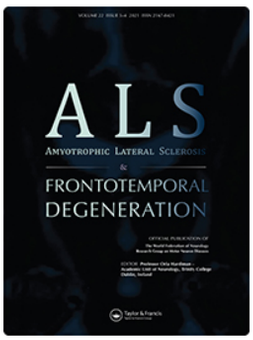

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RESEARCH ARTICLE

Challenges and opportunities for Multi-National Investigator-Initiated clinical trials for ALS: European and United States collaborations

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Abstract

An inherent challenge to clinical trials that aim to test the efficacy of experimental therapeutics for patients with amyotrophic lateral sclerosis (ALS) is the relative rarity of the disease. A promising solution to this problem is a multi-center approach that ideally includes sites distributed across a broad geographic area. In support of such an approach, the European E-RARE program and the United States National Institutes of Health (NIH) partnered to support the investigator-initiated ROCK-ALS trial (Eudra-CT-Nr.: 2017-003676-31, NCT03792490) as a multi-national collaboration between centers in Europe and North America that is led by European investigators. During the set-up of this international trial, however, a number of unanticipated legal, administrative, and financial complexities emerged that required significant adaptation of the proposed trial scheme. Here, we report our experience navigating these obstacles and describe the potential solutions that we explored. Our experience may inform future efforts to implement multi-national investigator-initiated trials that involve both European and United States centers.

Keywords: *Clinical trial, sister trials, rare disease, international, regulatory*

Introduction

Clinical trials for rare diseases benefit from the contribution of multiple centers for successful recruitment of patients fulfilling restrictive inclusion/exclusion criteria; this frequently requires the involvement of an international consortium (1). Expertise from various highly specialized centers increases the scientific quality of the data by

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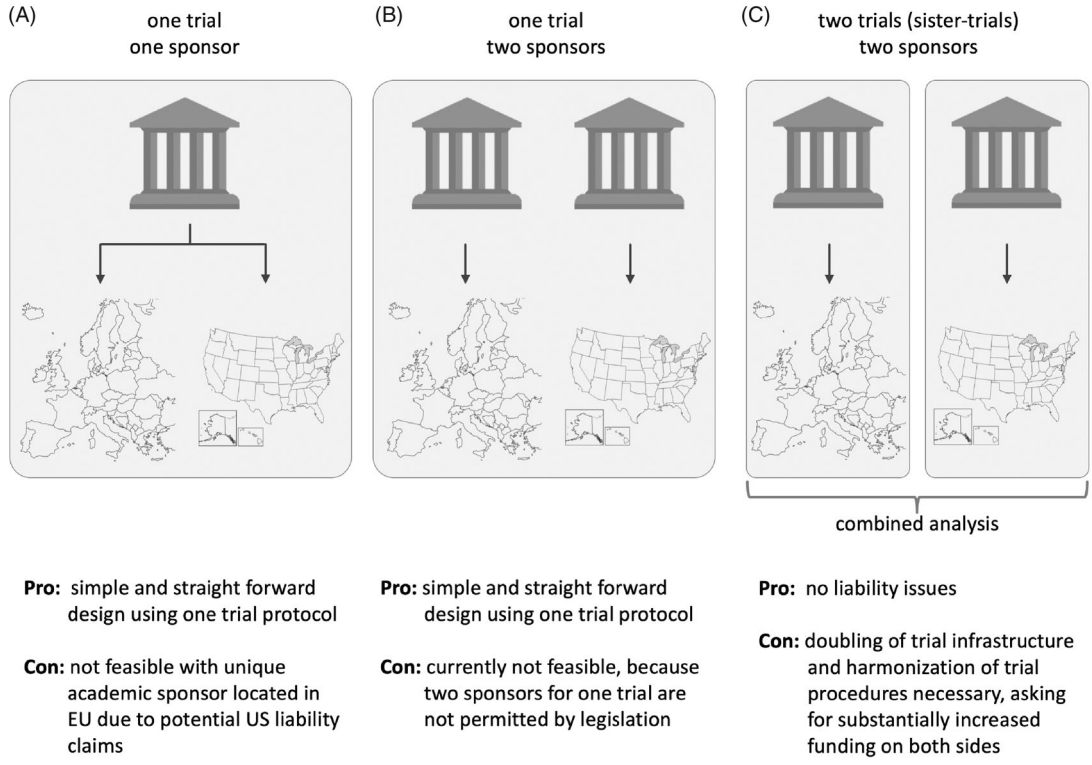

Figure 1. Concepts for the integration of academic European and US centers in clinical trials. (A) One trial, one sponsor: a joint clinical trial in Europe and the US is supported by a single sponsor that could be located in either country. (B) One trial, two sponsors: a joint clinical trial with one sponsor located in Europe and another based in the US. Responsibilities are split between the two sponsors. (C) Two trials, two sponsors: two separate clinical trials with independent sponsors are conducted in the US and in Europe, but both share the same trial protocol and agree on a subsequent combined analysis of data and joint publication.

exchange of research ideas, scientific techniques and tools. Participation of patients from different geographical, social and ethnic backgrounds equally adds to the value of trial results and yields more generalizable evidence than a trial confined to a single geographical location. Even in terms of budget, it is more cost-effective to perform a shorter trial with sufficient and constant patient recruitment than to rely on single national centers where patient recruitment may take many years (2). Long recruitment periods can also negatively affect data quality for example due to evolving standards of clinical care.

ROCK-ALS (Eudra-CT: 2017-003676-31, NCT: 03792490) is a multi-center investigator-initiated academic phase IIa trial evaluating the safety, tolerability and efficacy of the Rho kinase (ROCK) inhibitor Fasudil in patients with amyotrophic lateral sclerosis (ALS) that started to recruit patients in 2019 (3). Originally designed as a multi-national study in the scope of the European E-Rare call 2016, the NIH provided supplementary funding to the Clinical Research in ALS and Related Disorders for Therapy Development (CReATe) Consortium, with the goal of adding US centers to this international investigator-initiated clinical trial. Whereas the set-up of the trial in the three European countries (Germany, Switzerland, France) adhered to national and/or EU legislation, the establishment of mutual trial procedures with the US sites was challenging and required an intensive interaction between the European lead site and the team from the US. Although the initial application included two US sites as patient-recruiting trial sites in the ROCK-ALS trial (Figure 1(A)), this approach eventually failed to secure approval by the European academic sponsor because of unresolved issues in regard to liability, data protection, drug procurement, among other factors. Subsequently, we considered the concept of two sponsors for a single clinical trial: a European sponsor for the European sites and a US sponsor for the US sites (Figure 1(B)). This option, however, was not viable given current legislation. Finally, we evaluated the option of conducting two separate, parallel trials: one in European countries (ROCK-ALS) and one in the US (ROCK-ALS-US), with a pre-specified plan to merge the data from both trials through a combined meta-analysis (Figure 1(C)). This approach, although feasible, would have required the establishment of two separate trial infrastructures in Europe and the US. Even though funding from the NIH had been sufficient to support two US sites for trial recruitment, it was insufficient to support the establishment of an independent and parallel clinical trial. For this

reason, both EU and US members of this collaboration eventually concluded that this approach would not be viable within the available funding scheme.

We felt it would be valuable to share our experience on the set-up of ROCK-ALS as a multi-national transatlantic investigator-initiated trial (IIT), with other researchers, who may be interested in or are already involved in the preparation of a multicenter clinical trial. Here, we present a summary of trial set-up related considerations, which emerged as challenges. We also propose potential solutions for each of these factors and make suggestions for an optimization of trial procedures, particularly for multinational academic IITs involving European and US-American centers.

Challenges in the design of multinational clinical trials

Sponsorship and liability

Since the sponsor takes the overall responsibility for a clinical trial, (s)he is also liable for any potential indemnity claims resulting from the clinical trial on an institutional or individual level. Academic institutions in Europe have to negotiate a trial insurance with an insurance company, the terms of which depend on the individual risk and number of patients, whereas institutions in the US are usually covered by their institutional liability insurance. In contrast to the US, where coverage lacks national standards, insurance in Europe differs from country to country (4); in Germany for example, the minimum compensation sum is 500,000 EUR per trial participant (5). A European academic institution that sponsors a trial involving sites in the US would inevitably have to take the risk of unlimited liability, which would only rarely be accepted. On the other hand, this constellation would be less problematic if the sponsorship were to be held by an academic institution in the US. An alternative approach would be shared sponsorship between US and European institutions. While this option may be feasible in the future after implementation of the Clinical Trial Regulation EU No. 536/2014 into national laws, the currently valid EU Clinical Trial Directive (EC) No. 2001/20/EC does not permit two independent and parallel sponsors for one single clinical trial (6). Sister trials with two independent sponsors circumvent these sponsorship issues, but require an extensive harmonization of trial designs, which are discussed subsequently. Since industrial sponsors, regardless of their location, act on their own private liability, this issue is of particular relevance to academic sponsors.

Assessment by ethics committees and regulatory authorities

For a given clinical trial, the decision of the lead-ethics committee serves as a guideline for all other participating ethics-commissions. By contrast, sister trials would rely on independent assessments from two ethics-committees/IRBs. It is possible, perhaps even likely, that each ethics-committee will require different modifications, perhaps leading to divergence in some aspects of the protocol, yielding differences that may be challenging to fully harmonize. Although this challenge is not unique to sister trials or to a trial that entails an EU/US-cooperative arrangement, the harmonization of protocols for two legally independent trials may be more difficult than the resolution of diverging views of multiple ethics-committees/IRBs for a single trial. One solution would be the appointment of one central IRB which could coordinate the activities of the different IRBs in each participating country or to appoint two IRBs that closely and directly coordinate their country-specific activities. For example, the Voluntary Harmonization Procedure (VHP) within the European Union fosters a single approval process. Initially this regulation considered only the procedure between the competent authorities of those Member States where the clinical trial is carried out. Today, the participation of Ethics Committees is possible for some participating member states. Central IRBs have emerged as common models in the US, especially since the NIH requires this approach for all NIH-funded multi-center studies in the US. To our knowledge, however, the central IRB model has not yet broadened to encompass oversight of trial sites across national boundaries.

Biometry: sample size, power and stratification

The necessity to perform two separate clinical trials with a subsequently combined analysis requires sample size to be sufficient within each trial to yield appropriately powered studies. Each power calculation would have to be based on the respective primary endpoints, which presumably would be the same for each study. Two independently powered trials would inevitably yield a greater number of subjects overall than would be needed if power calculations assumed combined analysis of data from both trials, and overall trial costs would also be significantly higher. Regulatory authorities, however, might not accept two under-powered sister trials, even with the pre-specified intent to combine results from both trials in a meta-analysis. Stratification for randomization according to geographical regions and disease strata (e.g. spinal vs. bulbar onset in patients with ALS) also is a challenge: assuming sister trials, both would have to be

performed in an independent fashion, but the allocation of disease strata could become unbalanced, particularly if one of the trials has significantly lower patient numbers.

Drug procurement

Procurement of the trial medication is a critical point for interventional drug trials. Sister trials that use the same trial medication have to ensure that the formulation of the drug is identical for both trials. Ideally, this requirement can be achieved by using a central drug supplier, such as the identical manufacturer or central trial pharmacy. It has to be kept in mind that suppliers must comply with the requirements of various countries and possibly report to different agencies, e.g. the BfArM (Germany), swissmedic (Switzerland), ANSM (France) and the FDA (USA), in the case of ROCK-ALS. One central trial pharmacy would be possible for centers located in Europe, but a separate trial pharmacy as well as a separate drug importer would be required for additional centers in the US.

For both trials, a sufficient inventory of study drug has to be maintained. A central supplier can be instrumental also to keep costs for trial medication to a minimum, because this would avoid the need to keep excess trial medication in stock for both trials. In the case of one central supplier, differences in shipment times have to be acknowledged, particularly for drugs with a short shelf-life, and formulations will have to be adapted to longer shipment times. Likewise, costs for drug transport can be increasingly high, particularly if drugs have to be prepared and shipped in an individual fashion for each individual patient. Even if drug shipment occurs at room temperature, it requires temperature-controlled shipment and temperature logs adding to the costs. Finally, drug labeling has to be harmonized between countries, but at the same time comply with national regulations.

Concomitant medication

Regardless of who takes on the sponsorship, trial sites in the US and Europe may face differences in permitted concomitant medication. In the case of a trial in ALS, riluzole is a licensed and permitted concomitant medication in both the EU and the US. Edaravone, however, is approved for the treatment of ALS in some countries, such as the US and Switzerland, and could not be withheld on ethical grounds, whereas it is not licensed in the EU. These differences might result in heterogeneity of the trial population diluting possible disease-modifying effects. The use of concomitant medications should thus be harmonized as much as possible, acknowledging differences as potential confounding factors.

Processing of data and biomaterial, implementation of EU general data protection regulation (GDPR)

Clinical trials use electronic data capture (EDC) systems to enter data into electronic case report forms (eCRF). In multicenter international trials, patients will have to give consent that their data is possibly transferred and processed abroad. According to the recent EU GDPR effective as of May 25th 2018, patients form the EU are entitled to request a copy of data that are stored as well as deletion of these data (7,8). US institutions that are processing data from the EU have to comply with the EU GDPR, which requires additional administrative review. Anonymization, which entails complete de-identification and irreversible stripping of linkage between identifiers and codes, is the best way to protect a patient's identity, but usually is not a practical solution for clinical trials. In multicenter trials involving EU and US centers, the consent form will be more complex than in a single-country setting and must reflect the possibility that data/biomaterial will be handled in other countries, possibly also those that are not compliant with EU-GDPR. Under these conditions, some patients may refuse to give consent, which might threaten recruitment. Moreover, many US institutions have struggled to establish mechanisms and processes for GDPR compliance given complexity and cost.

Similar issues arise from the collection and storage of biological materials (e.g. DNA) in the course of the trial. This would either require duplicate biobanks (one in the US and one in the EU), or trial participants would need to be informed that their samples might be stored in a different country, with attendant requirements for informed consent and administrative approvals.

Monitoring

Monitoring plans can be harmonized between countries in one unique trial, but may differ depending on the ethics committee's assessment of the risk analysis in the case of sister trials. This may affect both the number and the type of site visits (remote or in person) and thus have consequences for data integrity in both trials, which is of particular importance when data with different monitoring quality will be merged in a subsequent meta-analysis. Monitoring plans should thus be harmonized as much as possible to ensure similar data quality.

Reporting of serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR)

Although in the case of two separately initiated sister trials both are formally independent and would each follow separate pathways for reporting of

Table 1. Summary of trial-relevant topics that may represent an obstacle in the design and conduct of multi-national clinical trials.

Topic	Recommendations to academic trialists	Recommendations to institutions
Sponsorship, liability	Resolve sponsorship issues before proceeding with any other trial preparations; consider sister trial design	LEG: Implement legislation on double sponsorship for academic trials
Ethics assessment	Consider the need to adapt trial documents for submission to different authorities and to incorporate changes rapidly	EC/IRB: Ethics committees/IRBs should be able to formally cooperate on the assessment of sister trials
Regulatory assessment	Consider the need to adapt trial documents for submission to different authorities and to incorporate changes rapidly, consider making use of the voluntary harmonization procedure (for EU member states)	NCA: harmonize decisions with other NCAs in order to facilitate academic clinical trials, keep processing times to a minimum
Biometry	For sister trial design: perform power calculations considering both trials, provide explanations for underpowered sample size in each sister trial to the review boards; describe plans for the meta-analysis.	EC/IRB: acknowledge meta-analysis of sister trials as strategy to acquire sufficient patient numbers in two formally independent trials FA: educate reviewers and funding agency about potential need to evaluate power considerations across two sister trials
Drug procurement	Ideally identify one central pharmacy providing trial drug and capable to address the requirements of multiple countries	NCA: Harmonize regulations and requirements for drug usage in clinical trials. Support international drug recognition agreements.
Concomitant medication	Consider licensed medication in all participating countries and anticipate market authorization of new drugs, include strategy to control for potential confound of differential use of concomitant medications	EC/IRB: take into account different approvals in participating countries, e.g. when licensed drugs shall not be withheld on ethical grounds
Processing of data and biomaterial	Identify data and material flow, include information in patient information material, consider EU GDPR	AI: implement procedures to comply with EU GDPR in US/EU cooperations
Monitoring	Sister trials: agree on joint monitoring plan considering particularities of each trial	EC/IRB: acknowledge that monitoring plan may also be influenced by sister trial
Reporting of SAE/SUSAR	Agree on pathways to inform both trials (in case of sister trials) about reported safety issues	NCA: implement international exchange of safety data for trials with the same active drug
Language	Consider the need for translation costs for official documents to be submitted to authorities	AI: Enable multi-lingual processes in contracting.
Trial budget	Anticipate increased expenditures due to double structures	FA: consider the need for higher costs in multi-national calls
Time lines	Select communication platform permitting rapid information exchange and turnover of documents	FA: Enforce rapid handling of funding applications

Recommendations to academic trialists and respective authorities are listed. LEG: legislators, national parliaments. NCA: national competent drug authorities, e.g. BfArM (Germany), swissmedic (Switzerland), ANSM (France) or the FDA (USA). EC/IRB: ethics commission/institutional review board; FA: funding agencies; AI: academic institutions.

SAEs and SUSARs, it is evident that both trials will benefit from sharing such information that arises in the other respective trial following a similar trial protocol. This may be particularly important for events with a rare occurrence, which may reflect a pattern of SAE/SUSAR only when aggregated between trials. Appropriate reporting pathways would have to be implemented to allow for notification of the corresponding sister trial team in a timely manner.

Language/translation

English is mostly used as common language for source documents in clinical trials even in natively non-English-speaking countries. However, multinational consortia have to make sure that all patient-related material, i.e. ICF, information brochures, web pages, are also available in the native language in order to be readily understandable by all patients. The same is true for information material that is distributed to general practitioners and patient organizations, e.g. for purposes of patient recruitment. Costs for professional translation of such documents must be budgeted. Last, but not least, the customary use of the metric versus non-metric system in the EU versus the US, respectively, has to considered for implementation in the data capturing interface.

Trial budget

In contrast to a trial with one sponsor and multiple trial sites, sister trials would require in most cases

the duplication of at least a part of the trial infrastructure and thus come with the respective increase in cost. This has to be considered from the very beginning of the design of such a trial in order to negotiate a larger and more realistic budget or to acquire additional support from supplementary funding sources. While this may be a less pertinent problem for industry-funded trials, as clinical trial budgets for industrial studies are often well above what academic sponsors can provide, funding agencies for academic IITs should be aware that trials that are set-up in this manner will need a larger budget than allocated to a trial with one sponsor. Funding schemes need to be flexible to adapt to these needs.

Conclusions

We are aware that not all considerations described above can be resolved in an optimal manner and not all aspects are currently covered by legislation that facilitates cooperative trials between sites in the EU and the US. Moreover, studies involving sites in the UK also have to consider the consequences of BREXIT, such as the need to establish a legal representative in the EU or the need for batch release in the EU (9). Based on the foregoing, therefore, we propose solutions that are intended as support to academic trialists who consider undertaking multinational trials. Furthermore, our recommendations also address legislators, regulatory, funding authorities, and academic institutions as they can provide the framework conditions for the successful implementation of clinical trials (Table 1). Other suggestions for improving the design of future ALS clinical trials, such as the use of biomarkers, the implementation of prediction models, or the use of harmonized, adaptive trial designs, have recently been discussed by members of the TRICALS consortium (10).

Multinational cooperations for clinical trials have multiple advantages, particularly in the field of rare diseases, ALS being just one example. In many respects, industrial sponsors face identical challenges as academic institutions, such as dealing with data privacy or SAE reporting. However, budget constraints and liability issues can make study set-up more difficult and even completely impossible for the latter. However, the fact that many academic research institutions as well as funding agencies are unfamiliar with different national regulations, can complicate or even make the design and implementation of multinational clinical trials impossible. This is particularly true of cooperation between academic centers in the EU and the USA, whereby European sponsorship represents an additional hurdle due to possible liability issues. Even though clinical trials are, *per se*, cost-intensive, the need to adopt multinational regulations further increases costs, which particularly disadvantages academic research and investigator-initiated trials that are already limited by the budgetary restrictions of public funding. Academic trialists therefore have to consider multiple aspects in the design of multi-national clinical trials and pay particular attention to the question of sponsorship, as it has major implications for all subsequent issues of trial design. Authorities involved in the regulation, administration and funding of clinical trials are encouraged to acknowledge these obstacles and implement regulations that facilitate the design and conduct of multi-national clinical trials.

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Author contributions

All authors have contributed to design aspects (PL, JCK, MB), administrative preparation (CH, TLa, RA, RT) or local implementation (SH, JW, ER, RG, BI, JKa, KK, JKu, AL, TLe, TM, CN, JS) of the ROCK-ALS trial (Eudra-CT-Nr.: 2017-003676-31, NCT03792490).

Disclosure statement

As potential conflict of interest, we report that PL is listed as inventor on a patent held by the University Medical Center of Göttingen on the use of fasudil for the treatment of ALS (EP 2825175, US 9980972B2). The other authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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