Vito Romita, PhD, MSc,
Senior Director, Global Project Management, Hematology/Oncology Therapeutic Unit, PPD clinical research business, Thermo Fisher Scientific

Delivering Operational Excellence in a Complex Environment of CAR-Directed Cell Therapies

Overcoming saturation in the cell therapy landscape.

Introduction

August 30, 2017, was historic for the FDA as it approved the first chimeric antigen receptor (CAR) T-cell therapy for treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (Tisangenlecluecel).

Currently there are more than 10 *ex vivo* gene-modified cell therapy products (herein referenced as "cell therapy") approved by FDA, and the application of this therapy is expanding beyond the treatment of hematological and/or solid tumor malignancies.[1]

The massive growth in the pipeline of cell therapy clinical research trials is creating challenges given the limited number of investigational sites equipped with cell therapy capabilities, the majority of which are large academic institutions. The geographic location of these specialized centers is far from patient communities, which can introduce barriers limiting patient access to these novel treatments often due to long travel distances and/or poor or modest socio-economic backgrounds. Together these limitations negatively impact study implementation, enrollment and study conduct.

This article will discuss approaches to potentially overcome the saturation level in the cell therapy landscape having a direct and positive impact on study conduct and patient access to potentially life-transforming therapies.

Strength in numbers: Responding to the growing pipeline of cell therapy studies by upskilling and recruiting new sites

Given the continued influx of cell therapy clinical trials, the available qualified cell therapy centers are challenged to accommodate the demand of these complex clinical trials competing for the same sites, resources and patient populations. These centers struggle to cope with the influx of work, thus delaying clinical trials startup time and patient enrollment while directly increasing the need for sponsor and clinical research organization (CRO) oversight. From patients, caregivers and health care professionals, navigating this landscape to find the right treatment center can be—and often is—a daunting experience. Strategies to overcome these issues involve minimizing site burden, leveraging existing databases to map candidate site and patient locations, and offering opportunities to upskill research centers interested in expanding their capabilities toward cell therapy with training programs.

Reducing the site burden at cell therapy established clinical sites: The low-hanging fruit

The COVID-19 pandemic has had a significant influence on the adoption of decentralized clinical trials (DCT) strategies to support clinical trial conduct during the pandemic. The FDA proposed that DCT approaches be implemented to lessen the burden during clinical trial participation while potentially improving recruitment and retention of diverse patient populations.[2,3]

The same approach is applicable to cell therapy trials where the use of electronic consent, software, technology, remote digital data collection capabilities using wearables or data collection devices (i.e., patient-reported outcome/clinical outcome assessments), telemedicine or tele visits and home health care professional visits can be utilized

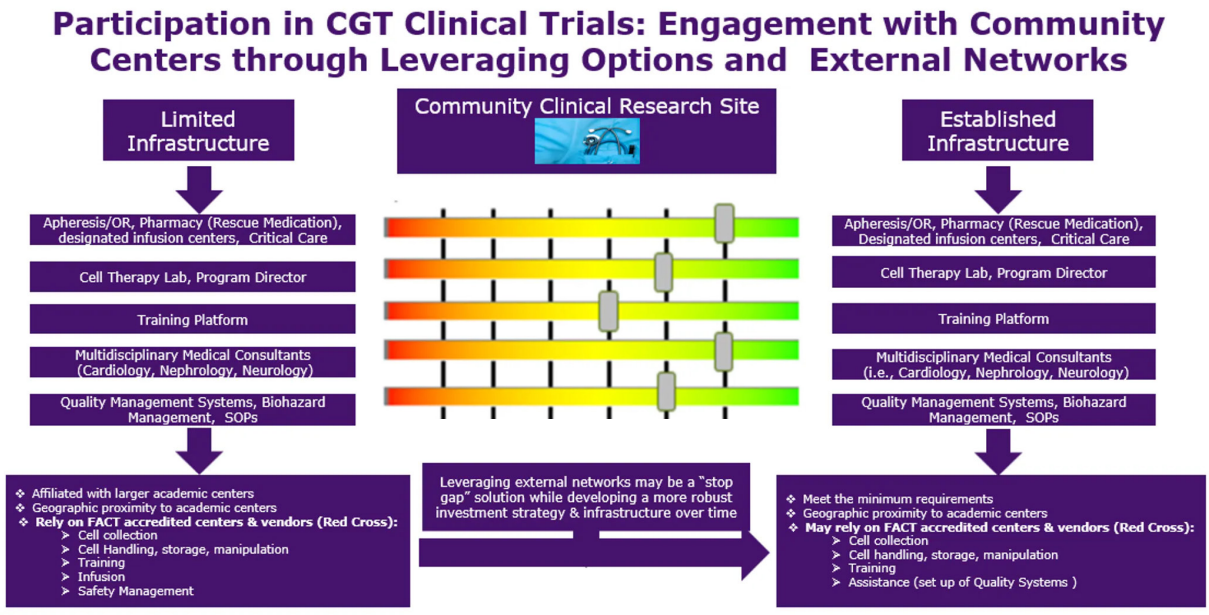

FIGURE 1. Red indicates attributes associated with limited site infrastructure. Green represents attributes associated with fully qualified sites to conduct cell therapy clinical trials.

SOURCE: PPD

to reduce site burden. For example, leveraging these strategies to protocol-required visits following completion of the cell therapy regimen can liberate site resources to concentrate on the labor-intensive management of the patient and cell journey from patient onboarding through screening, treatment and through post treatment safety surveillance often requiring in-hospital stays.

Additional external resources can be leveraged ("loaned") from sponsors and/or CROs to sites for support in chart reviews, data entry and administrative tasks. These tactics coupled with "white glove patient concierge services" in managing patient scheduling, travel and accommodation logistics can have a dramatic impact on freeing up site level resources. These efforts may accelerate the negotiation of clinical trial agreements, which could translate into quicker site startup and faster patient recruitment.

A "fit-for-purpose" flexible decentralized clinical trial strategy and framework intended to decrease site burden can be applied to several clinical trial scenarios which include "virtual" decentralized clinical trial setting, a hybrid "brick and mortar and virtual" or simply providing administrative support in a traditional "brick and mortar" clinical trial setting will certainly result in a more streamlined, cost efficient management and oversight conducive to improving site engagement, patient engagement and patient retention.

While DCT strategies offer a method to reduce site burden, this approach alone, however, does not address the bottleneck in the limited number of qualified cell therapy sites. To expand health equity, inclusion and diversity and bring greater patient access than current scale, regional hospitals and clinics should be incentivized to take an active role in participating in cell therapy clinical trials, either by partnering with existing cell therapy sites for patient referrals or expand their infrastructure to offer these therapies within their institutions.

Data-driven approach to finding the right sites and the right patients

Data mining from various data repositories is currently used to identify sites and patient populations across the diverse spectrum. However,

Most cell therapy naïve research centers do not have existing transplant program to leverage as a starting foundation to build their cell therapy capabilities. Therefore, significant investment in infrastructure and staff training is required.

some databases, such as patient demographics, may not be available, which causes a challenge for sponsors as there's mounting pressures from regulatory agencies to seek patient genetic diversity data in clinical trial participants. Hence, mining of multiple databases and triangulation of information from various data sources is required to locate a network of sites that align with the right site profile, in strategic locations to maximize enrollment for the desired disease with access to community centers where there is greater representation of racial, ethnic and/or minority groups within the targeted indication.

Access to data repositories (i.e., National Cancer Institute Center of Cancer Genomics, The Cancer Genome Atlas Program, etc.) and proprietary network electronic medical records (EMR), together with CRO clinical trial experience and advanced data mining capabilities are a means to establish treatment history at clinical trial centers. These data, coupled with available census data alongside prevalence/incidence and mortality data, allow for identification and localization of indication-experienced clinical trial sites with access to patient populations differentiated by age, race, sex, gender, and cell surface biomarkers (i.e. tumor mutational burden).

Engagement with research-experienced community centers to develop mentoring and training opportunities focused on cell therapy know how

Most institutions with established cell therapy programs have built their expertise on the backbone of their existing bone marrow and stem cell transplant capabilities and infrastructure, while over time introducing treatment paradigms handling immune-effector cells. Many of these sites possess "FACT (*Foundation for the Accreditation of Cellular Therapy*) Standard" and/or "FACT-JACIE (*Joint Accreditation Committee ISCT|EBMT*) Standard International" accreditation and operate under established quality management systems. When considering a site for participation on a cell therapy clinical trial, these sites must show evidence of appropriate infrastructure and systems including:

- A "site champion" responsible for oversight of the cell therapy program, inclusive of quality management systems, standard operating procedures and procedural documents detailing all processes required to manage the patient journey, safety surveillance and cell journey
- Cell therapy laboratory facilities
- Cryopreservation facilities
- Designated treatment/infusion centers
- Pharmacies with access to on-demand rescue medication
- Critical care units
- Multidisciplinary medical consultants (i.e., cardiology, nephrology, neurology, etc.)
- Training programs that meet FDA-mandated requirements focused on the prevention, detection and treatment of safety/adverse events that may arise

Most cell therapy naïve research centers do not have existing transplant program to leverage as a starting foundation to build their cell therapy capabilities. Therefore, significant investment in infrastructure and staff training is required.

To facilitate and encourage interested centers to onboard cell therapy infrastructure, experienced cell therapy sites, sponsors, CROs and regulators should play an active role to these regional centers by providing incentives, training, coaching and sustained mentorship. Through this partnership, regional clinics may be more amenable to refer patients to the larger academic hospital sites for

short-term treatments as they develop their own cell therapy infrastructure. Additionally, CROs also could lend their cell therapy expertise to support site training by helping them complete a self-assessment and gap analysis to identify their development strategy and implementation plan.

An example of how this undertaking can be achieved is illustrated in the following scenario (see Figure 1). A regional center collaborating with an established cell therapy center within relative geographic proximity can gain experience over time while developing infrastructure toward establishing full capabilities to support cell therapies.

Consider a scenario where regional clinics with limited capabilities may have access to a FACT-accredited apheresis facility—whether onsite or through a FACT-accredited vendor—and can perform initial screening and onboarding of the patient, collect the initial cell harvest, then transfer the patient to larger academic centers for treatment with the cell therapy regimen (i.e., conditioning treatment followed by treatment with manufactured cell therapy product). Once clear of potential safety concerns following completion of the cell therapy treatment regimen at the larger academic center, the patient can be discharged and returned to the community center for continued follow-up. With appropriate mentoring, support and investment, a site with limited infrastructure—in the red spectrum range (figure 1)—can develop its capabilities over time and evolve into a site with fully established infrastructure—the green spectrum range (figure 1)—becoming an independent standalone treatment center enabling the site not only to participate in clinical trials, but also potentially qualify as a commercial cell therapy treatment center and by so doing serving patients in their communities.

The takeaway

In summary, the rapid increase in cell therapy clinical trials is drawing on the same highly specialized cell therapy sites globally. These sites, typically large academic hospital centers located in metropolitan areas, are limited in number and are saturated by the high volume of incoming clinical trials in an increasingly competitive landscape. Due to a shortage of resources, inability to meet the high demands, study timelines are protracted, driving high costs and causing delays in the development of the cell therapy assets. Additionally, these highly specialized academic hospitals may not be accessible to a majority of the patient population.

Industry stakeholders and experienced cell therapy centers are encouraged to partner and develop knowledge-sharing strategies with regional clinics and hospitals to bring life-transforming therapies to patients and accelerate cell therapy development timelines.

References

1. US Food and Drug Administration. Approved cellular and gene therapy products. Content current as of 02AUG2024.
2. Van Dorn, A. COVID-19 and readjusting clinical trials. *Lancet 396*, 523–524 (2020).
3. Vasisht, K. P., Nugent, B. M. & Woodcock, J. Progress and opportunities for women in clinical trials: A look at recent data and initiatives from the U.S. FDA. *Med 2*, 456–459 (2021).