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WHITE PAPER

Pediatric Gene Therapy:

Considerations for Planning, Execution & Long-Term Follow-Up

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Executive Summary: Best Practices To Ensure Success

The European approvals of Glybera® in 2012 and Strimvelis® in 2016 seem likely to be the vanguard of the therapeutic revolution heralded by the decoding of the human genome. Both of these treatments originated from academic centers of excellence and became the subjects of agreements with pharmaceutical companies (Uniqure/Chiesi and GSK, respectively) with the experience to navigate the manufacturing infrastructure and regulatory approvals processes that led to the products' commercialization. The EMA has indicated the level of follow-up it expects to see for these patients, and the FDA's perspective will likely be revealed with the first US approvals of gene therapies anticipated in 2017.

The pharmaceutical industry has been responsible for the successful execution of hundreds of thousands of trials of new drugs and vaccines. Gene therapy trials are unique, combining established experience and new approaches previously unnecessary for developing new drugs.

Sites and Patients

The success of clinical trials often depends on identifying sites that treat the target patient group and tracking referral pathways to the source. The reverse is true for most gene therapy trials. Gene therapy is typically administered at the originating academic center of excellence, with a second or third treatment center identified later in the program. At present, given the restrictions on advertising unapproved treatments in most countries, conventional recruitment campaigns are unnecessary and are unlikely to be productive. Instead, the academic centers publicize their success, and potential patients and/or their caregivers contact the center directly and referrals come from physicians world-wide. However, the limited patient pool and the small number of suitable sites raise questions about transnational enrollment.

Transnational Enrollment, Language & Consent

So far, most gene therapies under development are aimed at truly rare diseases, for which, in many cases, no effective treatment exists. The advantage of such a targeted approach is that the manipulation of the gene identified as the cause of the condition means that patients receive truly individualized and potentially curative treatment. The disadvantage is that the rarity of patients with these conditions means that transnational enrollment is unavoidable, and this creates several challenges.

The first potential challenge to be considered before any subjects are enrolled is a regulatory one: following gene therapy, the patient returning to a home country that has not been made aware of the risk assessment of the product. This can be compounded by issues of the classification of the gene therapy, which is not the same in all countries.

Additional challenges relate to the management of patients who go on to become trial subjects. The first of these is relocating a child and at least one family member/caregiver to another country for a long period; the challenge is exacerbated by the need, in some conditions, for air ambulance transportation. Countries with centralized national healthcare systems may be willing, in some cases, to meet or at least defray the costs associated with transporting a child to another country to receive innovative medical treatment. For low-income countries and those with private healthcare systems, financial support is less likely, and parents/caregivers may need to rely upon their own resources to relocate the child to the treating center and to support themselves for the duration of the treatment period. However, very few countries are likely to meet the costs of transportation associated with participation in a commercially-sponsored clinical trial. In most cases, ethics committees will expect these costs to be met entirely by the sponsor, and the question becomes, "Which costs can

reasonably and ethically be covered?" The pharmaceutical sponsors of such trials need to navigate a fine line between legitimately compensating parents/caregivers for incurred costs (travel, hotel accommodation, subsistence, telephone calls) and possible loss of earnings, and being seen as providing unacceptable incentives.

In later-stage trials, when some clinical experience in the use of the gene therapy has been gained, it may be possible to avoid such potential criticism by decoupling the provision of treatment from enrollment into a clinical trial. The gene therapy administration may be classified as an innovative medical treatment, but only the follow-up would constitute participation in a clinical trial – only after the gene therapy is given is a conversation initiated regarding a clinical trial, and the desire for follow-up data. Of course, this timing can be criticized on the basis that the request to participate is made when the parents/caregivers are most vulnerable because they are grateful that their child has received potentially life-saving treatment. However, the alternative—seeking participation in the trial before traveling, or before the therapy is given—carries a significant risk of being perceived as conditional, ie, "Your child will receive this treatment if you agree to the collection of follow-up data." Neither is ideal, but the post-treatment timing currently seems to be the most prudent option.

The other issue that arises from transnational relocation is that of language. If the gene therapy is considered an innovative medical treatment rather than an investigative product within a clinical trial, normal medical practice would consider verbal explanations (perhaps involving a staff member with a basic understanding of the patient's language) acceptable. However, this would clearly not be the case for a clinical trial. In conventional trials, countries are selected in advance to allow sufficient time for relevant documents to be translated through certified processes (often involving specialized vendors). The normal lead times for these activities may not apply to gene therapy trials, although the impact of this can be mitigated by adopting the convention of starting the trial after the therapy is given. In that sense, this aspect of gene therapy trials is similar to the situation of acute intervention studies, particularly for infectious diseases, and sponsors may need to emulate and amend the process used in such trials to support gene therapy trials.

Although the translation of relevant documents can be managed, that does not address the language barrier faced by the patient during the immediate post-therapy period, when the family is in a foreign country. Everyday activities relating to transport to and from the hospital, buying food and other necessities, possibly making contact with family members who have remained at home, banking, and—critically—holding a meaningful dialogue with treating physicians, can be rendered almost impossible without at least a basic command of a language used at the treating center. Once again, however, this issue is not unique to gene therapy trials, nor, indeed, to clinical trials. A number of specialized agencies exist that can provide fluent translators who are familiar with the infrastructures and procedures in the host country to support patients and families. With appropriate planning, these agencies can be engaged to support the family from the point of arranging travel to the treating center until the return home, and often beyond.

Much of the previous discussion is based on the assumption of a nuclear family. The reality is that many families now are single-parent/caregiver and many children have siblings. Consideration may need to be given to transporting at least part of a larger family unit to the treating country, accommodating them, and arranging for sibling education there. The principles of distributive justice would seem not to be met if a child who was a suitable candidate for such treatment could not receive it because care provisions could not be made for a sibling.

Post-Treatment Follow-Up & Communication

The release of the child from the treating hospital represents the beginning of the next stage. The treating physicians will naturally wish to be apprised of the child's progress and any problems, while the parent/caregiver will need to know whom to contact with any issues or concerns. This again raises the issues of communication and language barriers; how, for example, can a parent/caregiver who speaks only Urdu or Kurdish discuss concerns with a treating center where the

native language is English or Italian? In conventional clinical trials, this issue rarely arises; the investigator will always be able to speak the national language of the country in which the patient lives, and will often be able to speak at least one other language which would enable communication with the sponsor, whether directly or through one of the sponsor's or CRO's country offices. Few conventional clinical trials involve countries in which the sponsor or CRO does not have a representative; in most cases, such representatives are required to be fluent in a language that enables ready communication with the sponsor. Having said this, it is surprising how often translators are now needed for standard clinical trials; Urdu in the UK is a common example, and with the recent refugee crisis, the number of translators in hospitals is increasing. However, those developments do not come to the aid of an anxious parent trying to reach an investigator in a different country when neither speaks the same language.

Three follow-up models—not mutually exclusive—are possible. One model, closest to the one used in conventional drug trials, is to have the patient return periodically to the treatment site. This would seem to have many potential advantages from a medical perspective, but is subject to 2 considerations. One is cost: even if the visit itself takes only part of a day, depending upon the location of the patient, the travel time could be 2 days in each direction and involve accommodations. The second is that the advantages of routine visits in conventional trials are largely driven by the fact that treatment is ongoing, so assuring compliance with the protocol and drug accountability are important, as is the assessment of emerging adverse experience data. In a gene therapy trial, these advantages may not be so obvious.

A second model, again akin to that deployed in conventional studies, is to create "satellite" sites in each country in which a patient resides and at which patients are seen by a "sub-investigator." This has the advantages of defraying costs and provides many of the advantages of ongoing direct medical oversight, accepting that the sub-investigators may not be as knowledgeable about the therapy as the treating site. However, creating such sites still incurs significant costs.

The third option is a "virtual" model in which the patient does not present in person at routine visits, but is monitored remotely. This option also reduces costs, and the lack of direct medical oversight may not be as concerning as in a conventional trial. In both the satellite and virtual models, the increasing use of a wide range of electronic data capture approaches is potentially helpful. Reports from satellite sites, including any sample analyses which may be appropriate, can be captured and sent to the treating site and direct contact between patients/caregivers and the PI is possible, provided appropriate internet connectivity can be established and parents/caregivers are taught to use the technology.

Who is the Investigator?

Who is the investigator in a gene therapy trial once the patient returns home? Patients may have been referred by a specialist or their primary care physician, or as a result of direct contact by the parent/caregiver or a patient advocacy group (PAG).

Parents/caregivers can never serve as investigators, regardless of their level of knowledge, because of their personal relationship with the patient. Primary care physicians are generally less experienced in the conduct of clinical trials, and on that basis alone may be considered unsuitable, but perhaps especially so for an approach as novel and complex as gene therapy. That leaves the referring specialist as a possible investigator; however the duties would be somewhat different from those in conventional trials. For example, the referring specialist would not be the one deciding whether the subject could enter the trial; that responsibility would lie with the treating center. Given gene therapy is a single-instance administration, further treatment, normally the responsibility of the investigator, may not be required. In the absence of further investigational treatment, compliance assessments and drug accountability are not required, just as is the case in a surgical trial, in which repeated surgical interventions are not required. Routine blood tests may be required after therapy to assess the emergence of risks such as vector tropism and mutagenesis, but the samples would most likely be analyzed and interpreted centrally, with any relevant information being fed back to a referring specialist. In such a situation, the referring specialist may be doing little more than acting as a phlebotomist. Of course, the sponsor may wish the child to be seen periodically by a physician to assess whether the child's development is normal, but this hardly seems a basis upon which to declare a referring physician an investigator and incur the resultant financial and resource costs.

Does Gene Therapy "STOP"?

Conceptually, a related question is whether the investigational treatment is still being given. In a conventional trial, even of a single-dose drug, there is a clear period during which treatment is being "given." For drugs with particularly long half-lives, such as amiodarone, the treatment period may be defined as "X days after last dose administered," or "when the plasma concentration is below the limit of detection." For a surgical trial, the surgical treatment period is conventionally defined as ending at the point at which the investigator decides that additional visits to assess the effectiveness of the experimental surgery are no longer necessary (either because the condition has been corrected or has reached a new steady state). Such a convention has not yet been defined for gene therapy trials.

The EMA guideline indicates follow-up for life, while FDA guidance indicates 15-year follow-up.[1,2] Given that a new (hopefully condition-free) steady state has been attained after gene therapy, while active treatment may no longer be "given," its benefits are still being received, much as in a surgical trial. In effect, the treatment benefit continues throughout the patient's life, somewhat similar to a vaccine.

Assuming that the sponsor does not see an investigator-like role for a referring specialist in the country from which the patient came, and that the "investigator" is the physician in the treating center who administered the treatment, how can patients be monitored when they have returned to their homes? Given the language and possibly time-zone issues, the most obvious solution is to engage a CRO with staff in or close to the home country for each patient who speak a language the family/caregiver understands, and who are sufficiently familiar with the healthcare system in the country to help the patient seek medical help where appropriate. In some circumstances, a PAG may be able to fulfill such a role. To do this, of course, the CRO or PAG would need to hold personal information relating to the patient, and this raises an evolving range of challenges. Ideally, this matter would be addressed in the risk assessment.

Follow-Up Requirements & Data Privacy

Such long follow-up periods raise additional challenges. While a parent may be happy to give their consent to being contacted by a CRO (or PAG) engaged by the sponsor to check on the child's progress over a number of years, the need exists to accommodate the developing maturity of the child, particularly as the child enters adolescence. At that age, in conventional medical practice, most physicians would address questions directly to the child, and most likely see the child in the absence of the parent if the conversation turned to issues relating to pregnancy, contraception, or sexually-transmitted diseases. It would therefore seem quite reasonable that the follow-up conversations would at least include the child, and perhaps as the child matured further, those conversations would be directly with the child, and not necessarily include the parent/caregiver. To an extent, such a process is already with us, in the form of pregnancy registries, although the durations of follow-up have not, as yet, become as demanding as required for gene therapy.

Succession of Consent

This transition of follow-up discussions from the parent/caregiver to the child raises 2 issues. The first is that, recognizing the developing maturity of the child, the child may reasonably be asked to assent to such discussions. What is the position if the child declines assent? One might argue that the parent/caregiver retains the right to discuss their child's health with a third party until the child attains the age at which, by law, his or her consent is legally required. That may be a reasonable

[1] Committee for Medicinal Products for Human Use. Guideline On Follow-Up Of Patients Administered With Gene Therapy Medicinal Products (CHMP) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013424.pdf. Published October 22, 2009. Accessed April 21, 2017.

[2] U.S. Food and Drug Administration. Cellular and Gene Therapy Guidance. Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm072957.html. Published November, 2006. Accessed April 21, 2017.

approach for conventional medical care for a minor, in which the information is disclosed only to a member of the medical care team, but is it reasonable within a clinical trial setting, in which the information is being collected not with the primary aim of assuring the child's safety or welfare, but pursuant to a regulatory obligation, and shared with sponsors, CROs, PAGs, and possibly regulatory authorities, none of which is responsible for the child's medical care? The general position regarding clinical trials is that if a child withholds assent, then the child cannot be enrolled into the trial, and if the child withdraws assent, the child cannot be retained in the trial against his/her wishes. So, it would seem that this transition carries with it a chance that the adolescent child will refuse further participations and that the parent/caregiver may no longer share the child's health information with third parties.

The second issue is even more sensitive. In many countries, background checks are made on individuals who interact directly with children. This commonly applies to teachers, doctors, nurses, other healthcare professionals, youth leaders, and sports coaches, and so it may be prudent for sponsors, CROs, and PAGs to consider whether staff allocated to such activities need to have undergone relevant checks.

As mentioned above, the attainment of legal capacity creates a specific point at which an individual may elect not to continue to provide personal health information, and withdraw from the study. In most countries, legal capacity is conferred between 16 and 19 years of age – around the same age at which many children leave home to attend college or university. At that point, the home location may change, and if children spend part of their time at college and part at home, then multiple communication pathways may be required. Once these patients reach their mid-20s, many are likely to be involved in long-term relationships (and so may prefer partners not to know about regular calls), and some will move to a different country for continuing education or career development. Thus maintaining communication with patients becomes increasingly difficult.

The 15-year follow-up specified by the FDA is perhaps less vulnerable to these issues than may be the case in the European environment, as few if any patients will attain legal majority before the follow-up period ends.

Conclusions

Gene therapy trials are in their infancy and scientific and medical advances are preceding legislation and regulation; as a result, these trials must be conducted by adapting existing practice. As this paper describes, existing practices from single-dose conventional studies, surgical trials, vaccination programs, and pregnancy registries may all be adapted to the gene therapy trial setting, but the major challenge is in the duration of the follow-up period currently required by the EMA in particular, with all the issues related to balancing patient tracking and data privacy requirements. The question of whether a principal investigator must be identified, and the decision about who that may be, given the geographic and temporal dimensions for such studies, must be considered by regulators to provide proper hoc guidance to sponsors rather than to identify retrospective failings. The philosophical question of whether gene therapy ends at the point of administration or continues indefinitely may not need to be resolved if gene therapy trials are considered a specific class—rather than being classified as "advanced therapy"—and specific requirements are created for such studies.

The main regulatory bodies are aware of the rapid advances of science and technology, and share the aim of making advanced, potentially life-saving treatments available quickly.[3] They are increasingly amenable to inventive study designs and aware of the issues related to accruing sufficient subjects with rare conditions. Before embarking on such studies, thorough discussions with the authorities—addressing risk assessment in particular—will do much to help sponsors anticipate potential problems and plan solutions.

Contact Information

For further information, or to discuss any aspect of PRA's services offered, please contact your Business Development Manager, or the employees listed below:

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