



Relocation of study participants for rare and ultra-rare disease trials: Ethics and operations

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ARTICLE INFO

Keywords:

Relocation
Assistance
Clinical trials
Ethics
Rare disease

ABSTRACT

Clinical trials for investigational new products to treat rare and ultra-rare diseases typically involve a limited number of research sites recruiting from a small pool of patients dispersed over a large geographical area. When remote access is not possible and participants must be present at a trial site, participation in research may require individuals and their families/caregivers to travel great distances, often at significant cost personally and financially and, frequently, for the duration of the trial. This article addresses the ethical and practical issues associated with the practice of sponsors offering financial and other assistance for relocation to trial sites from significant geographical distances, providing both foundational analysis of the ethical issues as well as actionable policy-level guidance on how to best approach these situations.

1. Background

Clinical trials of investigational products for rare and ultra-rare diseases may involve a limited number of research sites recruiting from a small pool of patients dispersed over a large geographical area. Definitions vary, but in the United States a 'rare' disease is generally considered one affecting less than 200,000 people in the U.S., while the European Union defines a 'rare' disease as one that affects fewer than five patients per 10,000 people and an 'ultra-rare' disease as affecting one patient per 50,000 people [1–4]. When remote participation in clinical trials for these populations is not possible and participants must be present at a trial site, participation may require patients and their families/caregivers to travel great distances, often at significant cost for the duration of the trial. In such cases, study sponsors are sometimes willing to provide financial and other support to relocate eligible individuals to an established trial site and underwrite the costs of participation.

Under what conditions would it be ethically acceptable for sponsors to provide such support? What are the risks of offering such support and what appropriate safeguards help mitigate them? If financial support is acceptable, how much is appropriate and advisable? What are the appropriate ethical and process considerations that should guide these decisions and interactions among and between sponsor, investigator,

and participants?

While the practice of paying people to participate in research is a perennial topic of debate [5–10], the ethical and practical considerations related to relocation have received far less attention. Generally, participants should not undergo financial sacrifice for their participation and contribution to science; at the end of trial, they should not be economically "less well off" for having borne the expenses directly associated with research participation. This expectation is supported by the revised Council for International Organizations of Medical Sciences (CIOMS) guidelines as well as United States Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP) guidance, all of which clarify that reimbursing participants for costs incurred as a direct result of participation is ethically permissible, does not raise concerns about undue influence, and indeed (in the case of CIOMS and OHRP) is desirable [11–14]. However, it is not clear whether or how reimbursement and other payment practices should apply when participation requires lengthy regional or international travel and with it long-term housing, meals, and other forms of social supports.

In this article, we examine the ethical and practical issues encountered by research sponsors when providing financial support for participants to travel significant distances to participate in clinical trials. Our focus is on cases where individuals relocate for the duration of the study but the same analysis would apply to situations where

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<https://doi.org/10.1016/j.cct.2019.105812>

Received 3 January 2019; Received in revised form 7 July 2019; Accepted 11 July 2019

Available online 19 July 2019

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individuals relocate for part of a study or make one or more trips to the study site from significant distances. In [Section 2](#), we present a case study illustrating the types of situations in which relocation may arise and the ethical and practical challenges it may present. In [Section 3](#), we enumerate four threshold considerations that should be addressed before relocation is considered a live option. [Section 4](#) examines how foundational ethical norms apply to offers of relocation and their implications for the practice. [Section 5](#) addresses practical issues, advancing points to consider at each stage of the relocation process and providing actionable guidance to sponsors and other stakeholders considering offers of relocation.

2. Case study

Spinal Muscular Atrophy (SMA) is a rare genetic disease most commonly caused by a mutation in the SMN1 gene on chromosome 5. The disease is characterized by loss of motor neurons and progressive muscle weakness. SMA type 1 is a severe, life-threatening condition affecting infants and very young children, typically diagnosed during the first few weeks to months of life when babies do not meet motor milestones [15].

Roche Pharmaceuticals is conducting a multicenter, international, open label clinical trial to assess the use of an orally-available investigational medicine in babies aged 1 to 7 months with SMA type 1 ([ClinicalTrials.gov NCT02913482](https://clinicaltrials.gov/ct2/show/study/NCT02913482)) [16,17]. All patients receive the investigational medicine. Conducting the trial requires special expertise and placed limits on the number and geographical location of trial sites that could be opened; therefore, initial trial sites were those with the highest level of clinical expertise in this rare disease. It became possible to open more study sites in additional locations during later stages of research.

When the trial started, there were several other clinical trials available for children with SMA, but no approved treatments. As study recruitment began, nusinersen, an intrathecal agent shown to improve the course of clinical progression in SMA, was approved by the US FDA and was under regulatory review in several other countries. Despite subsequent approvals in several countries, there were still patients who lacked access to treatment or who were not candidates for intrathecal administration. Early treatment, however, is necessary in this disease, to prevent irreversible and progressive loss of function. If treatment is successful, lifelong administration may be necessary.

Given the rarity of the disease, trial sites in limited regions, and availability of nusinersen in some countries, the study was difficult to enroll. However, parents in several countries, including developing countries, became aware of the trial via patient advocacy groups, their doctors, and the internet, and contacted investigators asking if children could travel to trial sites to participate in the study. Given the high unmet medical need of children with SMA and the importance of running the trial, Roche was willing to support travel and the costs of participation for infants and their families, even across international borders, when there were not study sites nearby and it was not feasible to open them in the region.

As this case study helps illustrate, a number of challenging ethical and logistical questions characterize situations where offers of relocation may be considered. When or under what conditions would an offer of assistance be acceptable? What, specifically, should such an offer include by way of support? What are the considerations that should guide these decisions?

3. Threshold considerations preceding relocation

Before relocation is entertained, several specific considerations that apply in many rare or in ultra-rare disease settings should be addressed. To start, the trial should typically address an unmet medical need. The FDA defines filling an ‘unmet medical need’ as “providing a therapy where none exists or providing a therapy which may be potentially

better than available therapy” (FDA). It is important to note that recruitment for rare and ultra-rare disease trials that meet this condition may nonetheless be challenging, and that the importance of enrolling enough participants to complete the study and successfully answer the research question—which is needed to make progress toward actually addressing unmet medical need—may provide initial motivation and grounds for relocation.

Second, alternative means of enabling participation by bringing the study to the participant should be considered. The most obvious of these is to add an additional site in regions where there is unmet need. However, it may not be feasible for sponsors to establish additional sites, due to infrastructure and logistical limitations, such as lack of specialized technologies or expertise (as in the case example). Other means that should be explored before relocation include enabling remote participation or, when there is sufficient supporting clinical data, facilitating expanded access to the investigational intervention.

Third, sponsors should consider whether relocation itself could impact the study outcome measures by contributing to differential responses between relocated versus non-relocated participants or other benchmarks. Such differences could be secondary to changes in social factors experienced by relocated individuals, such as having access to a different diet, living conditions, or social supports (either better or worse) than what they are used to. Sponsors and investigators should also consider whether there are known regional differences in treatment response and whether relocation could affect treatment response and analysis, for example, by contributing to a placebo effect in relocated participants.

Finally, any proposal to relocate individuals should be approved by the ethics committee overseeing the study in the jurisdiction where the research is conducted. Additionally, involving local ethics committees and other oversight bodies in the relocated individual's region of origin may sometimes be advisable (although not obligatory), given the potential for different cultural understandings and expectations between sponsors and participants, which local IRB review may help mitigate. Should relocation for clinical trial participation become more common, a global bioethics discussion on the obligations and interplay of oversight bodies in origin and destination locales may be needed.

4. Foundational ethical analysis

Relocation is not specifically addressed in regulatory guidance or international research ethics guidelines. In our view, the central ethical question with offering assistance for relocation is not whether it is obligatory. Because participants do not have an affirmative right to participate in research, there is no corresponding obligation to facilitate research participation by supporting relocation in these situations. Rather, relocation is an entirely elective action on the part of sponsors. The question is under what conditions it is acceptable or advisable and, importantly, whether any negative unintended consequences can be mitigated. Clarity can be gained on these points by thinking through relocation in terms of foundational research ethics principles.

4.1. Autonomy: informed consent and undue influence

A basic concern with paying research participants generally, reflected in both U.S. regulatory guidance and the bioethics literature, is that offering payment may unduly influence prospective participants, by clouding evaluation of the risks of research or otherwise distorting decision-making in a way that undermines autonomous and valid informed consent [13,14]. While IRBs are often wary of payment on this basis, it is, in our view, not clear how much weight this concern *should* carry, given a general lack of empirical support for the premise that payment hinders valid informed consent to participate in research [18–20]. There are, moreover, often ways to mitigate the risks of payment short of limiting payment offers, such as placing safeguards around informed consent and close attention by the IRB to eligibility

criteria and risk-benefit analysis.

Nonetheless, it is worth considering whether relocating participants from great distances may exacerbate the risk of undue influence. Covering reasonable out-of-pocket expenses associated with research participation is generally acceptable. Nonetheless, assistance for relocation may appear especially attractive if it carries the prospect of having one's basic needs, such as food and housing, cared for, potentially impacting voluntariness and making valid informed consent more challenging. It may also raise distinct concerns, such as tempting individuals to deceive about their eligibility for the study. Such risks may be exacerbated for individuals who are economically disadvantaged or reside in less developed or less stable regions. In these situations, relocating to a trial site may provide significant non-material benefits, such as access to better health care and greater security and opportunity, for the duration of the study. Moreover, while we do not assume that individuals will be eager to uproot themselves from their home and community, in some cases relocating may provide an opportunity for individuals who desire to permanently leave their home region to do so, even if this is not the intent of relocation and proactive measures to address it are in place, as they should be (see below, [Section 5.3](#)). In these cases, it may be the relocation itself, or non-monetary goods connected closely with it (e.g., better opportunity) that increases the risk of undue influence beyond what it would typically be when reimbursing participants for local travel and the like.

Such non-monetary benefits should be considered when assessing the potential for undue influence in these cases. It should not, however, be assumed that these benefits unacceptably increase the risk of undue influence or provide ethically inappropriate motivation. As with monetary payments, non-monetary benefits may be an appropriate source of motivation for trial enrollment, and this is no less true in cases of relocation [7,10,14]. The important question is not whether the prospect of receiving monetary or non-monetary benefits motivates a decision to relocate for trial enrollment, but whether it distorts judgment and leads to an ill-informed choice to do so.

In this regard, situations involving economically disadvantaged or otherwise vulnerable individuals undoubtedly require safeguards such as ensuring that the relevant consent documents are translated into the language of the prospective participant, that someone knowledgeable in clinical research and fluent in the native language conducts the consent process, and that the consent process includes mechanisms for evaluating and improving understanding. At the same time, we know of no empirical evidence suggesting that payment is more likely to distort decision-making or hinder informed consent for research among vulnerable populations or individuals in less developed regions, and it would be objectionably paternalistic to assume that the risk here is greater than elsewhere. Moreover, denying vulnerable individuals the potential benefits of relocation is a dubious way to address concerns about undue influence. Doing so amounts to further curtailing opportunities for people who already have limited options and making a bad situation even worse [21]. Instead, attention should be paid to context and whether there are ways to sufficiently mitigate the risk.

4.2. Beneficence: unmet medical need

As stated earlier, relocation will typically only be advisable when there is an unmet medical need that study participation may help to alleviate. In line with FDA's definition of 'unmet medical need,' we take this to mean that the study itself must ask and have the capability to answer a question relevant to advancing discovery of a novel or better treatment than what currently exists. Additionally, studies should hold the prospect of directly benefiting participants for relocation to be considered a live option. This is because of the risk that individuals willing to relocate for studies with remote or no prospect of direct benefit may suffer from a therapeutic misconception (i.e., over-estimating the chance that the trial will benefit them) that is incompatible with valid informed consent, or desire relocation for reasons not

connected to trial participation, which may exacerbate concerns over undue influence.

As the case example above shows, there may be unmet medical need even when approved interventions exist, due to those interventions being unavailable in certain regions because of cost, safety concerns, or insufficient medical infrastructure. Even when an approved intervention is available in the individual's home region, it may only be available in a form that is prohibitively expensive, more difficult to administer, portends higher risk, or has greater medical drawbacks than interventions available in clinical trials outside the region. Similar considerations hold for unapproved treatments tested in clinical trials. Even if there are accessible local trials, they may have less favorable risk-benefit balances or otherwise fail to address the need as well as a trial requiring relocation. In our view, these all may count as cases of unmet medical need in which beneficence may support relocation and that should be evaluated on a case-by-case basis.

While there is no obligation for sponsors to offer assistance, beneficence does require sponsors to refrain from abandoning participants. The extent of these obligations and exactly what they require (i.e., what exactly should be provided and for how long) may be controversial. In all contexts, we believe beneficence supports enabling post-trial access to promising or successful study therapy, in line with the Declaration of Helsinki and other guidelines [22,23]. In the context of relocation specifically, it also supports providing adequate assistance to enable participants to travel back to their home region once the trial is complete. Sponsors who choose to offer assistance for travel to the trial site but not assistance for travel back home could, with justification, be accused of abandoning participants by enabling participation in the study without adequate concern for their well-being once the study is complete, specifically, how they will return to their home region.

4.3. Justice: enabling access to research

Consistent with the Belmont Report [24], justice in research is often considered in relation to participant selection and ensuring that the risks and benefits of research participation are distributed equitably among individuals and social groups. When individuals reside in a locality that is underdeveloped in terms of global standards for health and well-being, relocation coheres with justice by enabling access to clinical trials for people who may not otherwise be able to participate in them.

At the same time, concerns may be raised that assistance for relocation to people in developing countries risks exploitation, by potentially capitalizing on a lack of local therapeutic options in those locales. We take this concern to be more than that the ancillary goods of research participation (e.g., standard medical care and screenings) could influence someone to relocate, since this dynamic is present for all trials and does not require protections beyond the typical ones operative here (notably, IRB approval). The concern must rather be that individuals may be motivated to relocate only because the trial offers them an existing treatment that is not available to them but that should be and, under more just conditions, would be.

However, such cases will be the exception in the context of rare and ultra-rare disease trials that meet the previous condition of addressing an unmet medical need. Many trials for rare conditions seek to discover an effective standard of care where none exists, in which case participating in the trial may be an individual's best therapeutic option. Moreover, as the case study shows, even when an approved intervention exists, there may be intractable obstacles to making it available to everyone who needs it, due to complexities in (for example) route of administration, available expertise, infrastructure, and the like. In these situations, an offer of relocation may be the best live option available to people in need and does not obviously conflict with principles of justice, given that the limiting conditions are not due to, and indeed are beyond the control of, sponsors offering relocation assistance. So long as careful consideration is paid to mitigating the risk of undue influence, offers of relocation need not raise concerns about fairness or exploitation.

Justice is also relevant for determining how much financial support to offer for relocation. In our view, it is ethically desirable to offer at least some support in most or all cases, based on the same principles that support expense reimbursement in more typical situations. In general, because research is not clinical care and involves volunteerism without guarantee of benefit, participants in research should not be expected to make financial sacrifices but rather be kept financially whole. Offering support acknowledges the costs of relocation and participation that would otherwise be borne by these individuals, as well as their valuable contribution to socially important research, and is to that extent desirable, fair, and supported by justice.

5. Policy and process

Different process and policy questions around relocation may arise at different phases in the clinical trial life cycle.

5.1. Initial sponsor program decision

The initial sponsor program decision concerning relocation involves, most basically, a choice about whether to offer assistance and, if so, what levels of support to provide. The following recommendations and points to consider may be helpful in guiding sponsors, in concert with sites, through these decisions.

- Sponsors should first consider bringing the trial to the patient by enabling remote participation, opening additional sites, or, when there exists sufficient clinical evidence, enabling expanded access programs. If insufficient infrastructure or lack of available expertise make these approaches infeasible, relocation may be considered a workable option.
- Sponsors should proactively determine whether any assistance offered will be limited to the participant only or participant plus one or more family members, such as parents, guardians or caregivers, and siblings.
 - o Supporting family members will typically be necessary for pediatric studies and for persons with impaired decision-making capacity; these situations may require greater protections.
- With respect to determining types and levels of assistance, it is important for sponsors to be consistent within a given study and transparent about the methodology and process for payment.
- Sponsors should, when possible, strive to cover the out-of-pocket costs of participation and retain financial equilibrium for participants.
 - o It is reasonable for reimbursement policies to reflect the fact that some individuals may travel further distances at greater expense than other participants. What is important is not that the specific amount reimbursed be the same across all participants but rather that the principle remain the same (e.g., “All participants will be reimbursed at x rate for expense types y and z”).
- Whenever complete reimbursement for out-of-pocket expenses is not possible, less robust offers of assistance are still desirable.
 - o In these cases, sponsors may offer assistance based on the economic need of particular individuals, resulting in different degrees of assistance between different participants in the same study. However, the underlying principle should be consistent and clearly communicated to dispel concerns about fairness or transparency.
- Sponsors should proactively determine the types of expenses and whether and how much support will be provided for:
 - o Travel arrangements including air travel and ground transportation
 - o Cost of travel visa(s) or other immigration-related expenses
 - o Accommodation and short-term hotel
 - o Medical travel insurance and medical expenses other than those associated with the clinical trial.

- As a best practice, sponsors may offer medical insurance coverage to participants and (when relevant) immediate family members to guard against situations where a participant or family member experiences illness or other medical event unrelated to the research.
- o Costs of child care for pediatric participants or children of adult participants when the child's parent(s)/caregiver(s) choose or need to work.
- o Cost of schooling for pediatric subjects and/or child family members of relocated participants.
- o A separate living stipend to cover the costs of groceries, local travel, and other miscellaneous expenses.
- For each type of expense above, sponsors should determine whether ceilings on assistance amounts will be set in advance and, if so, what the ceilings will be.
- Sponsors should determine whether financial payment will be by reimbursement, stipend, pre-paid debit cards, or some other mechanism.
- Sponsors, in conjunction with the sites that enroll relocated individuals, should determine who will pay for expenses if the participant fails to enroll (e.g. is not eligible) upon arrival at the site or withdraws early from the trial.
 - o Sponsors and sites should have policies in place for managing situations where relocated individuals screen fail on-site; the policies should address assistance and timing for travel back to their home locale.
- Sponsors, in conjunction with the sites that enroll relocated individuals, should determine whether there will be oversight of the assistance process, and, if so, who will provide it.

5.2. Recruitment and screening

Sponsors, in concert with sites, should determine the parameters of offers of assistance before recruiting candidates for relocation into the trial. The recruitment phase raises several important issues that deserve close scrutiny.

- Sponsors and sites should take steps to ensure eligibility by way of remote screening processes before initiating relocation.
 - o Eligibility criteria should be clearly defined and, whenever possible, objective measures should be used to determine the eligibility of candidates before relocation. Such measures might include screening for eligibility by medical third parties in the participant's home geographical locale, when possible, followed by re-evaluation and confirmation of eligibility at the trial site.
 - In situations where the individual arrives at the trial site and is determined to be ineligible, neither the sponsor nor the site has an obligation to facilitate access to alternative trials or therapies, should they exist. The sponsor's and site's respective approaches to these situations should be considered beforehand and disclosed to the individual before travel relocation takes place.
 - Emphasis on remote screening and determining eligibility before travel may mitigate concerns about the perceived benefits of relocation motivating individuals to deceive about eligibility for trial enrollment or otherwise ‘game’ the system. This is less of a concern for disorders where there is a high confidence in the diagnosis (such as a genetically or biopsy-defined disorder).
- Early in the recruitment process, sponsors and sites should be transparent about their intent to offer assistance, for whom assistance will be offered (participant only or family members as well), the types of expenses supported, and the ceilings on assistance amounts.
- Sponsors and sites should incorporate safeguards around informed consent throughout the process, which can mitigate the risk of undue influence.

- o Such measures should include reliable translation services, when applicable; and measures, such as quizzes and teach-back, to ensure comprehension of the parameters of assistance, the risks of the research, expectations that the participant will return to their home locale, and expectations around the extent of the sponsor's post-trial obligations.
- o Emphasis should also be placed on the fact that the individual is being relocated for medical research, not established care or proven therapies, which may help to temper the risk of therapeutic misconception.

5.3. Relocation

Once eligibility has been confirmed (to whatever extent possible) through remote screening, the process of relocation can begin.

- Sites should proactively discuss with participants the logistical process for making travel arrangements, securing accommodations close to the trial site, and, when applicable, arranging schooling. Clarity and focus on which actions participants, and which actions sponsors, will be responsible for are important.
- Sponsors and sites should be transparent about the extent to which relocated individuals should expect assistance with immigration issues that may arise when crossing international boundaries, such as obtaining a passport and visa.
- Sponsors and sites should consider executing a formal, written agreement with relocated individuals specifying the parameters of financial and other support, expectations and obligations of the sponsor, investigator, and trial site, sponsor, and the obligations and expectations on participants, including returning to their home region when the trial is complete. The formal agreement is ideally executed prior to relocation.
- o As a best practice, a third party (such as a clinical research organization specializing in relocation) may be used to mediate the agreement and economic interactions between sponsors, investigators, and relocated participants. This can also serve to maintain privacy between sponsors and participants, so sponsors do not communicate with participants directly but via the site or a third party.

5.4. Trial conduct

Once actual trial participation has begun, trial sites should plan for regular check-ins with relocated individuals to reinforce expectations and mutual obligations related to the relocation itself, monitor for unforeseen risks and challenges, and facilitate a smooth transition for participants and families to a new and unfamiliar environment.

- The sponsor should have policies and procedures in place for addressing situations where participants decide to withdraw from the trial prior to completion. If the participant withdraws voluntarily from the trial prior to completion, there is no obligation to provide post-trial access to the investigational product. Policies should address timing and support for the participant's return to their home country.

5.5. Trial end and post-trial

A significant issue at trial end concerns the sponsor's post-trial obligations to enable access to the study drug if it proves beneficial for the participant during the course of the study.

- In line with the Declaration of Helsinki (Article 34), sponsors should make every effort to enable access to the investigational agent for participants who have benefited from the study drug, especially when receiving the intervention is the only or most promising way

to continue to treat a chronic or lifelong condition.

- o Sponsors should strive to enable continued access under these conditions even in situations when the relocated family decides not to return to their country of origin (see below).
- o If the investigational product is approved by the regulatory authority where the participant resides, sponsors are no longer obligated to enable access and should strive to transition the participant to access the intervention through other means. If the approved intervention is not reasonably accessible (e.g., cost or lack of insurance coverage), sponsors are advised to consider continued, albeit elective, provision of the product.
- In some situations, participants may decline to return to their home region, despite having previously agreed to do so. Efforts should be made by sponsors, communicating through investigators, patient organizations, and the CRO, to remind participants of the mutually agreed upon expectations in this regard and encourage return.
- o If participants and/or families nonetheless decline to return to their home region, the sponsor is not responsible for providing continued support (other than, potentially, continued access to the investigational product if the participant completes the protocol and continued access is indicated).

6. Conclusion

Sponsors are never obligated to assist with relocation and offering support for relocation to enable trial participation typically occurs only in rare and exceptional circumstances. Nonetheless, relocation is a reasonable ethical option when there are safeguards in place to mitigate the risk of undue influence and assisting with relocation would enable well-informed individuals to access research opportunities and clinical trials in which they desire to participate. Under these conditions, foundational research ethics principles support the permissibility and even desirability of offering support for relocation. Consideration of relocation requires care, communication, planning, and sensitivity; the process and policy challenges raised by relocation are significant and deserve careful reflection. While they require a commitment from sponsors, investigators, and participants to transparency, proactive planning, communication, and a willingness to build mutual trust, they are far from insurmountable.

Acknowledgments

The authors would like to acknowledge Kristina Gelblin, Roche Patient Partnership Manager for rare diseases, for contributing knowledge regarding patient advocacy and pediatric clinical trial conduct. The authors are also grateful to Susan Kornetsky and Christine Grady for helpful discussion on the project and feedback on an earlier draft of the manuscript.

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