Navigating Through Uncharted Waters

The challenges associated with setting clinical trials into motion for gene-based therapies are notable and come with numerous patient safety and ethical concerns

Dr Michael F Murphy, Dr deMauri Mackie, Sophie Humphrey, and Dinah Otieno at Worldwide Clinical Trials

Gene-based therapies are members of a larger therapeutic category characterised as advanced therapy medicinal products (ATMP). Most stakeholders recognise the potential impact of new gene-based therapies: improved outcomes and quality of life for patients with some of the most complex and chronic genetic conditions, which can be presented with considerable clinical variation.

In particular, the industry witnessed several milestones in 2017, including approval by the FDA that allowed the first gene-based treatment for an inherited eye disease in the US (1). Earlier in 2017, the FDA also cleared two other gene-based treatments targeting advanced haematologic malignancies (2).

Such industry developments underscore a renewed readiness to advance gene-based clinical trials after a series of high-profile setbacks in the late1990s prompted the FDA and the EMA to develop additional guidance for clinical trials involving gene-based therapies – including oversight procedures emphasising short- and long-term patient safety. A layered and either sequential or overlapping review process includes institutional review boards, institutional biologic committees, and the National Institutes of Health assuring protocol adherence and proper handling of therapeutics.

Current Study Context and Practices

Since 1989, the number of clinical studies evaluating gene-based therapeutics has increased on a yearly basis, approximating 2,600 studies worldwide through to 2017. Over 100 new studies have taken place per year from 2012 through 2017 (3). Since Gendicine was approved in October 2003 for head and neck squamous cell carcinoma, six gene therapy products have been approved across nine therapeutic areas, with oncology being dominant. The latest, Luxturna™ (voretigene neparvovec-rzyl), was approved by the FDA in December 2017 for retinal dystrophy (biallelic RPE65 mutation).

At least 10 vectors have been used (adenovirus, retrovirus, and naked/plasmid DNA prominently), and most trials (77.7%) are in Phase 1 or 1/2 studies. Thus, an emphasis exists upon early phase experimental designs cognisant of the need for long-term outcomes to evaluate persistency of efficacy and safety. Patient segmentation inherent within gene-based therapeutics limits the number of patients available during clinical development. All development strategies under this remit attempt to minimise the total sample of patients required and to maximise treatment on the investigational agent.

Minimising the Sample

Minimising the patient sample for interventional studies occurs through six approaches, although not all are applicable for gene-based therapeutics. Designs include:

- Adaptive randomisation (assigned treatment shifts based upon accrued data)
- Longer trials powering on events rather than on patients
- Risk stratification selecting patients with features likely to be more responsive to treatment
- Use of composite measures or a multi-domain response index, which increases power and accommodates heterogeneity in presentation and outcome
- Use of less conservative, relaxed alphas at an interim analysis to permit decision-making for adaptation with small patient samples
- Design based upon Bayesian approaches

Decision nodes influence the choice of design and are based upon reversibility of outcome, rapidity of response, and the amount of time on control treatment (4).

Maximising Treatment

Maximising time and the number of patients receiving active therapy occurs through options including imbalanced randomisation favouring active versus placebo, a 'delayed start design' in which a control (placebo) phase precedes active therapy, and adaptive randomisation playing the winner and dropping the loser designs among other permutations. Other options include crossover and Latin Square designs (in which every patient receives every treatment) and 'n of one' studies or alternating designs (which imply a time series design). However, these are not applicable for gene-based therapies.

International Clinical Trials, November 2018, pages 30-33. © Samedan Ltd 2018

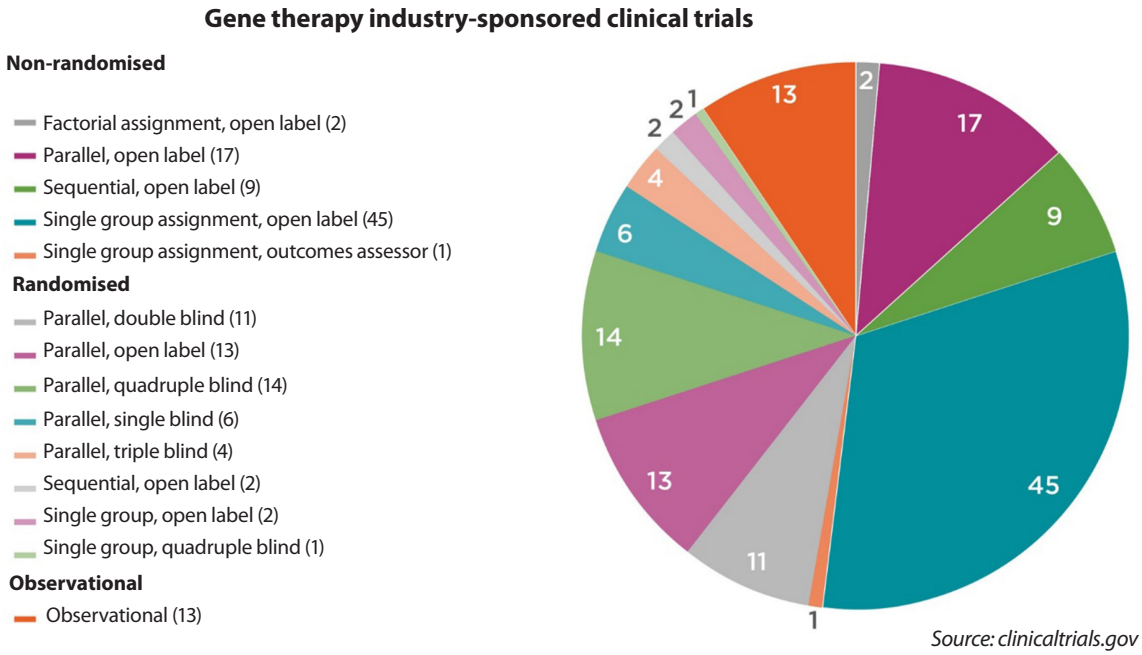

Figure 1: Trial designations extracted from study design section of clinicaltrials.gov from 2000-2018

Applicability to Gene Therapy

For gene-based therapeutics, options for clinical trial design are constrained by the long biological activity of the genetic material introduced. Among 12 designs for rare diseases, six are noteworthy: parallel, delayed start, randomised placebo phase, 'pre- versus post' designs, stepped wedge design, and adaptive randomisation. Only a fraction of these possibilities have been utilised, as exemplified by a survey of designs employed since 2000 (see Figure 1).

However, a framework exists within regulatory guidance (5). Staggered enrolment with conservative dose escalation is uniformly cited. Noted are product-specific adverse events such as inflammatory responses to vectors or mechanical injury due to the procedure for introducing gene therapy and immunological responses to vectors, the transgene product, or modified autologous cells. The need for long-term follow-up for gene therapies adds an additional operational demand contingent upon the nature of vectors. Due to the difficulty of implementing double-blind or placebo-controlled studies, historical controls increasingly provide a reference for clinical and biostatistical contrasts.

clinicaltrials.gov was searched using the keywords 'gene therapy' and then filtered for only industry-sponsored trials. The resulting trials were sorted by randomisation status, group assignment, blinding, and interventional/observational classification from 2000-2018.

Long-Term Follow-Up

The properties of the vector and the nature of the targeted gene shape requirements for long-term follow-up with the length of follow-up balanced against the nature of the viral vector and the targeted gene.

For example, adeno-associated viruses (AAV) have low potential for integration into the host genome. Therefore, AAV vectors are exempted from a standard 15-year follow-up requirement. However, herpesvirus-, gammaretrovirus-, and lentivirus-based vectors are not exempt (6). Other considerations for determining the appropriateness of long-term follow-up intensity and duration include the duration of *in vivo* vector persistence and transgene expression and the expected survival rate within the study population.

Short- and medium-term assessment of complications from the integration of the viral vector into the host genome may be warranted, creating monitoring conventions that stand apart from those of small molecules and biologics. This may include assessments of the immunogenicity of the vector and the recombinant gene and the persistence of viral shedding. Monitoring conventions may also be influenced by country-specific regulations (7-8). Developing a list of adverse events of special interest may help guide monitoring efforts during the study, as well as the content of study reports.

Regulatory Environment in the EU

In Europe, the governing directive 2001/20/EC created united procedures for trial authorisations, yet national-level procedures and lack of harmonisation of ATMP definitions across member states can lead to differing assessments and country start-up timelines. However, 2019 will see the implementation of the Clinical Trials Regulation (EU) 536/2014 harmonising the clinical trial submission assessment process through a single EU portal (9). Review process and timelines across member states will be

Timeline: ~7 months

Approvals:

MHRA:
- Clinical Trials, Biologicals and Vaccines Expert Advisory Group to review gene therapy and first-in-human aspects
- Monthly meetings – date selected once data package provided to MHRA (14 days for response)
- Submit application 21 days before meeting
- Opinion within 90 days for gene therapy

GTAC:
- The UK Ethics Committee for gene therapy research
- Pre-application advice no longer required
- Choice of research ethics committee
- Application via integrated research application system
- 30 meeting dates per year
- Legislative review timeline of 90 days from validation

Key:
*Medicines and Healthcare products Regulation Agency
** Essential document review
***Gene Therapy Advisory Committee

Figure 2: Current clinical trial start-up process for gene therapy in the UK

streamlined, although possibly extended, by 50 days from standard review time (10).

EMA Scientific Advice

The EMA offers developers an opportunity to discuss scientific challenges given the range of products and study methodology employed. Requests have increased significantly in the last five years. The EMA's Committee for Advanced Therapies provides a regulatory framework for the approval of ATMPs in the EU and is routinely involved in all scientific advice procedures for these therapies (11).

Early Access Programmes (EAPs)

EAPs in Europe include the Compassionate Use Programme and the Named Patient Programme. Therapy may be imported to provide for individual patients upon request of their physician for pre-approval access. Differences in physician compensation and liability make EAPs in the EU more challenging compared to the US (12). EAPs across countries also can differ in terms of process, requirements, and barriers. One example of a robust EAP is the Early Access to Medicines Scheme (EAMS) in the UK, launched in 2014. The review process for an application is generally four months with an accompanying promising innovative medicine designation, indicating that a product may be a candidate based upon Phase 1/2 data.

Since the launch of EAMS, the EMA's Priority Medicines scheme also provides regulatory assistance for products under development, where the aim is to apply for initial marketing authorisation through the centralised procedure (13).

Assuring Access, Approval, and Outcomes

The difficulty of integrating design and trial operations with a regulatory and commercial strategy is accentuated in gene-based therapeutics. Frequently accelerated pathways for clinical development and product registration are sanctioned as 'breakthrough therapy', resulting in a limited clinical database encumbering the evaluation of product 'value'. Specifically, challenges shaping formulary placement and reimbursement decisions include high initial acquisition prices that are difficult to modify, necessitating cost containment measures such as prior authorisations or the use of step-edit therapy. Incorporating these perspectives into a clinical development programme to inform healthcare utilisation becomes a strategic companion effort as important as product authorisation.

Little debate surrounds the potential of gene-based therapeutics to positively change the course of treatment for some of the most complex clinical conditions. However, clinical trials must be designed to balance regulatory requirements, operational challenges, and patient safety with therapeutic innovation. An understanding of the evolving regulatory landscape is essential, as is the expertise to design and coordinate rapid, well-planned studies against a backdrop of an increasing demand for expanded patient access.

References

1. Visit: www.washingtonpost.com/news/to-your-health/wp/2017/12/18/fda-approves-first-gene-therapy-for-an-inherited-disease-childhood-blindness/?noredirect=on&utm_term=.704c2852fd66
2. Visit: blogs.fda.gov/fdavoice/index.php/tag/oncology-products-approved-in-2017
3. Ginn SL *et al*, Gene therapy clinical trials worldwide to 2017: An update, *J Gene Med* 20(5): e3015, 2018
4. Nony P *et al*, A methodological framework for drug development in rare diseases, *Orphanet J Rare* Dis 9: p164, 2014
5. Visit: www.slideserve.com/yeva/fda-perspectives-on-clinical-trial-development-of-gene-therapy
6. FDA, Gene therapy clinical trials – Observing subjects for delayed adverse events, *Guidance for Industry*: 2006
7. Swiss Agency for Therapeutic Products, Gene therapy/GMO environmental data, *Swissmedic*: 2017
8. Visit: www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011392.pdf
9. Visit: ec.europa.eu/health/human-use/clinical-trials_en
10. Visit: ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
11. Visit: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/03/news_detail_002923jsp&mid=WC0b01ac058004d5c1
12. Visit: www.executiveinsight.ch/application/files/9415/2101/8279/14_initiatingearly.pdf
13. Visit: embed.topra.org/sites/default/files/regrapart/1/6579/2_focus_-_real_world_experience_of_prime_and_pim_applications.pdf

About the authors

Dr Michael F Murphy's professional career has spanned 30 years, and his positions emphasise the integration of medical and scientific acumen with operational excellence. He is board-certified in psychiatry, with a doctorate in pharmacology, training at Tulane University, Stanford University, and the Icahn School of Medicine at Mount Sinai, US. In 2017, he was the recipient of the Clinical Research and Excellence Lifetime Achievement Award and selected as one of the 100 Most Inspiring People in the life sciences industry. His supervisory responsibilities as Chief Medical and Scientific Officer at Worldwide Clinical Trials are international in scope.
Email: michael.murphy@worldwide.com

Dr deMauri Mackie is a member of a unique fellowship programme at Worldwide Clinical Trials, which combines didactic and experiential training across R&D activities for novel chemical entities, biological products, and devices. She has a BA in biochemistry from the University of Pennsylvania, US, and a PhD in cellular and molecular medicine from Johns Hopkins University, US.
Email: demauri.mackie@worldwide.com

Sophie Humphrey has worked in the clinical research industry for over 10 years, five of which have been at Worldwide Clinical Trials, filling lead roles within regulatory affairs, business development, and study start-up in fast-paced CRO environments. Sophie has experience of submission management, as well as providing expertise on legislative framework, project representation, and strategy on regulatory and development activities of trials. Her regional experience extends to EU, the Middle East, Africa, and Asia-Pacific across a wide range of therapeutic indications.
Email: sophie.humphrey@worldwide.com

Dinah Otieno has worked in global clinical study start-up and regulatory affairs for the past decade and has been the Global Start Up and Regulatory Manager at Worldwide Clinical Trials since 2016. Dinah is responsible for site regulatory compliance and drug release activities for country site activation. She has over 17 years' experience within the academic and CRO industry, where she oversees preparation of various strategic and process improvements for streamlined working procedures in regulatory and clinical start-up submission to country-specific regulatory agencies. Dinah obtained her undergraduate degree in Psychology from the University of North Carolina at Greensboro, US.
Email: dinah.otieno@worldwide.com