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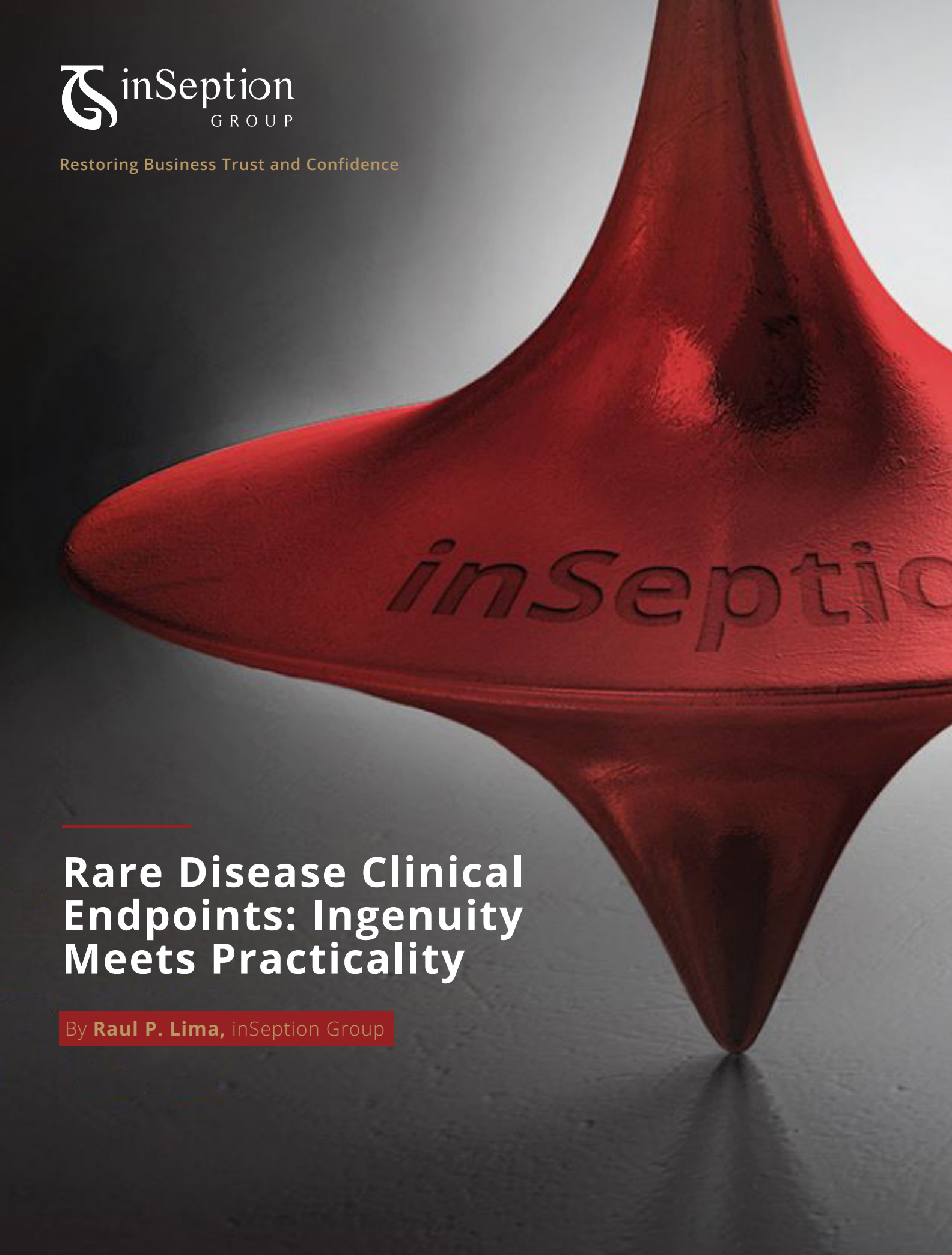

Rare Disease Clinical Endpoints: Ingenuity Meets Practicality

By **Raul P. Lima,** inSeption Group

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Determining gene therapy endpoints that make sense, as well as then contextualizing those endpoints so they are accepted by regulators and payors, is an enormous challenge. Little to no data exists for many of the rare diseases targeted by gene therapies — in terms of how change could be defined, the implications of that change, and/or what "normal" disease progression looks like (i.e., natural history data).

Additionally, basic science is not the only driver for a clinical study; great science can be undermined by sloppy execution or when control of a lab does not translate well to clinical practice. It's no surprise to anyone who works in translational or clinical research that choosing the right endpoints is one of the most important decisions you will make.

Endpoints determine patient/nurse travel requirements, number of doses to be administered (where and when), how that relates to future visits, etc. In short, endpoint science must intersect with endpoint practicality for a clinical trial to be successful. So, the sooner a sponsor considers endpoints and begins discussions with regulators and payors to discover their expectations, the better.

SCIENTIFIC RESEARCH IS ONLY STEP ONE (NOT THE ONLY STEP)

Scientifically speaking, most, if not all, gene research fundamentally does the same thing: attack the known monogenic target in creative ways,

by suppressing it, overexpressing it, whatever is necessary. But defining meaningful biomarker endpoints is more nuanced than just figuring out whether the protein of interest is being proliferated or silenced (which itself is often very hard!).

Assays must be developed to gauge whether, and to what extent, the therapy is accomplishing its target task, and if it is doing it with specificity. Typically, you are going to clinic without the benefit of volumes of animal research or studies performed in healthy patients, neither of which are feasible/possible in gene therapy development. So, it often is hard to describe what is occurring, mechanistically, at any given time — or, more importantly, over a period of time — in humans.

In gene therapy, a vital potency assay, for example, might not even be developed by the time research begins in humans, or it might not be refined enough to proceed to market. Still, even without the assay, you may have sufficient safety data (i.e., it has a positive safety profile) to begin human studies and generate more meaningful human data. Either way, CMC and clinical are generally running in parallel, without the same translational time typical of small molecule development, which will create pressure on both the CMC and clinical teams.

"MEANINGFUL" MEANS DIFFERENT THINGS TO DIFFERENT STAKEHOLDERS

After you have a metric to gauge therapeutic effect and have developed an assay, the findings must be studied and then contextualized to determine efficacy. For example, researchers discover a therapy expresses 30% more protein in a target. But what meaning does that metric hold? This is why natural history studies are so vital: they establish meaningfulness and context.

Take an example of a patient suffering from a degenerative genetic disorder that attacks neurons, slowly costing them limb control. Assume that 30% uptick in target protein expression has granted the patient improved mobility. We might measure this clinically through a six-minute walk test where we track change in total distance over time. The hard part is determining how that 30% protein expression translates into increased walking distance (or lack of decreased distance, in the case of slowing degeneration). Then you also have to take into account what that distance means to patient health or quality of life — enough to warrant the therapy's cost over current treatments (or lack of therapy)?

This meaningfulness question, while basic, is often central for rare disease studies because it has not been answered as satisfactorily as for many larger diseases. Those other diseases often have an established regulatory pathway. With many rare diseases, you will be blazing your own trail.

So, therapy developers not only need to prove clinical benefit, they need to prove the benefit is meaningful to the patient. An objective biological benefit is unlikely to be compelling for regulators and certainly will not convince payors; the results have to impact real life, or what is the point of treatment? Accordingly, the key question to answer regarding endpoints and their collection is, "What is the minimal clinically important difference [MCID]?"

Consider that cardiovascular or asthma endpoints are well understood. For afflictions that resemble those diseases, endpoints can be cobbled together with some sense of surety. But rare genetic diseases do not necessarily look like other diseases. Or, they may have long courses of degradation.

For example, the genetic disorder described above, which diminishes a person's ability to walk: one patient may shuffle a bit in their 40s and end up using a walker during their geriatric years. Another patient may be in a wheelchair

by 25. It takes time for the disease to attack the neurons to a point where symptoms manifest, and it is unclear why. Due to this variability, it is extremely difficult to show cessation, slowing, or (potentially) reversal of the disease in a timeline that is amenable to the scientific and financial constraints of drug development.

Scientifically, patients are often very rare. Many are locked behind doctors who don't participate in clinical trials, so there will never be a large, powered mega-trial in a rare disease. From a business standpoint, endpoints must be identifiable within a year (maybe two years, at most). To work within this structure, the definition of MCID within a clinical endpoint may actually comprise a combination of factors: a mix of observable, measurable elements moving in the same direction when data is pooled.

Thus, the goal becomes establishing a preponderance of evidence, versus a single endpoint. Throughout this discovery process, the therapy developer should be speaking with regulators to interpret what they will accept. That developer should also consider early discussions with payors to understand what efficacy must be shown, and what data must support it, to make a case for reimbursement.

Notably, many advanced technologies and processes (even though they seemingly make a compelling case for efficacy) are not validated in a way that regulators or payors will accept. For example, in researching limb movement disorders, one can test patient movement with sensitive gyroscopes that gauge incredibly small changes in foot angle, distance between strides, and other parameters. The data is fascinating and scientifically informative, but it is not validated for regulators; they do not know its implications or understand how to interpret it.

Again, this is where natural history studies prove invaluable in establishing a baseline for "normal" disease progression. But it also is an opportunity to work with vendor partners, many of whom are eager to work with their clients toward the end of seeing their technology or process validated.

TRANSLATIONAL MEDICINE HAPPENS IN THE WORLD, NOT A TEXTBOOK

From a scientific research perspective, finding a way to proliferate or silence (as needed) the protein of interest equals success. But once medical scientists become involved, the translational bridge must be constructed — arguably, the hardest step in gene therapy development. How do we apply that science and make it meaningful? In traditional (i.e., small molecule) studies, animal studies are conducted and Phase 1 work is completed in healthy volunteers to get a sense of the molecule's behavior. By the time Phase 2 arrives, the molecule is relatively well understood.

But every gene therapy company, in my experience, plans Phase 1 studies in patient volunteers. There are no healthy volunteer studies. Phase 1 studies are planned, written, and included in the IND application. Simultaneously, the GLP toxicology study is ongoing. In small molecule studies, GLP tox studies are complete by the time a treatment reaches patients. In gene therapy, for example, we may submit an IND with 3 months of tox data, as well as agree to submit 6 and 9 months of GLP tox data once available.

That compression of activities brings discovery research and medical science much closer on the development timeline. So, to avoid (potentially) years of additional development, the individuals and teams conducting translational work in gene therapy must be adept and nimble.

A Phase 1/Phase 2 study might enroll 10 patients. Context, however, is that a Phase 3

study might only have 50 patients. That means 10 of the 60 patients who receive this therapy before approval will provide a full 17% of your safety data and all of your long-term data. Organizations cannot afford to waste that opportunity or that data. Again, the criticality of an ongoing conversation exploring and understanding what regulators and payors expect to see, beginning as early in development as possible, cannot be overstated.

START EARLY… BUT WHERE?

Simply put, almost everything has to be started early in a gene therapy study. Because of the compression of activities once the study begins in earnest, the process is comparable to a rocket launch: months or years of research, planning, failures and successes, all leading up to a high-stakes flurry of activity. Those conceiving the study often do not know what is practical (or what is meaningful), because the therapy approach has not been attempted in either the academic or clinical realms. So, researchers are throwing everything at the problem to see what sticks. From a checklist standpoint, it is very boutique.

For example, clinical operations might have to submit 10 RFPs to 10 different sensitive measurement companies to find out what equipment is available. They may have to ask numerous hospitals how they measure progression of this disease, and practice across institutions and HCPs often varies far more than it does for more well-known diseases. How do they measure progression in this other indication that presents similarly? What are the various ways they could do it? These exploratory discussions extend to finding out what equipment each hospital has and whether it is validated to accomplish the study's aims.

Additionally, because rare diseases often are poorly understood, neither the diseases themselves nor the way they attack the body have been well studied, so identifying patients is challenging. One must start early to find sites and key opinion leaders that have encountered these patients. Then, the study must account for the fact that rare disease patients commonly are misdiagnosed, or physicians might disagree on current best practices for managing/tracking progression, as well as treatment options.

This is another reason for the shift toward a "preponderance of evidence" approach, versus one or two focused endpoints. That adaptation has been necessary to effectively study and treat rare disease (and gene therapy tends to focus on rare diseases). If fewer than 10,000 patients worldwide have been diagnosed with a disease, you cannot run a statistically powered study to show a clinical endpoint. That might take a thousand patients, whom the drug may never actually ever be used in. The study will not be able to open sites close enough, so you often need to bring patients to the site. But many patients do not want to travel or can't get away from work and/or family. Moreover, some patients will have no interest in participating in a clinical study or lack the means to do so.

CONCLUSIONS

The speed and narrow focus of a gene therapy clinical trial become problematic if an organization is not thinking about endpoints early, because then they lack critical data when it becomes necessary to provide to regulators and/or payors. The organization then may be forced to add development time to go back for that data. Avoiding this outcome means creating a funnel of potential strategies and tools early: shoot broadly in your earlier study, whether that is a natural history study or Phase 1/Phase 2.

Creatively implementing as many elements or angles as possible in this early study teaches

researchers a lot about which endpoints do not matter or cannot be accomplished, be it remotely or in the clinic. Ultimately, the goal is to narrow that funnel significantly early in development, empowering researchers to move forward only with meaningful data, control the trial more closely, execute it more tightly, and lower its general late-stage burden.

To learn more, contact the author and visit inseptiongroup.com.

To learn more, call:
Joseph Arcangelo Sr.
Co-Founder and Managing Partner
of **inSeption Group**
jarcangelo@inseptiongroup.com
267-498-5092

ABOUT THE AUTHOR

Raul P. Lima is Executive Vice President of Clinical Operations at inSeption Group. He is a proven leader in clinical operations with over 20 years of strategic, tactical, and hands-on experience in the management of global, multi-center clinical trials. He has extensive experience with timeline, clinical trial budget, and people management, and has successfully led cross-functional teams, including at CROs. Raul has repeatedly executed strategies ensuring that clinical operations activities supporting clinical trial management are conducted effectively and efficiently, are quality-driven, and comply with all applicable regulations. He possesses an uncanny vision and expertise in communicating that vision to influence strategies that progress cross-functional projects, as well as an unwavering passion for championing development.

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inSeption Group is a full-service, global outsourcing organization built on a foundational culture of exceptional service and quality. This culture attracts a subset of people who take a personal responsibility to deliver on what has been promised. inSeption Group's ability to custom-build teams with these experts, while providing valuable continuity, distinguishes our approach from traditional outsourcing options.

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