Challenges Become More Concentrated in Gene Therapy Development, Experts Say

By Conor Hale

Experts came together to speak at a WCG Rare Disease Day webinar on the main scientific and ethical considerations of research in rare and ultra-rare diseases, the majority of which are driven by hereditary genetic mutations.

Institutional review boards continue to face the same challenges in clinical research as the industry begins to explore novel gene therapies, said Lindsay McNair, WCG’s chief medical officer. The theoretical risks of cutting-edge technologies, and the challenges of conducting trials in smaller patient populations, are much more concentrated in a gene therapy setting, she added.

“It’s always a consideration if the risks of a therapy are reasonable, in relation to potential benefits,” McNair said. “But this can be really difficult to assess with new mechanisms and new therapeutic approaches that we just don’t know much about.”

Citing previous cases of secondary cancers that developed in patients as the result of errant placement of introduced genetic material, McNair described the task of weighing a treatment’s short- and long-term risks against the unknown.

“If you’re treating a cancer, the risk of secondary cancer may be a risk that you’re very much willing to take. But if you’re treating a rare disease that causes progressive deafness over several decades, and one of...

Mayo Clinical Reports Treatment Benefits May Be Exaggerated in Early Clinical Trial Results

By Conor Hale

The first two randomized controlled trials of treatments of chronic medical conditions are much more likely to overstate any beneficial effects when compared to later clinical research, according to a group led by researchers from the Mayo Clinic, which urged regulators to be wary of data from early studies in a product’s chain of evidence.

Early RCTs in conditions such as stroke, chronic obstructive lung disease, diabetes, coronary artery disease and kidney disease can demonstrate extreme, unpredictable fluctuations in the measurement of treatment effects, along with large exaggerations of benefits, they wrote.

Dubbed the Proteus phenomenon, subsequent clinical trials and replications tend to contradict or moderate treatment effects over time. Researchers are encouraged to take many early RCTs with a grain of salt.

“Clinical and policy decisions made using the early exaggerated effect may be misguided and based on incorrect estimates of benefits and harms,” they wrote, in their paper published in Mayo Clinic Proceedings. “Considering the increasing morbidity and mortality of chronic medical conditions, decision makers should act on early evidence with caution.”

The researchers examined 70 meta-analyses, published between January 2007 and June 2015, that covered 930 clinical trials with...
NIH RA, Lupus Research Program Releases Cellular Datasets to Industry

An NIH research collaboration of rheumatoid arthritis and systemic lupus erythematosus has made its datasets, which characterize disease cells, available to the public. The program hopes researchers mine the data to accelerate the development of products and explore potential targets for new treatment options. The Phase I study, part of the Accelerating Medicines Partnership, analyzed individual cells from the lining of joints affected by rheumatoid arthritis and from kidneys damaged from lupus, hoping to better understand the specific pathways at play, and help to provide a new approach to understanding autoimmunity. The data also has potential implications for precision medicine, the NIH said. The program is one of three launched in 2014 as part of a public-private partnership, lead by the NIH’s National Institute of Arthritis and Musculoskeletal and Skin Diseases, in cooperation with the National Institute of Allergy and Infectious Diseases. Investigators are currently conducting Phase II studies, including larger cohorts of patients. The Foundation for the NIH manages the partnership with industry, including AbbVie, Bristol-Myers Squibb, Merck, Pfizer, Sanofi and Takeda Pharmaceuticals, as well as nonprofits such as the Arthritis Foundation, Lupus Foundation of America, Lupus Research Alliance and Rheumatology Research Foundation. The Phase I data are freely available through the NIAID-sponsored Immunology Database and Analysis Portal, at www.immport.org. Genomic data are also being submitted to be made available through the NIH’s database of Genotypes and Phenotypes, at: www.ncbi.nlm.nih.gov/gap.

FDA Adopts ICH’s E6(R2) Addendum to its GCP Guideline

The FDA adopted an update to the ICH’s E6 guideline on good clinical practice, including an addendum on advances in clinical trial design and processes to improve efficiency. In addition, the document recommends that sponsors develop a systematic, prioritized, risk-based approach to monitoring clinical trials. Dubbed E6(R2), with the final version adopted by the international group of regulators in November 2016, the guidance includes standard operating procedures for electronic trial data system setup, installation and use, as well as descriptions of system validation, functionality testing and data collection. It also reflects the increased use of electronic communications since the initial publication of the guideline in 1996. Other amendments include a recommendation that sponsors document their rationale for choosing on-site or centralized monitoring, or a combination of the two. Reports of on-site and/or centralized trial monitoring should be provided to the sponsor with documentation of the results in enough detail to verify compliance with the monitoring plan. The full guidance is available here: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM464506.pdf.

Market Research Report Predicts Large Expansion in Global Clinical Trials Management

The size of the global clinical trial management (CTM) market is estimated to more than double over the next five years, reaching $1.37 billion by 2023, according to a report by Allied Market Research. Clinical trial management accounted for $570 million in 2016, with North America being the largest contributor. The sector is expected to grow by 13.4 percent annually by 2023, with China and the Asia-Pacific region seeing the largest gains, the report said. The growth is being driven in part by the need for novel drugs and medical devices, as well as increasing trends in outsourcing and the globalization of clinical trials. Additionally, demand has increased due to the growing R&D expenditures and the benefits of employing clinical trials management strategies. However, according to the report, high costs and a lack of skilled professionals is projected to hamper growth efforts. Software is currently the dominant segment in the market. Enterprise systems contribute the most toward market growth, but site-based systems are expected to overtake, through their ease of use.

NIH Launches Global Study to Track AMD Progression

The NIH, through the National Eye Institute, is launching a five-year clinical study to examine the natural history of early age-related macular degeneration (AMD). The study plans to follow 500 people — visualizing structures within the eye, and measuring their function — to identify biomarkers of progression before the disease advances to later stages and causes loss of vision. AMD is the leading cause of vision impairment and blindness among people age 50 and older in the U.S., the NIH said, with 10 to 20 percent of early AMD patients progressing to late-stage disease within five years, influenced by a combination of age, genetic and other factors. Researchers have identified 52 independent genetic variants associated with AMD, but further research is needed to determine how these variants influence disease development and progression, the NIH said. The study, NCT03092492, is funded by the NEI, with sites located throughout the U.S., United Kingdom, Australia, Germany and Italy.
Gene Therapy (continued from page 1)

the potential theoretical risks is a secondary cancer, where do you find the balance?”

“We think with the newer vectors that risk is reduced, but we don’t have a lot of long-term data to be able to really understand that,” she said.

In addition, protocol designers need to work to avoid misconceptions about their products, and balance optimism and realism when dealing with patients or families seeking effective treatments, to avoid IRB issues and streamline ethics reviews.

Sponsors should adhere to the descriptions “study drug,” “study regimen” and “participant or volunteer” in their protocols and informed consent documents, to avoid confusion over what is experimental and what is medical care, McNair said.

New is not always better, she added, warning that the majority of products in development don’t make it to approval. It’s important that patients have a realistic understanding of potential risks, and not just hope for the benefits.

For sponsors looking for a place to start in developing gene therapies, experts said retinal diseases provide an attractive early target for testing in vivo technology.

Treatments for the retina, including indications that cause progressive blindness, present good test cases for a variety of convergent reasons, said Daniel Kavanagh, WCG’s senior director of biosafety and gene therapy.

Primarily, risk to the patient is mitigated because the therapies do not target a vital organ, and treatment can be administered one eye at a time, Kavanagh said. In addition, sponsors are not required to produce a large amount of vector to deliver the therapeutic genetic material.

The eyes are also immune-privileged — they are isolated from the body’s immune system as a whole, so any injections are less likely to cause an inflammatory response in the patient, he said. Meanwhile, the retina itself is a highly specialized tissue; the targeted genes and proteins may not be expressed elsewhere in the body and have no function, which can help contain the effects of the treatment.

Clinical trials in these indications can be very attractive to researchers worried about their statistical power, Kavanagh said.

“It turns out it’s much more powerful to test one person in one eye, and have a comparator eye untreated, than it is to have a control in the form of a placebo-treated person,” he said. “These clinical trials tend to use both kinds of controls built-in — but it’s a significant, practical advantage to be able to treat one eye first and the other eye later, and to do your statistical comparison that way.”

The risk-benefit ratio also can be more favorable because study participants are already at a high risk for blindness or advanced disease.

“If you can fix the retina, and if the target protein is uniquely expressed in the retina, then you’ve cured the patient,” Kavanagh said. “So it’s an attractive prospect for your first indications for novel gene therapies.”

While the precise definition of what makes a gene therapy a gene therapy can vary depending on who you talk to in the industry, the FDA describes Spark Therapeutics’ retina-targeting Luxturna (voretigene neparvovec-rzyl) as one of the first gene therapies, and the first approved to treat an inherited disease caused by mutations in a specific gene.

In August 2017, the FDA approved what it described as the first gene therapy, Novartis’ CAR-T immunotherapy Kymriah (tisagenlecleucel), for younger patients with B-cell precursor acute lymphoblastic leukemia.

Last December, Luxturna was approved in biallelic RPE65 mutation-associated retinal dystrophy, which can cause complete blindness, and affects approximately 1,000 to 2,000 patients in the U.S.

After launch, the one-time treatment was widely described as the most expensive medicine available, with a $850,000 price tag that Spark justified with the therapy’s durable, long-term benefits to vision.

Luxturna uses a naturally occurring adeno-associated virus as a vector to deliver a normal copy of the RPE65 gene directly to retinal cells, spurring production of the protein that helps convert light to an electrical signal and restore vision. The FDA requires the therapy be administered in each eye at least six days apart.

Safety and efficacy were established in a clinical development program accruing a total of only 41 patients. A Phase III trial with 31 participants measured the change in a subject’s ability to navigate an obstacle course in low light, with 90 percent experiencing improvement over one year.

“We’re at a turning point when it comes to this novel form of therapy and at the FDA, we’re focused on establishing the right policy framework to capitalize on this scientific opening,” said FDA Commissioner Scott Gottlieb following Luxturna’s approval. Currently, the vast majority of gene therapy studies are in early phases, with 75 percent in Phase I and 20 percent in Phase II, compared to less than 5 percent in Phase III.

In 2018, the agency plans to issue a suite of disease-specific guidance documents on the development of gene therapy products, Gottlieb said, including new clinical measures for evaluation and review, starting with hemophilia before more common single-gene disorders.
Free Online Transparency Tool Tracks Clinical Trials Reporting Compliance

By Conor Hale

The FDAAA TrialsTracker, an online tool that charts whether individual sponsors report their study results on ClinicalTrials.gov in compliance with federal laws and regulations, launched Feb. 19. The data transparency project was developed by the University of Oxford’s Evidence-Based Medicine DataLab, and is available to the public.

Updated daily, the online tool also calculates the amounts the federal government could fine for noncompliance — although, to date, this number remains at $0, according to the tracker.

“In the absence of formal sanctions from the FDA and others, we argue tools such as ours — providing live data on trial reporting — can improve accountability and performance,” the developers wrote in a prepublished paper outlining the methods and results of the tracker.

“In addition, our service helps sponsors identify their own individual trials that have not yet reported results: we therefore offer positive practical support for sponsors who wish to ensure that all their completed trials have reported,” they wrote. Sponsors can immediately improve their ratings by reporting their results, as opposed to more static, academic publications on clinical trial transparency.

To date, 116 of 131 trials have reported their results, amounting to 88.5 percent in compliance. According to the tracker, the U.S. government could levy fines against the 15 overdue sponsors totaling just north of $1.2 million. The database also allows a search of more than 15,000 currently ongoing clinical trials.

The ClinicalTrials.gov reporting requirements began with 2007’s FDA Amendment Act, and were later expanded by an NIH final rule that came into effect in January 2017, encompassing 42 CFR Part 11. Although sponsors are required to disclose results for applicable clinical trials within one year of their primary completion date — regardless of the product’s approval status — legal deadlines have begun to pass unfulfilled, as of January of this year.

Applicable trials include interventional studies of FDA-regulated products outside of Phase I or device feasibility testing. The studies include at least one U.S.-based site, initiated after Jan. 18, 2017. The FDA may fine sponsors up to $10,000 for each day results are not submitted past the deadline.

The tracker lists a study as due to report results after one year plus 30 days, to allow for reasonable delays in processing by ClinicalTrials.gov. The 30 days also represents the 30 days also represents the deadline for reasonable delays in processing by ClinicalTrials.gov.

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With about one-in-three meta-analyses demonstrating the Proteus effect, regardless of the cause, users of early evidence in patient care should consider this effect when weighing harms and benefits, the researchers said.

And with recent increases in the rate of global clinical trials, even a small number of questionable trials could pose dangers.

“This is even truer for clinical trials published early in the chain of evidence, because a new breakthrough usually has more impact and media attention,” they wrote.


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an average follow-up of 24 months. The meta-analyses were selected from the 10 general medical journals with the highest impact factor. Those with fewer than five RCTs were excluded.

They found that 37 percent of the meta-analyses demonstrated exaggerated early effects in the first two trials — with an effect size almost three times larger than the overall size, on average — or showed the strongest heterogeneity between the first and second trial.

The effect was more frequently demonstrated in endocrinology, compared to cardiology, oncology, nephrology or pulmonary medicine, and was much more frequently seen when evaluating a medication, as opposed to a procedure or other intervention.

The causes of this are unclear, with the exaggerated effects not being significantly associated with several different aspects of clinical trials potentially linked to a risk of bias — such as the study’s size, length of follow-up, number of sites, blinding, funding sources or whether the trial was stopped early. Eighteen percent of RCTs were funded by nonprofit or governmental sources, and two-thirds were conducted in outpatient settings.

Researchers stated that possible explanations include shifts over time from efficacy evaluation in earlier trials to effectiveness evaluation in later trials, and that subsequent trials have wider inclusion criteria compared with earlier trials that may be highly selective in their enrollment.

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“This is even truer for clinical trials published early in the chain of evidence, because a new breakthrough usually has more impact and media attention,” they wrote.

Investigational sites must be evaluated based on each element of contribution to form a fully dimensional picture for study consideration. Some sites excel at recruitment, but lack therapeutic expertise. Some sites with inexperienced staff have tactical/logistical expertise. Those sites lacking in some areas may tip the scales in their favor with other valuable strengths. We may miss out on good sites if we do not consider the entire picture.

While research experience is an essential factor, it is not the only factor when considering investigators for studies. It is not a mere yes-or-no checklist, with cut-and-dry questions regarding staff research experience. You owe it to the study, and to the investigational site, to dig deeper than an initial dismissive reaction when evaluating an inexperienced investigator. You should consider factors such as weighing individual value against overall research experience. Look at their clinical experience in the therapeutic indication. An investigator may be a clinical expert in the disease under treatment with little-to-no research exposure, so you must ask the critical questions such as, is the study design straightforward enough to justify the clinical expertise in lieu of clinical trials expertise? Has the investigator aligned themselves with a mentor who can advise on the responsibilities and role of an investigator? Has the investigator completed GCP and human subject protection training? Has the investigator acquired an experienced study coordinator or have access to credible support staff? How much have the staff accomplished along the training pathway to compliance? These preliminary findings can greatly influence the decision to use a new investigator.

There are inherent qualities that make the fabric of a great investigator; humility, diligence, compassion, willingness to seek knowledge and accept assistance and take all necessary steps in pursuit of this massive assimilation. All adjectives that describe an experience with Dr. Smith.

Dr. Smith’s (name changed for story) transition to clinical research read like textbook instruction on how to become a successful principal investigator. His transparency and integrity helped me to be more open in my consideration of new research sites/staff during site selection and to never dismiss someone for lack of experience alone.

I came to know Dr. Smith many years ago during a primary care hypertension study. His site was being considered as an add-on site because the study enrollment was critically behind schedule. The project need for additional sites/subjects was so great that they were considering sites with no prior history with the sponsor, including inexperienced investigative sites. The first couple of sites I assessed were not appropriate for the study, and I did not have especially high hopes for a successful evaluation of Dr. Smith’s site due to his lack of clinical research experience. What I found after concluding the evaluation visit with him was the direct opposite of my inaccurate, preconceived misgivings.

Dr. Smith was a busy primary care physician who had been methodical in uncovering what it truly meant to be a principal investigator — the commitment, the level of education, the responsibilities and the fiscal and clinical demands of attracting and sustaining a clinical trial, to include staff, infrastructure and equipment.

Dr. Smith spent an hour discussing his plan for patient enrollment and produced a redacted list of patients from his database to confirm access to potential patients. He was so scrupulous with his site information that it was as if he had been coached on the most effective processes for site creation and presentation. To bring in a clinical research consultant to teach him the correct order of establishment from the beginning was a significant investment in training, a demonstration of due diligence far beyond what was expected.

Dr. Smith reviewed the study design with me and understood the concept of clinical research vs. clinical practice. He verified that they could accommodate the schedule of assessments, as many of them were already completed as standard in his clinic. He was familiar with the class of drug and genetic predisposition to the disease state, far better than some of the more experienced investigators in the trial.

The study design was straightforward and perfectly complimented the standard of care and his level of experience. It was ideal for a new investigator as it allowed for therapeutic expertise contribution that did not overshadow simple inexperience with its complexity.

I was impressed with his extensive efforts to set up the ideal research site, his diligence in completing his research education and the level of preparation taken to prepare his site staff for clinical trials. Dr. Smith’s financial and personal investments in this role thundered due diligence more loudly than an experienced research site resting on its laurels. I recommended his site for the study, but left the project before I confirmed if it had been selected. It would have been a missed opportunity had they not been chosen by the sponsor.

Elizabeth Blair Weeks-Rowe, LVN, CCRA, has spent nearly 14 years in a variety of clinical research roles including CRA, CRA trainer, CRA manager and clinical research writer. She also is author of the novella Clinical Research Trials and Triumphs. Currently she works in relationship development/study startup in the CRO industry. Email ebwcra@yahoo.com or tweet @ebwcra.
# Drug & Device Pipeline News

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DBV Technologies Announces Results for Milk Allergies

DBV Technologies announces results from Phase II study of Viaskin Milk in milk-allergic patients. Positive preliminary results support Viaskin Milk’s potential as the first treatment for patients suffering from IgE-mediated cow’s milk allergy (CMPA), an unmet medical need for which there are no approved therapies. A statistically significant desensitization to milk was observed in children ages two to 11 treated with Viaskin Milk 300 µg for 12 months. The Viaskin Milk Efficacy and Safety (MILES) trial is a multi-center, double-blind, placebo-controlled, randomized Phase II/III trial to study the safety and efficacy of Viaskin Milk conducted at 17 sites in North America where 198 patients were randomized 1:1:1:1 into four treatment arms to evaluate three doses of Viaskin Milk, 150 mcg, 300 mcg and 500 mcg, compared to placebo. Patients received a daily application of the Viaskin Milk patch over 12 months. Following analyses of the data, the 300 µg dose was identified as the most effective tested dose for children.

ObsEva SA Reports Positive Results from Trial for IVF

Geneva reported positive top line results of the IMPLANT2 Phase III clinical trial of its oral oxytocin receptor antagonist, nolasiban, which is being developed for improving pregnancy rates following in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) procedures. IMPLANT2 is a Phase III, randomized, double-blind, clinical trial assessing nolasiban compared to placebo for improving the rate of pregnancy in patients undergoing IVF or ICSI due to low fertility. The Phase III trial included 778 patients from across nine countries. Following ovarian stimulation, egg retrieval and fertilization, eligible women were randomized to receive either a single, oral dose of 900 mg nolasiban or placebo four hours before D3 or D5 fresh, single ET. Patients received either a single 900 mg dose of nolasiban or placebo (1:1) orally on the day of embryo transfer (ET). The primary endpoint of the clinical trial was met, with an absolute increase in ongoing pregnancy rate at 10 weeks of 7.1 percent (placebo 28.5 percent and nolasiban 35.6 percent, p = 0.031). This represents a relative increase of 25 percent in the ongoing pregnancy rate after administration of nolasiban compared to placebo.

Amgen Receives Positive Opinion Expanding Use Of XGEVA

Amgen announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion to expand the current indication for XGEVA(denosumab) to cover skeletal-related events in patients with multiple myeloma. The study was an international, Phase III, randomized, double-blind, multicenter trial of XGEVA compared with zoledronic acid in the prevention of skeletal-related events in adult patients with newly diagnosed multiple myeloma and bone disease. In the study, a total of 1,718 patients were randomized to receive either subcutaneous XGEVA 120 mg and intravenous placebo every four weeks, or intravenous zoledronic acid 4 mg and subcutaneous placebo every four weeks, plus investigators’ choice first-line antimyeloma therapy. XGEVA successfully met the primary endpoint, demonstrating non-inferiority to zoledronic acid in delaying the time to first on-study skeletal-related event in patients with multiple myeloma (HR=0.98, 95 percent CI: 0.85-1.14). The median time to first on-study skeletal-related event was 22.83 months for XGEVA and 23.98 months for zoledronic acid.

Intensity Therapeutics Reports Positive Data from Cancer Trial

Intensity Therapeutics announced completion of the first safety cohort (A) of the Company’s Phase 1/2 international clinical study evaluating lead product, INT230-6. Following intratumoral drug injections into superficial lesions in six patients with either ovarian, thyroid, head and neck or skin cancers, there were no dose limiting toxicities. INT230-6 is a novel, anti-cancer drug for direct intratumoral injection. The product contains potent anti-cancer agents that disperse throughout tumors and diffuse into cancer cells. INT230-6 was identified from Intensity’s DfuseRx platform and is being evaluated in a clinical trial; IT-01. In preclinical studies INT230-6 administration eradicated tumors by a combination of direct tumor kill coupled with recruitment of dendritic cells to the tumor micro-environment that induced anti-cancer T-cell activation. The study will characterize the systemic pharmacokinetic profile of multiple doses of INT230-6’s drug substances after single and then multiple intratumoral injections. Exploratory analysis will characterize patient outcome, as well as evaluate various tumor and anti-tumor immune response biomarkers that may correlate with response.
Upcoming Event Highlights

Conferences
APRIL 4-5, 2018
Let’s Improve Clinical Trials Today!
Oxon Hill, MD

Webinars
MARCH 15, 2018
Getting Real About Real World Evidence - Practical Next Steps for Drug and Device Manufacturers
Sonali P. Gunawardhana Esq., one of the sharpest legal minds to emerge from the FDA in recent years, will walk you through the fast-moving RWE changes currently affecting agency and business decisions alike.

MARCH 20, 2018
Paying Clinical Trial Subjects Deconstructing the Most Important Ethical & Practical Considerations
Reasons to pay research participants, in regard to fairness and the role that payment plays in facilitating recruitment. Find out what the regulators think you should be doing — what’s ethical and what’s legal.

Interactive Workshop
APRIL 10-11, 2018
Clinical Quality Assurance: Roles and Responsibilities for Auditors and Managers
Learn what FDA investigators use to evaluate your sites, and how to develop risk-based CQA processes and compliance readiness.
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