PERSPECTIVE

Guidance on communication and informed consent with patients and their families for experimental individualized treatments

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Summary

With advanced tools and techniques, it is now possible to genetically diagnose an increasing number of individuals with rare diseases for which no disease-modifying treatment exists. For a subset of affected individuals, it is possible to develop individualized interventions to modulate and/or correct the underlying genetic defect. Communicating to such individuals and their guardians about the potential risks and benefits of such experimental therapies poses special challenges. In addition to typical procedures used for consenting subjects of clinical trials or off-label therapy, individualized therapy protocols involve a complex interplay between biological plausibility, preclinical data, risks, uncertainties, and ethical considerations of equipoise, especially since individualized treatments are usually developed for serious conditions. While no formal guidance exists, this perspective was drafted from the shared experience of clinicians and developers involved in treating affected individuals with individualized antisense oligonucleotides (ASOs) to provide preliminary guidance on communication and consent. As additional experience and expertise accrue over time, we anticipate that these principles will evolve with subsequent modifications to this document.

Introduction

Drug development involves testing therapeutic compounds for safety and efficacy in humans in clinical trials. The informed consent process is established to ensure that participants are aware of the risks and uncertainties involved in participating in a clinical trial. To achieve this, affected individuals should be well-informed about the research goals, which data and samples are collected and shared, the benefits and risks of the clinical trial, and the voluntary nature of participation: they can refuse to participate or withdraw at any time without affecting their medical care.[1] Despite the informed consent process being clear about the research nature of clinical trials, especially for individuals with a fatal disease or a rare disease with unmet medical need, participation in a clinical trial may be seen as the only way to have access to a treatment (therapeutic misconception). While hope is an important coping mechanism, unrealistic expectations of what a trial compound can achieve can be detrimental, as affected individuals or their legally authorized representatives (LARs; see Box 1 for a list of definitions used in this publication) may be willing to accept high risks for perceived but unrealistic benefits.[2]

Therapeutic misconception (misunderstanding the purpose of a clinical trial) and therapeutic misestimation (overestimating the treatment effect, underestimating the risks, or both) occur often in fatal diseases or progressive diseases with unmet medical need.[2] Studies, consensus documents, and guidelines to help avoid therapeutic misconception and misestimation for these patients have been published.[1,3–6]

Nevertheless, in a clinical trial setting, there is at least an extensive dataset to estimate possible benefits and risks. By contrast, for individualized treatments, the dataset is very limited, making consent discussions more challenging. Antisense oligonucleotides (ASOs) are the most advanced individualized treatment modality with over 40 different ASOs now clinically applied in affected individuals.[7] Individualized ASO development occurs in several stages, which include proof-of-concept studies in (patient-derived) cells, followed by abridged safety studies

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Box 1. Definitions used in this paper

Antisense oligonucleotides (ASOs): single-stranded pieces of chemically modified nucleic acids that bind to gene transcripts via Watson-Crick base pairing. While our document has been drafted from the experience of developers and clinicians treating affected individuals with individualized ASOs, many of these considerations will likely apply to other therapeutic modalities, such as individualized gene editing, base editing, and gene therapy.

Clinician: the healthcare professional treating a patient with an individualized ASO.

Developer: the person developing the individualized ASO (can also be the clinician).

Individualized treatment: a genetic treatment developed for a single affected individual deemed to have a treatable genetic variant; it is possible that additional individuals will be identified later who would benefit from the same treatment.

Legally authorized representative (LAR): the authorized person consenting when the affected individual lacks sufficient decision-making capacity (e.g., minors or individuals with intellectual disability or due to psychological factors).

and good manufacturing practice (GMP) production of ASOs. While roadmaps have been published on ASO eligibility and individualized treatment development by the International Rare Disease Research Consortium (IRDIRC) and guidelines on ASO development and subject eligibility have been published by the N=1 Collaborative (N1C) and 1Mutation1Medicine (1M1M) in the setting of the ERDERA network,[8–13] no guidance on communication and consent with regards to individualized ASO treatments is available. Here, we present best practices for the various developmental stages of individualized ASO development as presented and discussed by experts involved in the development of and/or treatment with individualized ASOs (summarized in Figure 1). The vast majority of affected individuals treated with individualized ASOs reside in the US; thus, these best practices now primarily comply with US and FDA regulations. However, we anticipate that they will also be useful for researchers and clinicians embarking on individualized ASO treatment in other geographic areas.

Guidance on communication and consent

Early preclinical development phase

Individualized treatment development is ideally done in cell models derived from the affected individual themselves and requires the collection of individual data and bio-samples for pre-treatment natural history assessments. However, at this stage of development, there is no guarantee of success. There are many reasons why ASO development stops or why it takes longer than anticipated. It is possible that eligibility was based on the wrong therapeutic hypothesis or that no effective ASOs can be identified. Furthermore, timelines are uncertain in research due to aspects that researchers have little control over but that do slow down experiments, such as an infection of the cell cultures, a machine that breaks down, or a shipment of a crucial enzyme or antibody that is delayed. Additionally, as ASOs in this context are usually developed in academic settings, the caveat that sufficient research funding is required, needs to be accounted for. Developers often understand from experience that timelines in this kind of research can be unpredictable. For the affected individual and families, however, these delays can be deeply frustrating or difficult to understand, especially in rapidly progressing disease.

As such, communication with the affected individual and LAR to obtain consent for data and sample collection needs to set clear expectations: (1) there is no guarantee for success. (2) If the work leads to a clinically deployable investigational therapy, there will be additional uncertainties, as the treatment will be "first in human," with limited knowledge of safety and effectiveness due to limited toxicity studies (usually done only in rats). (3) If the development stops for whatever reason, receiving consent for data sharing is still important, as collective iterative learning will be key to making individualized (ASO) treatments more commonly applicable. Sharing and publishing what is learned through this process is currently not common practice, but this should change, as it will not only allow a more informed estimation about the chance of success for developing a clinically deployable ASO but also avoid unnecessary work, e.g., when others test the same faulty hypothesis.

By emphasizing the exploratory and preclinical character of the research, rather than its potential therapeutic implications—which may never be realized—one can help reduce false expectations and reduce profound disappointment that may arise if the therapeutic hypothesis proves incorrect or if the research progresses too slowly for the affected individual to personally benefit.

When discussing the possibility that research might one day lead to a new treatment, developers should recognize that affected individuals and their LARs may naturally focus on the hope this creates and may underappreciate disclaimers about risks, uncertainties, and limitations. It is important to communicate this information with care, ensuring that discussions also clearly and gently address the remaining uncertainties and potential risks. Sharing an honest estimate, or even a broad time range, for how long preclinical development might take can help set

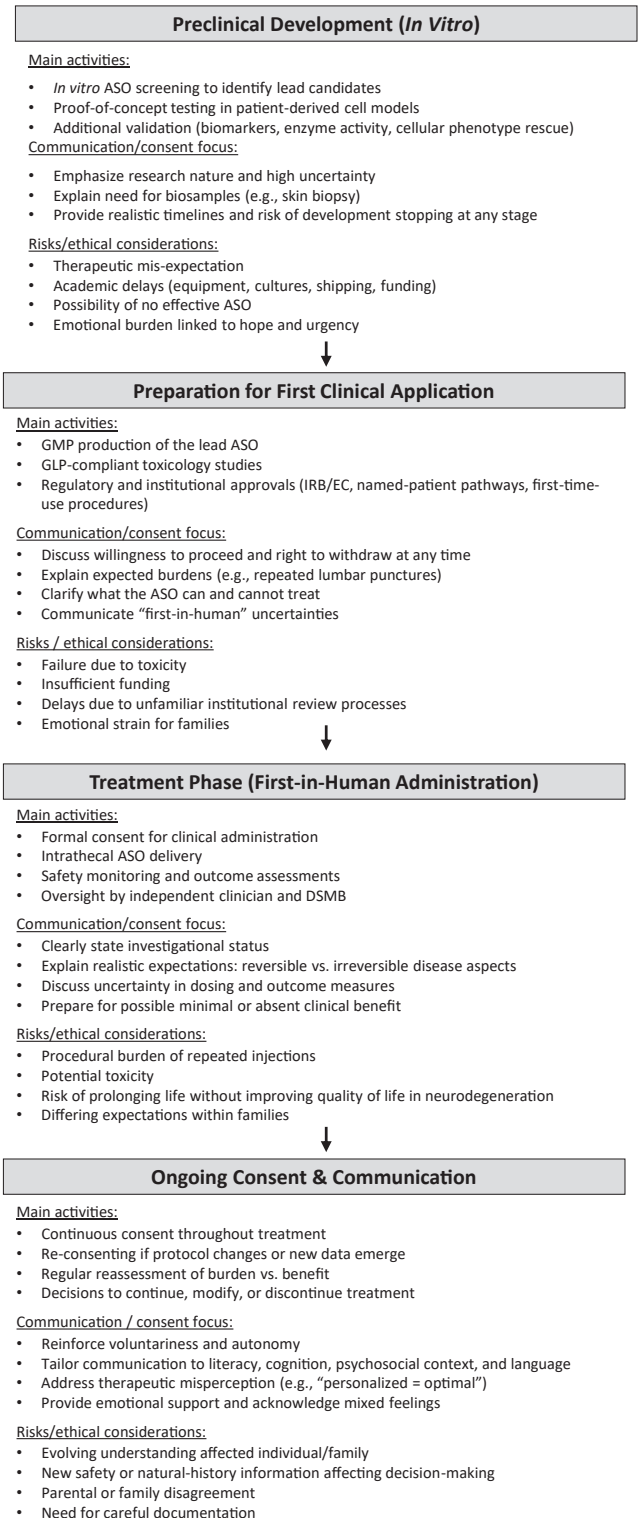

Figure 1. Activities, communication focus points, and ethical considerations during the different development steps

ASO, antisense oligonucleotide; DSMB, data safety monitoring board; EC, ethical committee; GLP, good laboratory practice; GMP, good manufacturing practice; IRB, institutional review board.

realistic expectations and reduce unnecessary disappointment. On the other hand, it is important to show empathy and understanding for affected individuals and their families in a difficult, burdensome situation, where hope can be an important source of power to live on and cope with the challenges of the disease. Here, it is also important to individualize the communication based on how the ASO development was initiated: by the clinician realizing the genetic disease might benefit from ASO treatment vs. the affected individual/LAR or an advocacy organization initiating the research on the ASO treatment.

Late preclinical development (IND-enabling studies in the US)

The steps required to prepare for clinical application are expensive, with costs for GMP production, fill-and-finish procedures, and *in vivo* toxicity studies often exceeding €600,000/$700,000. However, the timelines are more predictable, as these are processes and studies that have a fixed duration and/or turnaround time. The largest risks for failure to develop an ASO that can be clinically delivered to affected individuals are that the lead candidate(s) turn(s) out to be toxic in safety studies or that there is insufficient funding to cover the costs involved with GMP production of the ASOs and/or the safety studies. For institutes where an individualized ASO will be used for the first time, potential approval processes may take longer than expected, especially since approval might be a precedent.

Given the substantial effort and resources required to prepare an individualized treatment for clinical use, it is essential to confirm beforehand that the affected individual or LAR is currently willing to proceed with such treatment and to appreciate that they may change their mind at any time during the process. Once the research becomes more advanced and promising, developers and clinicians should have more formal discussions about the treatment option involving an individualized ASO.

This should also include communication about the expected effects, potential burdens (such as repetitive lumbar punctures) and risks of the treatment, and, if applicable, which aspects of the disease cannot be modified by the ASO treatment. Furthermore, these discussions should include uncertainties related to the expected benefits and risks of the treatment, especially given its individualized and first-in-human nature. Finally, it should include discussions of related unknowns regarding safety and efficiency and their limitations (i.e., ASOs are not a cure but a treatment).

The communication with affected individuals and LARs should be viewed as an ongoing, iterative dialogue rather than a single conversation. The developer and clinician should continue to discuss potential benefits, risks, and related uncertainties while assessing the affected individual's and LAR's understanding and expectations over time. During this time, ancillary support (for example, a social worker or counselor) should be offered to deal

with emotionally charged feelings and—in cases involving minor subjects—parental disagreement. Patient support groups may also help support affected individuals and LARs during this time.

Notably, due to the extensive and recurrent discussions about individualized treatments, strong relationships between the researcher and the affected individual and family/LAR may develop. This can be positive and facilitate the individualized approach toward communication that is required. Yet one should also be cautious that it does not impede objective communication and decision-making, as decisions to stop ASO development or treatment may need to be made.

Clinical treatment phase (clinical trial phase in the US)

Additional and more comprehensive consent is required before initiation of treatment. At this time, the developer and clinician have all the information from the preclinical research and safety studies. These data can guide the discussion about what to expect from the clinical application of the individualized treatment. This depends on the disease pathogenesis, its natural history (when available), the affected individual's condition at the start of treatment (is there still a therapeutic window?), and the mechanism of action of the proposed individualized therapies. These discussions and the treatment protocol should also include information about when the treatment will be stopped. For neurodegenerative diseases, the goal may be to slow down or stop future loss of function. It should be acknowledged that there may be a risk of extending poor quality of life with an added treatment burden (i.e., if treatment extends life without improving quality of life or function). It should also be acknowledged that some aspects of the disease may be only partially reversible, while for other aspects, loss will be irreversible. In some neurodevelopmental diseases, cell migration, synaptic pruning, and/or cytoskeletal abnormalities may have caused irreversible structural changes in the nervous system (e.g., anatomic malformations). However, due to neuroplasticity, individuals with neurodevelopmental diseases often gain and acquire skills, and it is possible that personalized treatment may actually facilitate gains. These aspects will be disease and subject specific, highlighting the need for treating clinicians to be content experts in the disease of interest. It is important to carefully explain which aspects of the disease can or cannot be modified or improved if the treatment works. This facilitates affected individuals/LARs appreciating the possibility of therapeutic failure or more nuanced outcomes of efficacy without meaningful treatment benefits (e.g., improvement in biomarkers without appreciable change in quality of life).

The discussion should also include the risk of ASO toxicity and burden, as well as the frequency of intrathecal injection of ASOs, based on safety studies done for the individualized ASO but also from the broader context of intrathecally injected ASOs (approved and individualized).

The implications of the first-in-human nature of the study should be clearly explained. There are inherent uncertainties, including the possibility that the chosen dose may not be optimal or that the selected outcome measures may not fully capture the treatment's effect. This means that during the treatment process, the dose or the outcome measure may need to be adjusted. It is also important to be mindful of different expectations and beliefs among family members regarding treatment effectiveness and the burden of participating in a clinical research trial.

Safety oversight and stopping rules must be carefully defined for each individual subject rather than based on a larger group experience and extensive preclinical data.

Finally, the clinician should explain the processes for monitoring safety, ideally involving an independent clinician in addition to an independent data safety monitoring committee. After treatment initiation, the treating team, including the developer, should meet regularly and ad hoc, based on treatment effects, side effects, and perceived burden of the treated individual, with carefully defined rules for treatment discontinuation and dose and/or treatment frequency adjustments.

General principles for informed consent during the clinical trial phase

Communication should be based on the following principles.

Transparency and comprehensive disclosure

The clinician should clearly and concisely explain that the ASO is investigational and has never been used before (though it was built on the knowledge of other ASOs of the same modality and chemical modification, this specific ASO sequence has never been tested in a human). Furthermore, they should disclose information about the research, its scope, how and why it was performed, and should stress the risks and uncertainties (the knowns and the unknowns), possible benefits, and alternatives. Transparency about the study's methods is essential. Given the uncertainties involved, the study protocol may need to be adjusted as new information emerges. Any changes should be communicated and discussed openly with the participants. The process of ethical review approval should be explained. Finally, the information should be presented in a balanced manner to reduce the possibility of undue influence on the potential participants.

When it is not yet clear whether the ASO has a therapeutic effect or not, one should avoid words like "therapy" or "treatment" and instead use "research" to reduce the risk of therapeutic misconception, therapeutic mis-expectation, and unrealistic hope.

Emphasize the voluntary nature of participation

The affected individuals and LARs should never feel any pressure to take part in the study. Even though developing

an individualized ASO requires significant time and effort, participation is entirely voluntary and should be based on what feels right for the affected individual and/or LAR, and consent can be withdrawn at any time. Especially when the clinician treating the affected individual is also the person developing the ASO, an independent clinician should be involved in the communication and consent processes. The affected individual or LAR should be aware that if they decline the individualized ASO or stop the treatment at any time, this will not negatively affect their ongoing care. Consent for research should be separated from consent for the ASO treatment, as terms and conditions will differ for the two, and one wants to avoid making participation a prerequisite for receiving other services or participating in research.[11]

Ensure sufficient decision-making capacity and understanding of the affected individual/LAR

Communication should be tailored to the individual needs, literacy, cognitive ability, psychosocial capacity, level of understanding, and native language of the affected individual or LAR. Given the complexity and uncertainty involved, it is important to take the time to ensure that the affected individual or LAR clearly understands the information provided. In cases where LARs will provide the legal consent, affected individuals should also be involved in the communication process whenever appropriate, based on their developmental maturity. If possible, they can be asked for an assent to the ASO development and study participation.

The clinician should use clear and simple language without medical terms or jargon and visual decision aids or interactive tools to enhance understanding. To make sure the information is fully understood, the clinician should invite the participant or LAR to describe the main points in their own words. It should also be clearly understood that participation is voluntary and can be stopped at any time.

When there are language barriers, a medical translator should be involved. Experiences with online translation tools or online translation services are suboptimal, as it is difficult to assess whether all involved have sufficient understanding. Especially with children, for whom parents will be consenting LARs, it is important to anticipate that parents will not always agree, e.g., on what is an acceptable burden, and to vocalize this ("you will not agree on everything"). Under certain circumstances, such as when there appears to be disagreement or discomfort between parents or guardians, the involvement of a consent monitor may be appropriate to help ensure that the consent process is fair and free from any undue influence or pressure and that all parents agree on their child being treated.

The clinician should document the participant's decision-making capacity throughout the consenting process. Furthermore, the clinician should familiarize themselves with the local legal and regulatory frameworks for consent, which vary in different jurisdictions (US vs. EU) and have different requirements for reconsenting procedures, the role of the LAR, and documentation standards.

Tailor the consent document and process to the individual patient

A separate, subject-centered consent document should be developed that focuses on the unique characteristics of first-in-human trials. Information that is crucial, such as the investigational nature of the ASO and the potential risks, limitations, and uncertainties, should be stated early in this document. The study schedule should be placed before the risk section, and a one-page summary highlighting essential information should be incorporated. An example consent form for individualized ASO treatment is provided in Data S1.

Provide ongoing communication and offer reconsent

The consent process involves ongoing communication extending throughout the development and treatment period. It is not a one-time event. As such, open communication, ideally via regular in-person meetings, needs to be maintained with participants, to address questions and concerns and to reaffirm the willingness to continue participation. When significant new findings develop or the protocol changes, participants should be informed and have the chance to reconsent. New findings can be unexpected treatment effects, side effects of the ASO, or adverse events reported in another individual in whom the same or a similar ASO is used. However, communication is also needed if an event occurs that relates to the natural history of the disease (e.g., irreversible loss of a function), which may affect the ability of the participant to receive treatment or reduce the likelihood that the ASO treatment will produce clinically meaningful effects.

Document the consent process

The consent process should be thoroughly documented, including conversations, the information shared, the questions of the participants, the responses to those questions, and the assessment of the participant's comprehension and understanding of the voluntary nature of the treatment. Hard-copy consent forms should be signed and dated by the participants or their LAR and the person obtaining consent.

Other considerations

It can be helpful when the researcher developing the ASO is not the same individual as the clinician who will treat the affected individual, where the latter is an expert in the disease of interest and its treatment or management. This separation may facilitate discussions and also foster mutual emotional support between professionals. If the

clinician who will treat the affected individual is also developing the ASO, they should also receive support (e.g., fellow clinicians) to discuss uncertainties and challenges and minimize bias. To facilitate this process, the 1M1M network has set up a multistakeholder "treatment board," in which multiple independent experts and representatives evaluate each individual and treatment, with the treating clinician presenting the case but excluded from the final evaluation and decision statement.[9]

In addition, a common therapeutic misperception relating specifically to individualized treatments is that because they are individualized or personalized, they should work very well—as most personalized or tailored items are the best one can get (e.g., a tailored suit). As outlined, it is important to explain which symptoms the treatment might or might not address. Mentioning the often-present subconscious misperception that a treatment individually developed for a given participant is optimal may help ("It is natural to believe that a personalized treatment could offer the best chance of benefit. At this stage, though, we do not have enough information to know whether it will help or not.").

Another idea, in line with the above, which may subconsciously lead to complex feelings, is that the personalized research participant is the "chosen one." This may lead affected individuals or LARs to overestimate treatment effect (as in, "it was especially made for me, it should be working") or incur feelings of guilt ("why should I deserve this treatment if others with the same disease with different genetic variants are not receiving it"). Supportive counseling can help with coping and can proactively make explicit that mixed emotions are normal in this situation.

Conclusions

In summary, the high level of uncertainty regarding timeline, feasibility, efficacy, and safety of individualized ASO treatments raises communication challenges with the affected individual or LAR. Contrary to typical clinical trial processes (where a detailed conversation typically occurs once), it may be best to consider the communication and consent procedure in personalized treatment approaches as an iterative process. In this approach, an ongoing dialogue is established in which developers and/or clinicians balance providing sufficient, comprehensive information with avoiding false expectations or creating unrealistic hope. This process does not stop when treatment is initiated; instead, it lasts throughout treatment, allowing for open discussion as to whether to continue or discontinue the treatment. Furthermore, like everything else involving individualized treatment development, the communication process must be tailored to the patient or LAR, based on their shared belief system, tolerance for uncertainty, level of understanding, and expectations, and the fact that these aspects may change over time.

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Declaration of interests

The authors declare no competing interests.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2026.05.002.

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