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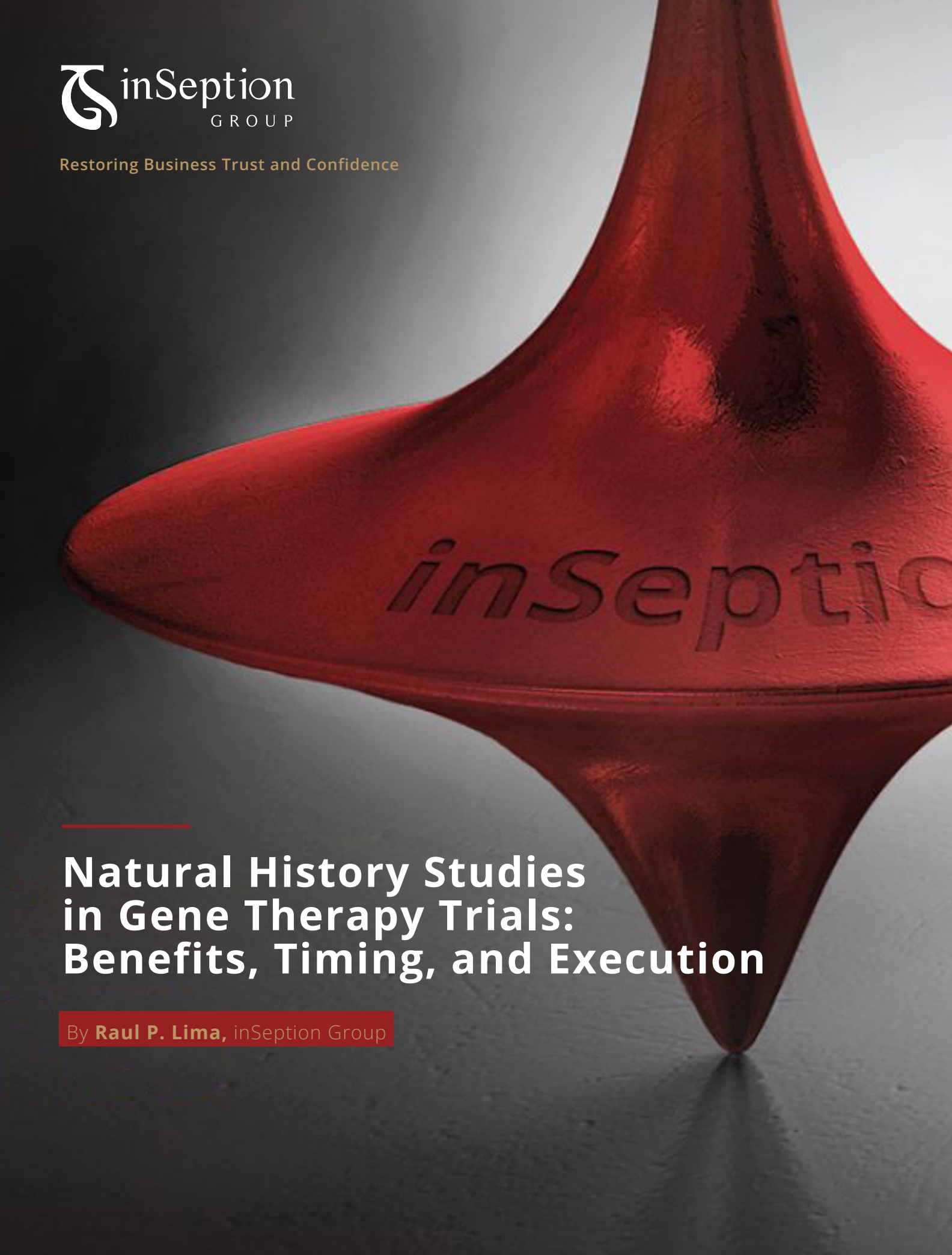

Natural History Studies in Gene Therapy Trials: Benefits, Timing, and Execution

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

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A traditional regulatory pathway requires being able to accurately describe the normal clinical course of the disease. This can be difficult with rare diseases because existing academic data is incomplete and/or often poorly controlled. Moreover, data rarely exists that is relevant to specific, high-sensitivity endpoints needed for a gene therapy study, because it would not be relevant in clinical practice or simply has not been done before.

Accordingly, companies focusing on gene therapy and other rare diseases should consider performing a natural history study (NHS) to confirm the veracity of their data. This should be considered at or before Phase 1/Phase 2 clinical trials because several years of natural history data may be needed to establish the real-world context for any change an organization wants to attribute to its therapy.

DEVELOP A FULLER PICTURE OF THE DISEASE

Monogenic disorders present an attractive target for gene therapy research because their etiology is well understood. With a single gene at the root of a disorder, fewer variables are associated with interrupting the function of that gene. However, most of these diseases are rare. Often, they are not well-studied in the current published literature.

Even a renowned tertiary institution (e.g., the Mayo Clinic) may only see a few cases of a given rare disease each year, so pharmaceutical sponsors exploring therapies are unlikely to be able to describe progression of the disease for the median patient in the population, which is a question the agency will often ask in some form.

Drawing that data from a limited number of patients (i.e., placebo/sham groups of your already very small studies) leads to extraordinarily high variability in the data produced.

Even if the sponsor performs a placebo/sham-controlled study of 50 patients, up to half of those individuals could be placebo/sham patients, so the study provides only a very small slice of the contextual pie. An NHS can be used to establish a background data set that is longer than the (interventional) clinical research to confirm the sponsor and its partners are not inadvertently misinformed by seeing a small part of the of the longer pattern of the disease.

Also, both disease progression and therapeutic intervention impact how patients lead their lives. Consider, a person wearing a helmet may (deliberately or unwittingly) engage in riskier behaviors than if they were not wearing a helmet. Similarly, if patients recover a previously lost faculty during a clinical trial (i.e., due to the therapy) — something for which they had developed coping mechanisms — their behavior will change. Those coping mechanisms must be understood so it becomes possible to anticipate/predict those behavioral changes and to account for them in the trial protocol. These sorts of behavior changes will not be easily captured through placebo/sham groups alone.

NATURAL HISTORY STUDIES ESTABLISH CLINICAL TRIAL FOUNDATIONS

Clinical trial researchers not only need to understand the course of the disease broadly, they need to understand how measurements should be interpreted throughout the course of that disease. But, while clinical trial researchers have access to a wealth of tests and equipment, practicing physicians generally do not hook up patients to finely tuned instrumentation or require patients to fill out numerous patient-reported outcome (PRO) forms.

Such precise measurements may increase the findings' scientific interest, but they rarely translate well into real-world medical practice. Sometimes, the inverse is the answer: commandeer doctors' measurement techniques and adapt them to a timeline palatable for a pharmaceutical company.

For example, with conditions like hemophilia, the course of the disease and the efficacy of a therapy are directly measurable (e.g., a change in clotting factors). But take a different example: neurological conditions — the efficacy of a gene therapy for neuronal degradation cannot be directly measured without taking cuts of the spinal cord. Thus, testing each patient's ability to walk and their very fine motor skills is the only feasible option.

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The NHS provides a venue to practice this collection of endpoints (e.g., use and utility of devices, visit schedules, remote visits, etc.), both scientifically and logistically. It reveals burdens that may affect the vendor, sites, or patients, and can expose information people commonly enter incorrectly into case report forms or the EMR.

Because patients are not being treated, it is easier to censor them from analyses without high risk attached to mistakes. Additionally, it is easy to segregate data from any mistakes. For example, erring with the first few patients in an NHS may cut the patient pool from 60 to 57. Conversely, erring with the first few patients in a rare disease clinical trial may cost a sponsor two of its 10 patients — a huge loss.

The NHS provides the clinical operations team the opportunity to perform a "dry run," which in classic drug development is typically part of Phase 2A — figuring out how to implement the protocol, defining the correct patient population, practicing data collection and patient flow — before the study that houses true efficacy data. It helps to establish biological endpoints that show the protein of interest is being either silenced or proliferated, solving for many long-term clinical trial problems. The sponsor and its vendors learn how efficacy information correlates over a long timeline (i.e., because patients can participate in an NHS for two to three times the amount of time they participate in an interventional trial, with far fewer visits, but longer overall duration).

EXECUTE THE NHS LIKE A CLINICAL TRIAL

The NHS provides valuable context for discussions with regulatory agencies and payors when clinical data is collected later. Organizations unable to provide that context generally hit a brick wall after Phase 2, scrambling to run an NHS while simultaneously running a Phase 3 study — which then directly compete for patients, personnel, and other resources.

While the NHS does not represent an official control group with true randomization, that bar does not need to be cleared for this information-gathering exercise. Data collection spanning multiple sites (and maybe multiple countries), performed with the structure and oversight of CRA monitoring, add to layers to the "quality onion" not typically seen in academic research. Performing the NHS like a clinical trial also means writing and submitting a protocol through institutional review boards (IRBs) and potentially submitting it to your IND/CTA, despite there being no drug involved. Agency feedback may be in gathering agreement on endpoints of interest and potential regulatory approval pathways.

Importantly, this strategy will also encourage hospitals to treat the NHS like a pharmaceutical study. Even though no drug is present, visiting monitors and similar infrastructure will be in place. Hospital administration typically treats sponsored trials very differently from NIH or academic-funded grant initiatives. Treating your NHS as a clinical trial models that they should, too, which can often mean getting valuable resources to be focused on the trial.

MAKE A CASE FOR FUNDING

Day-to-day operations can present major hurdles when research explores uncharted medical territory. Researchers are seeking to define regulatory agency-approved and time-effective endpoints to measure a disorder's progress or a therapy's effectiveness, including metrics by which to gauge that progress/regression.

Researchers are trying to standardize each of those practices along a timeline that harmonizes

with the company's funding cycles. Within an interventional trial, the aim is to show differentiation by one year and significant separation by two years. But payors will ask – again, particularly in gene therapy – what happens in five years? If a drug is approved and five-year data must be collected after the fact, reimbursement is five years away.

Still, a detailed, robust NHS can cost $5 million to $10 million and is best performed between Series B and Series C funding (around the entry into your Phase 1/Phase 2 trial). If you raise a Series B of $50 million, allocating 10 percent of a project's money is a tough sell when many stakeholders believe that funding should go toward the collection of toxicity, animal, or additional human data: something that visibly pushes the project toward its next milestone.

Consider, too, that payors value different data than regulators. Regulators want to vet whether your clinical trial plan will produce data, measurable in unambiguous metrics, that support claims of benefit based on the natural course of the disease. And while regulators will not generally accept NHS data as comparator data, it is publishable and meaningful for payors, the public, and the scientific community at large — and the latter two do not care about the same things regulators do.

Lastly, if started early enough, once sufficient data is collected, the NHS can be leveraged as a rollover mechanism, "seeding" the Phase 3 clinical trial. Patients can be discontinued from (or complete) the NHS and become treatment patients in future studies. This allows interpatient analysis and allows researchers to study each patient against themselves over a long timeline by merging data sets. This is in direct contrast to starting too late in the development cycle, where the NHS will compete with the main (now Phase 3) program and will not run long enough to answer long-term questions of the disease.

FINAL THOUGHTS

It is critical to consider the benefits and impacts of an NHS as early as possible. Considering it early allows it to be in the funding plan. This has many benefits to the program as whole, including collecting important contextual data that may not exist, taking a dry run of the expected clinical study visits, testing deployment of sensitive equipment, and testing endpoint sensitivity.

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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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