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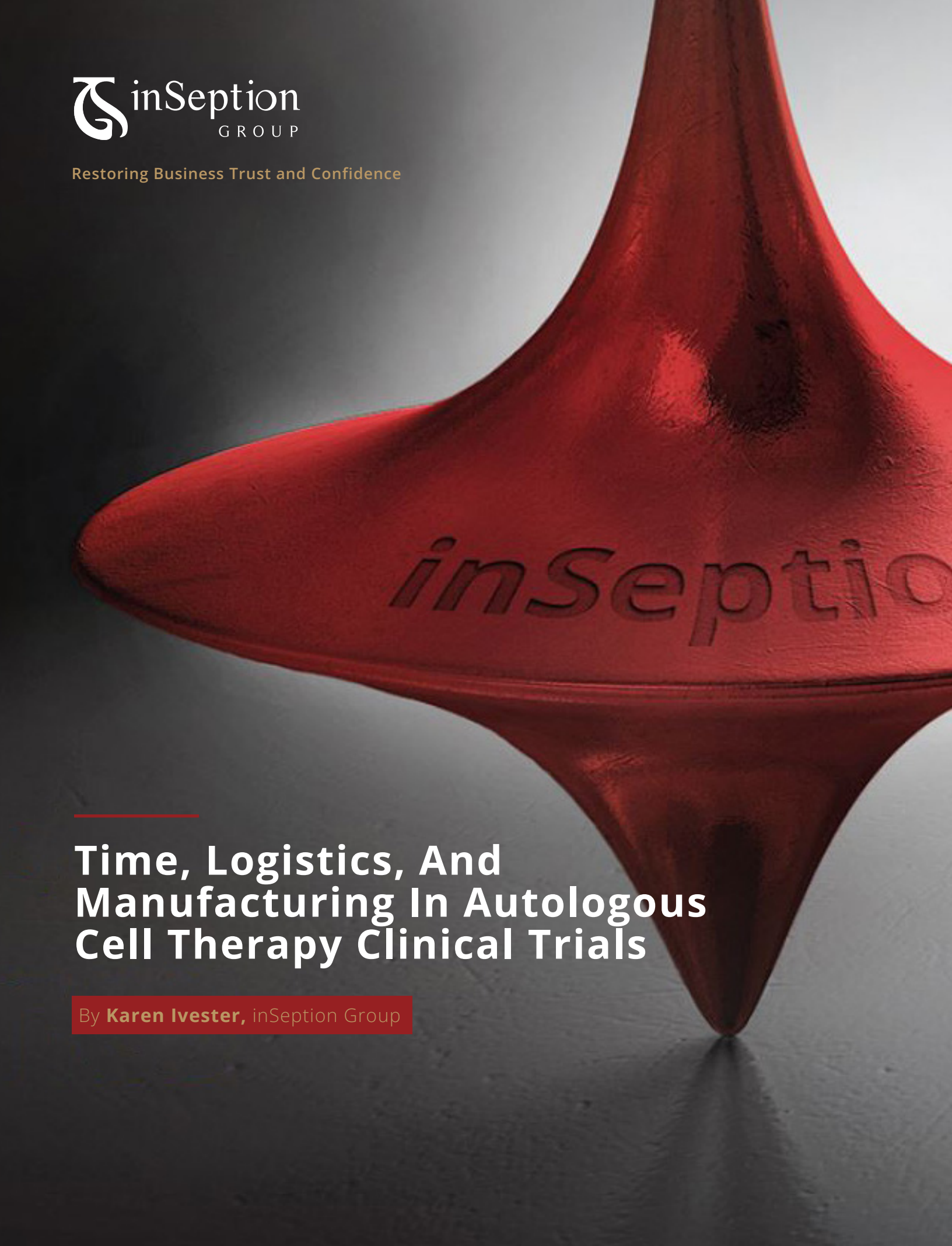

Time, Logistics, And Manufacturing In Autologous Cell Therapy Clinical Trials

By **Karen Ivester,** inSeption Group

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Time is of the essence at every step of autologous cell therapy development. Patients left to wait too long for treatment — often with no alternative therapies available — face progression of their disease, the chance they may slip out of eligibility, or even death. The establishment of effective guidelines and standardization relevant to cell therapy development can help to minimize delays and lead to more positive outcomes.

Unsurprisingly, collaboration is the key to fast, effective standardization. Even acknowledging that many elements of cell therapy development cannot be standardized (limiting the scope of this effort to a more manageable level), the list of stakeholders whose expertise would be required to inform a standardization effort is staggering: sponsors, regulatory agencies, principal investigators (PIs) and sites, apheresis equipment vendors, patient advocacy groups, nonprofit organizations, grassroots organizations, and payors, as well as CDMO personnel and laboratory personnel — just to name a few.

This assemblage of expertise, combined with mapping each patient journey and patient cell journey, will improve development timelines and standard of care. Creating every possible efficiency also serves to keep the price of these products affordable. This industry is too massive, its work too important, for collaborations of this kind not to occur. In fact, many such projects are already underway. What's missing is an initiative to formalize this coordination and apply it toward guidelines and standardization.

ASSAYS

Looking at focal points to begin formal standardization, assays are among the most critical — and problematic — areas ripe for improvement. Validating a single assay for release may require multiple technologists, each with different training. Accordingly, the laboratories creating these assays understand the need to dedicate adequate time and resources to the development of assay protocols, as well as the need for access to various starting materials.

The problematic part is that intellectual property (IP) is inherent in most assay processes and there is reluctance among organizations to share details. However, a common ground exists that the industry could use as the foundation for at least basic assay standardization without compromising any IP (excepting, of course, very niche exercises in specialty labs).

Starting standardization as early as leukapheresis is vital because manufacturers often receive cells from which they are unable to create a product to return to the patient. More robust viability measures can help to avoid that outcome. Despite the relative novelty of autologous cell therapy, at this point some companies have enough experience to recognize cells that are more viable, a fundamental characteristic of any cell therapy product.

Consider that processes using trypan blue are not the most accurate measure to determine cell viability. Numerous companies have created and are using better strategies for achieving confidence in cell assays, many of which are more precise and less harmful to cells and to the laboratory technicians using them. Is it possible to standardize some of those cell viability measurements to optimize cell fitness, as well as achieve manufacturing success per Good Laboratory Practices (GLPs)?

SITE BOTTLENECKS

Hospital and site bottlenecks that lead to delays include those associated with apheresis/leukapheresis, autologous cell therapy product receipt after production, storage, infusion scheduling, and product thawing. Every site has different protocols, from patient selection and collection volumes to nucleated cell count required and the type of machine used for leukapheresis. Everyone working at that site must be trained for each product, and every mistake is a deviation.

Major academic institution sites offer a possible starting point for standardization in this area, as they typically have robust standards and protocols. Still, all institutions differ to some degree. A biotech may prefer leukapheresis to be executed differently than the university facility is accustomed to performing it. The same applies to delivery and storage: academic institutions generally use the same vials or bag types, but the cassettes and liquid nitrogen storage can differ. Some sites prefer to keep the product in the liquid nitrogen shipper, as they plan to use the product while the shipping unit still has a charge.

For autologous products, the FDA does not require donor eligibility determination; however, labeling requirements may apply, such as: “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” (21 CFR Part 1271.90 (b)(2)) and “FOR AUTOLOGOUS USE ONLY” (21 CFR Part 1271.90 (b)(1)). Also, processing must be shown not to support propagation of infectious agents. Therefore, most sponsors, voluntary accreditation organizations (e.g., AABB, FACT-JACIE), and Institutional Biosafety Committees (IBCs) require infectious disease testing.

Consider, too, that most organizations perform the same type of screening for infectious disease or blood-borne pathogen testing (more so for allogeneic). For example, although the viral vector may differ for cell therapies (which will require additional testing), there is no reason HIV testing using the fourth-generation antigen/antibody combination HIV-1/2 immunoassay, HBsAG, anti-HBS, anti-HBc, and HCV IgG testing could not be standardized.

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MANUFACTURING

Standardization in manufacturing serves to reduce raw material shortages and de-risk the manufacturing process (i.e., modification and expansion of cells), as well as improve GMP batch record-keeping, in-process assays, and final release testing. While GMP record-keeping exists in the cell and gene therapy space, it can vary.

The same applies to training for quality control and quality assurance staff at the end of cell manufacture. Training for different types of cell therapies could be standardized so personnel understand the differences in challenges and logistics across different projects. Determining common facility types and the infrastructure required for autologous cell therapy (particularly as part of manufacturing scale-out) would be key to this effort.

Similarly, training for individuals in the chemistry, manufacturing, and controls (CMC) space varies and CMC packages are different for each cell therapy. However, each patient's cells have variability and, depending on the cell therapy, different modifications to the cells will necessitate different types of cell-based testing. So, process and release testing, whose success leans heavily on process changes made based on how the product changed over time, often needs refinement.

Additionally, the need for specific expertise in many areas of cell therapy manufacturing is being recognized and acted upon more often. Formal training is being implemented to meet these needs as collaborations grow. Excellent examples of this include the National Science Foundation (NSF) Engineering Research Center for Cell Manufacturing Technologies (CMaT) and multidisciplinary academic collaborations.

PATIENT AND CELL JOURNEY

Patient and cell journey are tracked, but not to the degree one might think. As autologous cell therapy expands more deeply into solid tumor (versus more commonly tackled, to date, indications in hematology oncology), more differences in that journey are becoming apparent (e.g., whether a patient is treated with combination of products or a single product).

For example, the materials collected from a patient at first typically are the only materials a developer receives. Another leukapheresis sometimes is possible in solid tumor indications, as the standard-of-care drugs with which they have been treated typically do not render their T cells nonviable. However, hematology-oncology patients have received numerous lines of chemotherapy and other standard-of-care treatments for their cancer that can impact T cell viability.

Patient-level cell variability in the leukapheresis material can be impacted by many factors, including low lymphocytes, advanced age, high platelet counts prior to leukapheresis, heavily pre-treated patients with lymphopenia, or timing of the procedure (which may be secondary to the patient's disease or treatment). Even before that, the cancer has impacted their bone marrow: it may not be producing cells that will grow into the types of T cells developers seek.

By collaborating, sharing, and comparing information, researchers can perhaps create viability tests and protocols to help us better understand which patients are more likely to respond positively to cell therapy. Standardizing that starting point enables researchers to spare patients who would not benefit from the burdens of the trial.

FINAL THOUGHTS

Standardization is coming; it's just a matter of when. Driven groups of people will strive to bring stakeholders to the table from clinical operations, regulatory, specialty labs, CMC teams, CDMOs, in-house manufacturing operations and — most important — key opinion leaders who understand patients in these in-

dications and can advise what would be most helpful or least burdensome to those populations.

In terms of collaborations, precedent has been set by other large collaborations, including platform trials like the I-SPY Trial by Quantum Leap Healthcare Collaborations and the Therapy Acceleration Programs (TAP)-supported assets executed by The Leukemia and Lymphoma Society (LLS). A similar effort is underway to increase collaborations and to develop guidelines around CRISPR (clustered regularly interspaced short palindromic repeats) technologies.

An incredible amount of information exists around gene editing, gene therapy, and cell therapy, just waiting to be put into a usable framework. But standardization seemingly is not a high priority, and some people are discouraged by concerns about intellectual property issues. But again, the critical health of patients at the other end of these therapies and the billions of dollars at stake demand more efficient cell therapy development — not only efforts to help sponsors, but initiatives that serve industry vendors, too.

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Karen Ivester, RN, MA, is the Executive Director of Operations, Cell & Gene Therapy Programs at inSeption Group. She has greater than 25 years' experience in the life sciences industry. Karen has 23 years' oncology experience (across multiple hematology and solid tumor indications). Prior to inSeption Group, she worked in biopharma, CROs, community-based research, and academic cancer center settings. She has worked across early product development and Phase 2-3 global clinical trials. Karen has extensive experience leading high-functioning project and clinical operations teams in portfolio delivery of highly complex clinical trials (including cell and gene therapy, umbrella, basket, and immuno-oncology research).

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