not be likely to benefit from sirolimus.

The sirolimus trial includes a range of secondary outcome measures carefully selected to help inform understanding of how different outcome measures perform in this population. This will help to establish an appropriate toolbox of outcome measures, most of which are not validated so far but can be used in different clinical trials of IBM, depending on the proposed effect of treatment. In the end this will minimise the unnecessary exposure of trial participants to meaningless outcome measures and save time and costs. The sirolimus trial has not included any biomarker outcome measures, with central serology and/or imaging studies unfeasible within the scope of this academic study funding resources. Factors considered when selecting outcome measures are summarised in Table I.

Challenges for the sirolimus trial

Funding

For this investigator-led trial, securing funding across all international sites/continents has represented the biggest challenge and has driven much of the delay in the study timeframe. Since conception of the study in 2018, over 15 large-scale grant applications have been submitted across the study regions to support this study. It was quickly ap-

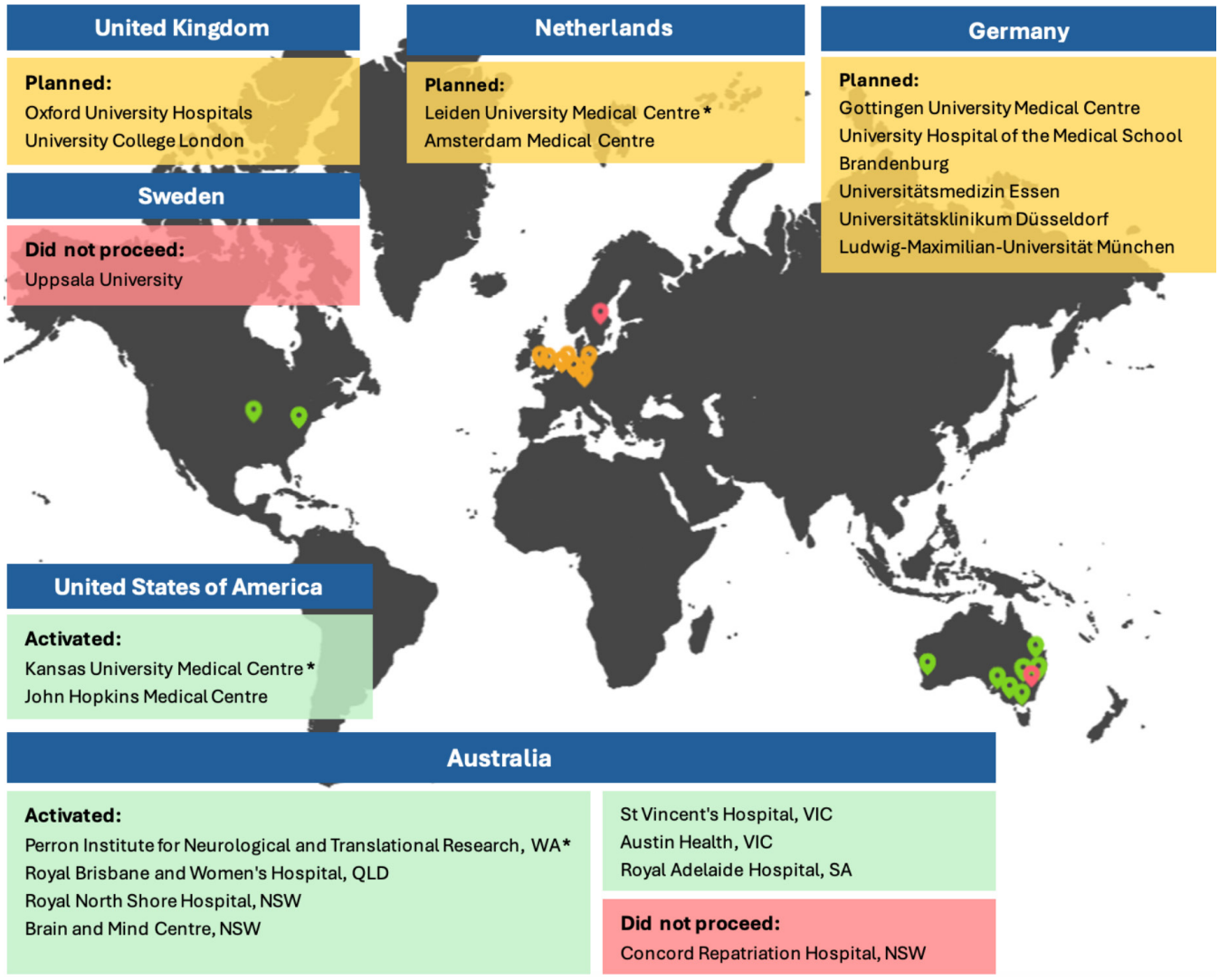

Fig. 1. Study sites.
** Lead sites for Australia, US and Europe.*

parent that it would not be possible to secure a single grant to fund all study sites and regions, and a 'patchwork' funding model would be required, with sites/regions needing to secure their own funding to conduct the study. In 2020, award of a substantial Australian government grant allowed the trial set-up to begin in earnest, with many central study coordination activities funded, as well as 7 Australian trial sites. A further 7 international sites continued to seek funding, with the US sites and Netherlands sites successfully funded by 2021 and most recently the German and UK sites receiving funding to conduct the trial. A site planned in Sweden could not proceed due to lack of funding. The UK and German sites were expanded to include 2 locations in response to that. Figure 1 shows an overview of study sites. The COVID-19 pandemic also contributed to funding challenges, with many grant programs as well as site and study teams focussed on COVID-19 research and associated conditions. The pandemic also resulted in significant cost increases across the clinical research sector, meaning that budgets agreed pre-pandemic no longer covered the actual cost. Where funding has been secured at a sufficient level to conduct the study locally, there remain gaps between the levels of funding and the resources required to deliver a safe and high-quality trial. Bridging these gaps requires in-kind support, creativity and goodwill from site teams, investigators, research office staff and administrative support at institutions.

Contractual and regulatory challenges

The second major challenge and driver of study delays is the complex web of contracts that must be negotiated and agreed across different regulatory environments around the world. As an academic investigator-led trial, there has not been budget available to employ a Contract Research Organisation to negotiate and manage these agreements, with responsibility resting with the Sponsoring Institution, investigators and individual sites to navigate, negotiate and execute the required agreements. Particularly resulting from the 'patchwork' funding approach, there are multiple contracts required, for example between Sponsor and sites, grant administering institutions and the grant

recipients, regional coordinating centres and regional sites. Where multiple contracts are required, there can be differing perspectives between parties as to the order of execution of agreements, and once again delays associated with reliance on in-kind support, where income-generating trials may need to be prioritised by institutions.

However, part of that second challenge is that ethics committees have to approve the initiation of studies at the investigative sites. While the US and Australia speak the English language, there are local context differences between the two countries which also applies to the United Kingdom. However, in the case of the Netherlands and Germany, ensuring that translation of the informed consent form into Dutch and German languages is performed accurately is another challenge for an international academic clinical trial. For regional coordinating sites (US, EU and Australia), there are additional challenges for study team members with balancing the requirements of their own site set-up, conduct and care of participants, alongside regional leadership tasks and responsibilities.

Manufacture of placebo

Supply of active drug for the trial was provided by Pfizer, however the study team needed to source/manufacture the trial placebo. The pilot study in France utilised the sirolimus liquid, manufacturing a matching liquid placebo for their double-blinded trial. The liquid form of the drug provided several challenges, including cold-chain transport and storage, limited stability at room temperature, and high cost of manufacturing the matching placebo. Replicating the tablet form of sirolimus was not possible due to the distinct shape and appearance of the tablet. A solution was found to over-encapsulate the tablet form of sirolimus using 'DB Caps', a specific capsule designed for this purpose. This method presented a feasible way to consistently manufacture study drug (both active and placebo) within a central pharmacy in each region, however once again un-budgeted complications arose, with the DB Caps requiring a specific packing machine to be used for manufacturing, adding both time and cost to the process, not to mention the large capsule size challenge in IBM patients with dysphagia. Delays to recruitment have also resulted in study drug needing to be replenished at both the Australian and US sites, contributing a further significant un-budgeted cost of the trial at these sites. The size of this capsule also provided a challenge that required investigator opinion as to whether the patient is/will be able to swallow the capsule during baseline procedures and to continue doing so throughout this study.

Successes of the sirolimus trial

Collaboration

Designing and implementing an investigator-led, international, multi-centre clinical trial in a rare disease has been an example of the power of collaboration. In rare and orphan diseases without large sources of disease-specific funding, collaboration is prioritised over competition, with an understanding that these trials cannot happen without working together. Without an industry sponsor dictating site selection and trial scope, there is potential for like-minded clinicians to come together and personally contribute to the design and development of the trial and to oversee its delivery. The reliance on in-kind support for this trial has placed a burden on sites and investigators, however it has also meant that investigators and study teams are motivated and committed to the project, investing their own time to make the study happen. A small example of that commitment are the regular investigative team leaders' meetings which are held at a time that is very late night in Australia, very early morning in the US and in the afternoon in Europe in order that this multinational collaborative can synchronise step by step and address challenges and opportunities in real time.

Creative solutions

Within investigator-led large scale clinical trials, necessity proves to be the mother of invention. Readily available software has been used to manage several processes usually delivered at high cost by a CRO. For example, for the study database we are using CastorEDC (12), a relatively low-cost 'DIY' Electronic Data Capture (EDC) where study teams build their own electronic case report forms (eCRFs) using customisable data collection instruments. eCRFs can be designed using the logical order of events during a study visit to facilitate direct data entry. To efficiently manage study governance and quality assurance activities (such as training, personnel, site approvals and documentation), the study team created a study management project within the REDCap database platform, which was freely available via an institution licence. To minimise costs of study-specific training, video tutorials were created in-house and Qualtrics (survey software freely available within the lead institution) was used for administering the study training modules, with videos and assessment questions embedded with training surveys. Training resources and important study resources, such as outcome measure instructions, were embedded into the EDC within a 'Events During Study' section, in place of developing a study-specific website or intranet environment. Cost-saving and sustainable approaches were employed across the study, including re-purposing surplus packaging materials from previous clinical trials for central lab kits, limiting paper documents and supporting direct data entry to the EDC. In the absence of funding for central laboratory services, the EDC has been used to provide partial automation of the review of sirolimus levels by unblinded monitors in each region who are firewalled from the blinded teams. The unblinded monitor would then recommend to the local blinded team dose modifications, possibly including modifications of placebo participants to maintain the blind within the study. An electronic weekly study diary has replaced traditional paper diaries, with great success. Study documents have been developed with patient involvement, facilitated by the direct links between the study team and patient cohort, resulting in simple, visually appealing documents including photos and infographics. The study team have been able to share many of

these innovative approaches with other research groups facing the same resource challenges.

Protocol and database fit for purpose

Perhaps the most significant benefit of running an investigator-led clinical trial is the ability for the protocol and wider study to be designed by, and for, disease experts and those who deliver the trial and care for participants. The sirolimus in IBM study protocol has benefited from a team of 60+ authors who have contributed their perspectives to the final document, including IBM clinicians, safety monitors, biostatisticians, physiotherapists, nurses, clinical trial coordinators, patients and sponsor representatives. As described earlier, outcome measures selected are relevant and well known, eligibility criteria are robust yet feasible, the study schedule is comprehensive but sustainable. The study database (EDC) has been built by the central study team, using a 'DIY' EDC platform, CastorEDC. This has meant that forms can be presented in a logical order for study teams and functionality has been included that makes using and navigating the EDC as easy as possible. The study team has encouraged sites to use direct entry to the EDC and optimised electronic PROs and diaries for participants, minimising duplication and embracing new methodologies available in clinical trials. This approach has also facilitated remote monitoring of the study, again presenting a cost-saving relative to in-person monitoring costs. The establishment of a Data Safety Monitoring Board led and operated by academicians has enhanced the study quality.

The protocol has remained flexible and responsive to change. Without layers of corporate administration to navigate, changes that are needed to support participant safety, comfort, and enrolment have been able to be swiftly adopted and the protocol amended. For example, the initial 6MWT minimum and maximum distances quickly proved too narrow to support the required recruitment to the trial. With direct feedback from sites to the study team, the protocol was quickly amended and recruitment expanded.

Conclusions and future directions

Optimism in IBM (NCT04789070; ANZCTR: ACTRN12620001226998p) has commenced in Australia and in the USA, with European sites preparing to commence. The prolonged set-up phase highlights the challenges in establishing a multi-centre trial across the world. In addition to securing funding, collaboration and coordination are both absolutely necessary in rare disease research. These require hard work, tenacity and dedication from clinicians and study teams, alongside strong commitment and patience of patients to be engaged at different stages and vigorous support from patient advocacy groups across the world.

Having a network of similarly-minded and driven clinicians with appropriate support staff across the world, who care for cohorts of well phenotyped patients, is a solid foundation for global clinical trials. Partnership in designing, supporting and advertising the study with patient advocacy groups is critically important. Whilst in an ideal world, these centres would simply follow the same protocol and combine results, the reality of the costs and time involved in running clinical trials and the governance required to ensure these are carried out in a standardised manner across the world, means that significant challenges and prolonged starting timelines remain even in established clinical trial networks. Moreover, if this network collaborated on natural history studies using shared measures and outcomes, then this could facilitate the ability of future trials to minimise prospective placebo groups, allowing the potential use of prospectively rigorously collected natural history data to more deeply understand the natural history of disease, and use of this data as retrospective controls. Moreover, the ability to share placebo groups between clinical trials in this type of collaborative network would allow more patients access to the active product in clinical trials.

We have outlined several challenges for an investigator-initiated clinical trial above. However, this list is not exhaustive and additional obstacles persist. For instance, the Clinical Trial Regulation, which came into effect in the EU in 2021, allows for obtaining ethical approval for all EU sites simultaneously. Since each submission/amendment incurs a cost and is very time consuming, there is an effort to secure approval for as many sites as possible at once. This often results in waiting for other sites to obtain funding first, thereby delaying the process. Grants designed for international investigator-led collaborative studies would streamline this process, as compared to the current patchwork solution.

It is now 6 years since the conception of the study in 2018, where we initially planned to complete data collection in mid-2024. As we write, 50% of the total patient cohort are now enrolled, with 9 out of 14 planned sites actively recruiting. Although still a long way to go until completion, we are actively planning for data analyses to bring results to patients as quickly as possible. Along the way, we believe we have established rigorous processes that enhance team collaboration and coordination that are essential for the successful initiation and completion of our study, Optimism in IBM.

Competing interests

M. Needham has provided consultancies to CSL and Abcuro, has received honoraria and is a member of the speakers' bureau of Sanofi, and has received funding from the Australian National Health and Medical Research Council.

U.A. Badrising has received grant support and other financial support.

M.M. Dimachkie has received consultancy fees, payment and honoraria for lectures, presentations, manuscript writing or educational events, and participated on a Data Safety Monitoring Board or Advisory Board for Abata/Third Rock, Abcuro, Amicus, ArgenX, Astellas, Cabaletta Bio, Catalyst, CNSA, Covance/Labcorp, CSL-Behring, Dianthus, Horizon, EMD Serono/Merck, Fortrea, Ig Society Inc, Ipsen, Janssen, Medlink, Nuvig, Octapharma, Sanofi Genzyme, Shire Takeda, and TACT/Treat NMD, and Wolters Kluwer Health/UpToDate. He has received grants from Alexon, AstraZeneca, Alnylam Pharmaceuticals, Amicus, Argenx, Bristol-Myers Squibb, Catalyst, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech,

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The other authors have declared no competing interests.

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