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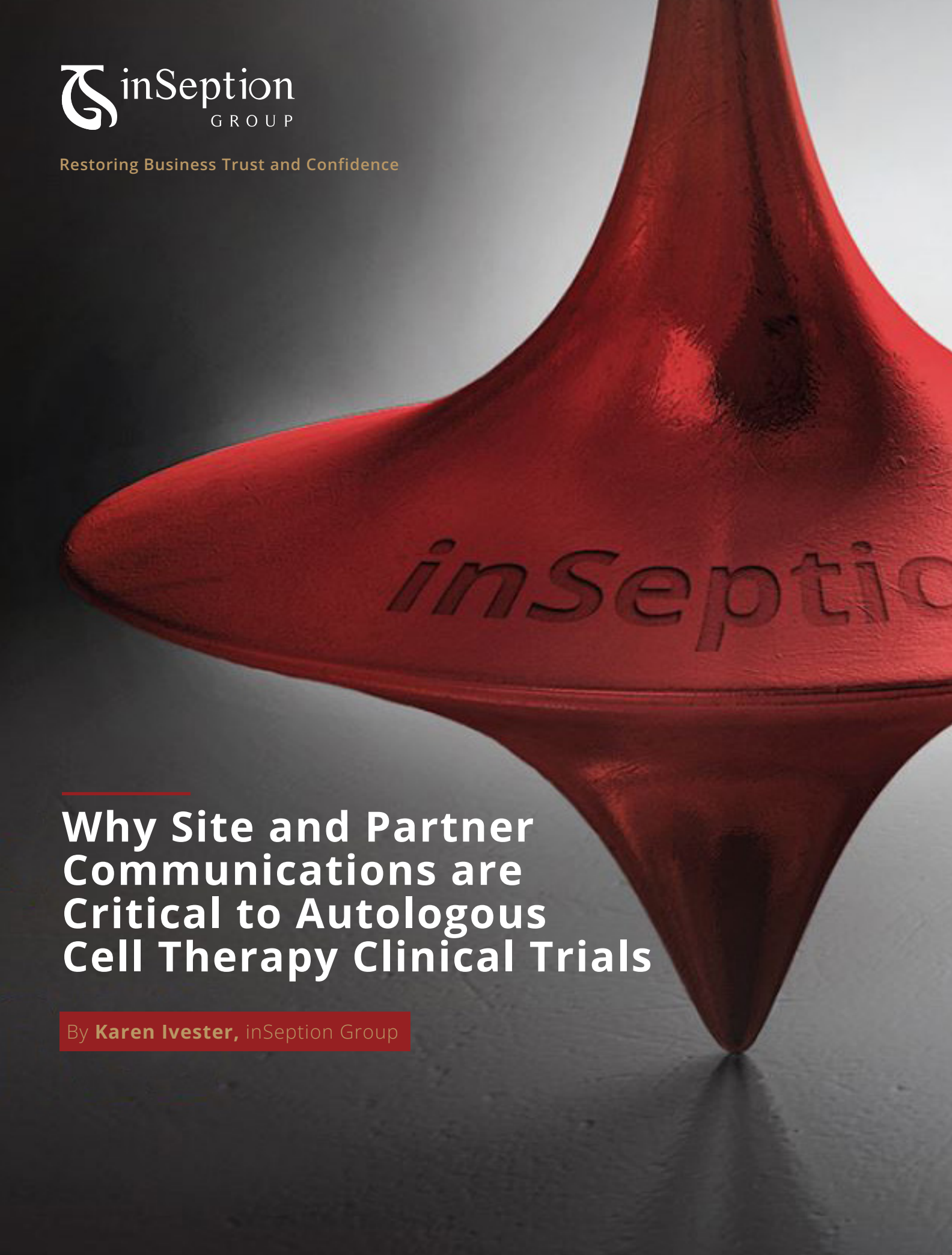

Why Site and Partner Communications are Critical to Autologous Cell Therapy Clinical Trials

By **Karen Ivester,** inSeption Group

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Autologous cell therapy expertise and service providers are simultaneously in short supply and high demand. But the dynamic nature of inherently complex cell therapy-focused clinical trials requires individuals with a keen understanding of site and partner needs. Moreover, to fully take advantage of these individuals' capabilities, responsive, high-touch coordination and a plan to communicate effectively across multiple stakeholders are necessary.

Such communication is critical to deliver the cross-functional, integrated clinical development activities necessary to decrease development time and to prevent and/or mitigate a myriad of risks. While clear, consistent communications are important to any clinical trial, the consequences of mistakes are exacerbated in autologous cell therapy clinical trials.

Plus, building a rapport with proficient sites is more difficult, since personnel with cell and gene therapy experience are highly sought-after and prone to moving around between organizations and projects. CROs often tout their experience with these sites in clinical trials, but the talented personnel who executed those trials may not even be there anymore. Thus, partners may not be "speaking the same language" or be focused on similar areas of concern during protocol development.

Consider that a protocol may go through Scientific Review Committee (SRC), Institutional Review Board (IRB), and Institutional Biosafety Committee (IBC) reviews; however, site research centers and partners often are not aware of the high burdens they face until patients are enrolled. If the protocol was not communicated early, before it was finalized, the principal investigator (PI) and other site personnel may be unaware of important trial elements (e.g., the timing of procedures or burdens placed on different stakeholders). Sponsors and service providers alike have a responsibility to discuss with prospective partners the elements or procedures that might differ from their expectation and/or from Standard of Care (SOC).

For example, while virtually all sites have their own procedures and processes for conducting leukapheresis, it remains incumbent on the sponsor to instruct all site personnel, including the PI, on the protocol's finer points and processes. Admittedly, this creates an interesting dynamic, wherein site personnel who conduct tasks relevant to the study daily are being walked through a process by a sponsor who may never have seen that process executed.

For their part, many sites are experienced and comfortable working with sponsors who may not understand every implication of pursuing their investiga-

tional product. That said, those sites see numerous protocols; they can quickly spot a well-written protocol versus one with ill-conceived procedures or high site burden.

START THE DISCUSSION EARLY...

Because autologous cell therapy trials are much more complex than traditional oncology or rare disease clinical research, biopharmas must be thorough in assessing a potential service provider's capability, resourcing models, expertise, and whether they (the sponsor) have a position of relative importance within the service provider's business model. If the partner is more focused on delivering large, global late-stage clinical trials, they may not be ideal to serve a smaller customer.

The service provider must understand the need for interrelated development activities and be able to grasp its customer's specific needs. This effort requires significant communication, time-consuming planning, and coordination across multiple workstreams and multiple vendors (specialty labs, clinical sites, safety and regulatory observers, cold chain logistics, couriers, manufacturing, imaging, patient reported outcomes, assay developers, etc.).

Also, expect more thorough feasibility and site selection. Providers operating in autologous cell therapy will know the go-to sites (e.g., FACT and/or JACIE accredited sites) but, most likely, everybody is targeting those centers. Viable centers less known to the sponsor or the service provider require early engagement and vetting. Some organizations send out questionnaires but, in cell therapy, that is not the most effective approach.

Proper vetting requires discussion between a regional site manager and CRAs, followed by a site initiation visit (either in person or remotely), allowing the service provider to gain a clear understanding of the site personnel's communication strengths, as well as to determine whether its personnel are adequately qualified. Note that, because of the limited patient populations associated with rare indication trials, a large number of sites may be necessary to complete even a small study.

PIs may not want to expose many patients to early-stage treatments. So, in oncology trials, the patient population often comprises relapsed and refractory patients who may lack other options. Additionally, cell therapy clinical trials have strict inclusion and exclusion criteria. Therefore, the available patient population may be smaller. Unfortunately, primary care providers (PCPs) and patients for whom such trials are relevant may not be aware of novel cell therapy investigational products' availability in a specific indication or of the sites/centers conducting these clinical trials.

An across-the-board effort is required to remedy this. For years, promising rare disease and oncology trials have been closed because of non-enrollment. Indeed, it is surprising how heavily many things in this industry are marketed, but (with the exception of some large Phase 3 trials) many small rare disease trials stop or never get off the ground because service providers were poorly selected, personnel lacked the appropriate rare disease experience, or there was not enough spin/promotion to get the message out to those rare patients. Therein lies a key difficulty of cell therapy: it is a niche, very targeted area of clinical research.

...AND KEEP THE CONVERSATION GOING!

Within the sponsor organization, autologous cell therapy trials require a hands-on, responsive, and malleable approach as they often require adaptive solutions to continue forward (i.e., because the sponsors are still learning about their cell therapy product and related processes). Briefly

consider the progression of an autologous cell therapy trial: once patients have been enrolled, even though mock runs have been completed, something inevitably will come up.

So, for sponsors and service providers — especially around clinical teams and regarding patient scheduling — clear information is required. Once the first patient is scheduled, a collective 'walk-through' of the patient's journey — by the site, sponsor, service provider, and the manufacturing team – should be taken with careful review of all procedures. For example, when will each patient be leukapheresed? This is important because the shipping containers in which cells will be stored must be on-site (if using a just-in-time shipper).

Then, any time cells or drug product are on the move, the logistics of courier pickup and cold chain custody must be planned. A system is tracking not only the GPS location of those cells but also their temperatures. Any deviations outside a specific temperature range could render those cells nonviable. In the case of autologous cell therapy, that would require another leukapheresis of that patient; therefore, the patient's journey must be clearly planned.

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Also, the PI, site, and treatment center communications must be prioritized. Autologous cell therapy development features inherently high site and patient burdens, even in early-phase trials (as these trials may have adverse effects specific to cell therapies and are highly regulated). On-site personnel can encounter safety issues if a particular viral vector or type of shedding is present.

Moreover, relevant to these trial types, regulators want to know what happens to each patient moving forward. They are in follow-up at least 15 years to determine whether RNA/DNA changes are taking place: any changes on a cellular level that could impact product safety.

In a single Phase 1 trial, we have central labs who help keep everything organized: multiple assays, often tested through at least six or more specialty labs, plus lots of other panels for cytokines, chemokines, and many other exploratory tests. This differs from the execution of other biologics in clinical trials because, along with complete blood count (CBC) testing and white blood cell (WBC) differentials, several unique assays are required. Many of these labs must be drawn during patient screening and baseline testing to clarify their eligibility. Indeed, it is staggering the sheer amount of money, coordination, and pre-work necessary (which can take from 10 months to a year to get assays in place) to properly set up and execute an autologous cell therapy trial.

FINAL THOUGHTS

Communications prioritization must be part of an organization's culture to truly be effective — whether that is the biopharmaceutical sponsor, a service provider, a CDMO, a laboratory, or a clinical

trial site. Many sponsors in this space are small, emerging entities that have discovered an exciting cell therapy. They have decided to develop it and then partner with a company to bring it to fruition through clinical trials. That partner often chooses other service providers to help develop the therapy.

Thus, a long, complex chain of discussions feeds the trial protocol. Have all relevant subject matter experts' knowledge and opinions been a part of those discussions at each step? Are critical conversations and decisions properly documented? Sponsors must be able to trust that their partners and the sites to whom they have committed are striving for transparency, as well as working to communicate vital information quickly and clearly. To learn more about the execution of CAR-T cell therapy clinical trials and thriving (versus surviving) through an economic downturn, contact the author and visit inseptiongroup.com.

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