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Processing laboratory considerations for multi-center cellular therapy clinical trials: a report from the Consortium for Pediatric Cellular Immunotherapy

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ABSTRACT

Cellular therapies first emerged as specialized therapies only available at a few “boutique” centers worldwide. To ensure broad access to these investigational therapies—regardless of geography, demographics and other factors—more and more academic clinical trials are becoming multi-center. Such trials are typically performed with a centralized manufacturing facility receiving the starting material and shipping the final product, either fresh or cryopreserved, to the patient's institution for infusion. As these academic multi-center trials increase in number, it is critical to have procedures and training programs in place to allow these sites that are remote from the production facility to successfully participate in these trials and satisfy regulatory compliance and patient safety best practices. Based on the collective experience of the Consortium for Pediatric Cellular Immunotherapy, the authors summarize the challenges encountered by institutions in shipping and receiving the starting material and final product as well as preparing the final product for infusion. The authors also discuss best practices implemented by each of the consortia institutions to overcome these challenges.

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Introduction

Cell and gene therapy has been growing rapidly, particularly since the seminal demonstrations of CD19-directed chimeric antigen receptor (CAR) T-cell therapy [1,2]. Although commercial CD19 CAR T therapy is available in many major medical centers, with more than 100 offering Kymriah (<https://www.us.kymriah.com/treatment-center-locator/>), most experimental cell and gene therapies are available in a limited number of clinical trial sites. These personalized products are manufactured in academic cellular therapy programs (manufacturing site) by their own manufacturing facilities, regulatory teams and clinical translational investigators. This approach limits the access patients have to these promising therapies because of the complexity of adding additional clinical sites. Indeed, the New York Times published an article in 2017 demonstrating that patients on immunotherapy clinical trials are >90% Caucasian [3], which is not representative of the US population as a whole. Although there are a

number of suggested causes for this disparity, access to a clinical trial site and the cost associated with traveling to one of these sites are major hurdles. In addition, multi-center clinical trials are essential for pediatric patients given the low prevalence of diseases that are treated.

One way to provide better access to cellular therapy trials is to optimize the ability of academic manufacturing sites to provide personalized cellular therapy products to US and international institutions (remote clinical sites). In this model, the manufacturing is centralized in an academic center, but the clinical trial is multi-institutional. The sponsor of the trial is ultimately responsible for ensuring that participating sites have the resources they need to safely perform the clinical trial, including qualified personnel, training and procedures. These multi-center clinical trials come with their own challenges, especially related to manufacturing, shipment, storage and infusion of products from a diverse range of centers, each with their own institutional standard operating procedures (SOPs) and processes. The logistical and quality challenges of providing cellular therapy products to remote clinical sites at multiple academic medical centers when manufacturing operations occur at a limited number of high-volume commercial manufacturing sites have been

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described by others [4,5]. These reports focused on defining the critical quality attributes and critical process parameters that ensure quality through the entire cycle of providing autologous cellular therapies. Elements that must be optimized include coordination of patient enrollment, scheduling, starting material collection, labeling, shipping, manufacture, storage and infusion.

Here, based on the experience of the Consortium for Pediatric Cellular Immunotherapy (CPCI), the authors extend these earlier reports and describe the formidable challenges when both the clinical site and the manufacturing site are at academic centers. The CPCI is composed of pediatric academic centers from five US Clinical and Translational Science Award hubs focused on accelerating the translation of cellular immunotherapy for pediatric disease. The consortium's goals are to expand current Good Manufacturing Practice (GMP) manufacturing programs with the capacity to supply cellular products for early phase clinical trials, establish infrastructure to efficiently implement cellular immunotherapy clinical research and increase efficiency and reliability of analytic assays to monitor both safety and clinical efficacy of cellular immunotherapy trials for rare pediatric diseases. In doing so, the CPCI seeks to train a cadre of clinical, manufacturing, research and regulatory teams capable of advancing cellular immunotherapy for a wide range of disorders, including cancer, infection and immune tolerance.

As clinical trials evolve from having elaborate current GMP manufacturing capacity, there is still a need for qualified processing laboratories at each remote clinical trial site to ship, receive and store starting materials and final products. Many remote clinical sites have established stem cell processing laboratories with years of experience with bone marrow, peripheral blood hematopoietic stem cells and other standard-of-care, minimally manipulated products. Few laboratories have experience with or infrastructure to support more than minimally manipulated products (called 351 products after section 351 of the Public Health Service Act of 1944). Such 351 products often require new equipment (such as an automated thawing device) and procedures, in addition to training beyond typical hematopoietic stem cell processing. For example, these products can have different product containers (vials versus bags) and specialized shipping and storage requirements (fresh versus frozen) and may need specialized

quality control testing on site before product administration; these requirements are not typically necessary—or are more straightforward—when processing and distributing minimally manipulated blood banking 361 products. Overall, these differences—especially the variability in container type, size and requirements—have resulted in non-standardized methods of manufacturing and processing cellular therapy products.

To overcome these challenges, the authors have outlined a number of best practices and examples of how to address practical and logistical obstacles based on our experience as academic manufacturing sites for—or participating in—a number of multi-center clinical trials at four different remote clinical sites. Some of these challenges include the logistics of shipping the apheresis product/starting material; receiving, storing and thawing/infusing the final product; and qualifying/training external cell therapy laboratories for product receipt and infusion. The many steps in the process from apheresis to infusion are shown in [Figure 1](#).

Regulations and Standards for Shipment of Starting Materials and Products

The authors first identified critical steps in the shipment and receiving process and linked them to respective federal regulations or guidances (US Food and Drug Administration [FDA]) or Foundation for the Accreditation of Cellular Therapy (FACT) standards ([Table 1](#)). The authors note that not all academic manufacturing centers are FACT accredited. Within the CPCI, two institutions are FACT accredited, two are in the process of obtaining FACT accreditation and one has elected to not become FACT accredited in the near future. Although FACT accreditation may not be a prerequisite for site qualification, it does provide an added level of confidence that remote clinical sites subscribe to SOPs and policies that conform to federal regulations. If remote clinical sites are not FACT accredited, they may be required to provide additional documentation, such as their quality plan and training records, and may even undergo an on-site audit or qualification, as described later. Further, a gap analysis revealed that regardless of FACT accreditation status, all CPCI institutions meet the requirements listed in [Table 1](#), likely because of the GMP-type

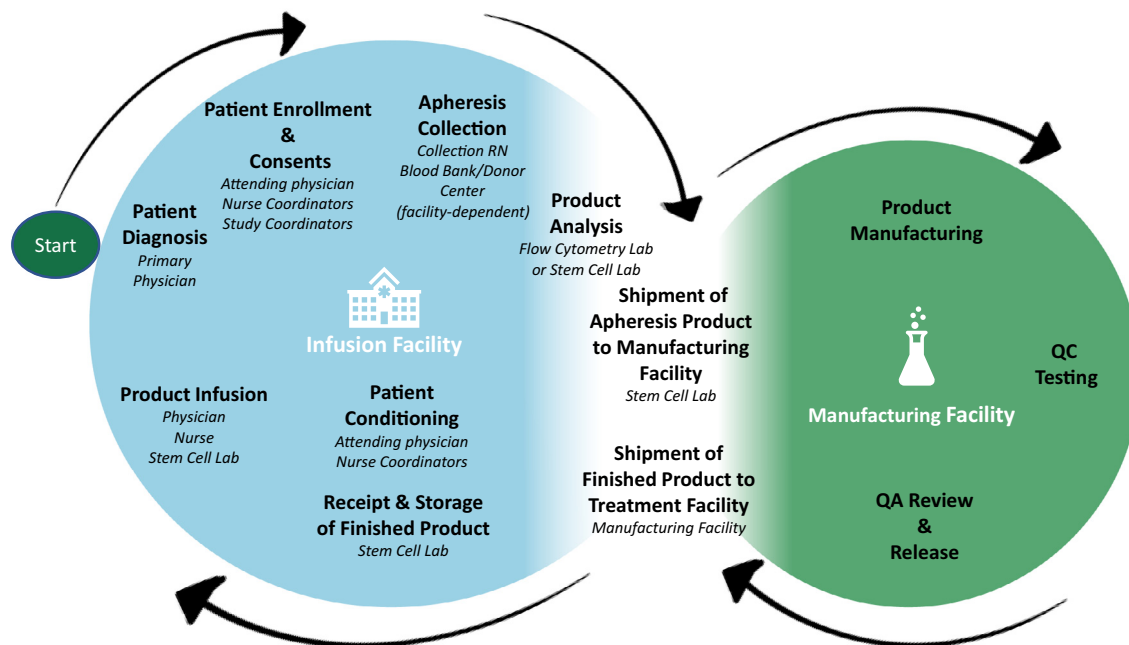


Figure 1. Multi-institutional flow chart for cellular therapy products. The life cycle of autologous cellular therapy products, starting from apheresis collection, moving to the manufacturing laboratory and finally being shipped to the infusion facility. QA, quality assurance; QC, quality control; RN, registered nurse.

Table 1
Shipping/receiving of starting material/final products.

Activity	Shipping	
	Regulations 21 CFR [6,7]	Standards FACT [8]
Select a qualified courier and qualify transit time		D10.6
Validate shipping container		
Protect integrity of product	1271.265	D10.1, D105.1
Utilize secondary container to prevent leakage		D10.2, D10.5.2
Control temperature (refrigerated or frozen) to meet expiration parameters	1271.265	D10.3, D10.5, D10.6
Prepare container for shipment		
Check request orders and confirm with clinical site arrival date and time		D8.2
Set and insert temperature logging device		D10.5.2.1
Insert study-required labels, certificate of analysis, chain of custody documents	1271.290, 1271.265	B1.2.1.1 ^a
Insert handling instructions ^b , including expiration date		D11.1.4.1, C10.5
Affix transport labels/stickers		D10.5.1, D10.5.5, D10.5.6, D7.3, D10.9
Use tamper-evident tape to close shipper		D10.5.4
Complete post-shipment tasks		
Receive completed product receipt from site	1271.290	
Analyze and document temperature tracking		D10.5.2.2
Provide mechanism for customer feedback	211.098, 1271.320	
Receiving		
Inspect packaging and physical conditions	1271.265, 211.82	D11
Follow instructions for temperature tracking		
Confirm receipt of accompanying documentation		C6
Chain of custody	1271.290	
Documentation of shipping and transport on public roads		Common Standards Appendix 2 [9]
Verify labeling matches donor/recipient identifiers	1271.370	C7
Assign unique identifiers and label materials/documentation	1271.290	D7
Confirm donor eligibility (as needed, for allogeneic donors)	1271 subpart C	C6
Quarantine material at appropriate storage temperature to protect safety and improper use	1271.265, 211.82	D11
Return documentation		

CFR, Code of Federal Regulations; EU, European Union.

^a Immune Effector Accreditation Manual 2017.

^b EU regulations require instructions for opening the container and package and any required manipulation or reconstitution be included as a document accompanying the starting material and/or final product.

nature of the processing they support. However, requiring FACT or AABB accreditation may become necessary as additional remote clinical sites are added with less experience processing 351 products.

Interpretation of the requirements in the Code of Federal Regulations can be variable. Therefore, the FDA has provided extensive guidance on various aspects of cell and gene therapy, including packaging. A searchable database of FDA guidance documents is available on their website (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents>). Therefore, the details of how each of these regulations, guidances and standards is implemented must be shared between the clinical trial site and the manufacturing site to ensure compliance with best practices.

Qualifying Infusion Sites

Cellular therapy processing facilities across the United States have primarily served as laboratories responsible for minimal manipulation of hematopoietic stem cell products. The processing required for these products requires extensive knowledge and training but by definition is typically more routine and less variable than processing of more-than-minimal manipulation products.

To qualify potential sites, the CPCI developed a questionnaire that is filled out by the processing lab at remote clinical sites (Figure 1). This questionnaire can be used to ensure that sites are FACT accredited and FDA registered and have the necessary processes, training and infrastructure in place to receive, store and administer products safely. Accreditation from other cell therapy accrediting bodies such as AABB may also be acceptable.

To qualify as a remote clinical site, each site must have SOPs in place that detail receiving and storing the product in a controlled environment and testing the product for sterility and viability and, most importantly, a procedure to notify the study sponsor and manufacturing site in the event of a positive sterility result after

infusion. Once the site qualification questionnaire is completed by the remote clinical site, it is reviewed by the laboratory management team, including quality assurance, the laboratory manager and the laboratory director, to ensure that they understand the procedure and have the necessary training to receive and properly handle the product. More specific details on training can be found in the following section. Additionally, verification of a completed training log confirms all pertinent staff have watched the video and are comfortable following the procedures.

Finally, each remote clinical site must attest that they will notify the manufacturing site within 24–48 h (or as described in the protocol) of any positive sterility reports related to the thawed product. This requirement is critical because these issues must be quickly investigated and reported to the FDA (if necessary), with expedited notification of the patient's treating physician, the patient and any other teams involved in the manufacturing.

Training at Remote Clinical Sites

After confirming that a remote clinical site is qualified to ship, receive and store a final cell product or starting material, or as part of the qualification process, the site typically requires protocol-specific training. As mentioned earlier, some of this training can be done during the qualification process. Training remote clinical site staff about collection, storage and transport to the manufacturing site of starting material and receipt, storage, handling and preparation of the final product for infusion is necessary. Some remote clinical sites may be highly experienced in handling CAR T products or other cell therapy products, whereas others may have little to no experience. The process of handling final products may involve a simple thaw and hand off to the clinical team at the remote clinical site for infusion, or it may involve processes requiring use of new devices, sampling of final products for additional sterility testing or other further aseptic

Table 2
Training and competency at external clinical sites.

	Task	Competency measure
Apheresis product shipment	Handling of apheresis product (visual inspection, preparation of absorbent material and sealing of wrap bag, sealing of insulated bubble wrap bag)	External site staff demonstrate proficiency without error following onsite training
	Preparation and placement of completed forms and documentation	External site staff acknowledge understanding of process following demonstration when questioned.
	Enablement and placement of temperature logger	External site staff demonstrate proficiency without error following onsite training
Final product receipt and preparation for infusion	Sealing and labeling of shipping container and airway bills	External site staff demonstrate proficiency without error following onsite training
	Receipt, inspection of dry shipper container, storage and documentation of received dry shipper	External site staff acknowledge understanding of process following demonstration
	Removal and thaw of cell product(s)	External site staff demonstrate proficiency without error after onsite training with an automated thawing device
	Recording verification of labels, date and time of thaw, expiration time and chain of custody	External site staff demonstrate understanding of process following demonstration when questioned
	Removal of subject dose from thawed product vial(s) into prepared and labeled syringe(s)	External site staff demonstrate proficiency without error following onsite training using aseptic technique

product manipulations. There are several ways to conduct training, each with its own advantages and disadvantages. As an example, the training process conducted and competency measurement used by one member of the CPCI (i.e., traveling to each collaborating remote clinical site with sample shipping materials and SOPs and providing on-site training) are summarized in [Table 2](#).

On-site training conducted by experienced members of the cell product manufacturing center is strongly recommended for the following reasons: (i) the trainer can provide and document uniform hands-on training for all aspects of the procedures while assessing the competency of staff, particularly in aseptic handling; (ii) differences between facilities, including suitable storage and work areas, personal protective equipment requirements, waste disposal and documentation policies, can be assessed and adapted in real time to accommodate any observed gaps or deficiencies; (iii) the trainer is able to address questions from infusion site staffing during the training. Some disadvantages or difficulties of on-site training include having a qualified trainer willing to travel, the travel expenses associated with sending the trainer to external sites and coordinating and scheduling a date and time that will work for all participants.

Another method utilized by some manufacturing centers is the use of training videos. For example, one CPCI site created a training video to demonstrate the thawing, sampling, preparation and administration of cellular therapy products at remote clinical sites ([Figure 2](#)). Making a training video is relatively inexpensive, and videos are easy to distribute to an external site. They can be viewed on demand and provide ongoing training support of new personnel at those sites. This training method does have some limitations, however. The manufacturing center is unable to assess the expertise and proficiency of the external site staff with procedures depicted in the training video, and if there is proprietary information in the video, there is no way to control the distribution and viewing of the video. It is also time-consuming to edit the video or re-film as the process evolves.

Although not as rigorous an assessment as in-person training, a written assessment can be given as a measure of competence. This method also does not allow for or address infrastructural, procedural and policy differences between facilities and requires the external staff to determine how to adapt. Using this approach, the manufacturing center relies upon documentation rather than first-hand experience to determine the effectiveness of training on-site staff.

In addition to on-site or video training, a handbook or SOP for final product preparation for infusion is recommended to codify all procedural steps, address frequently asked questions, provide contact information of the appropriate manufacturing center staff in case a

question or issue arises during preparation for infusion and instruct sites on documentation and return of forms as well as preparation of shipping containers to be sent back to the manufacturing center or shipping vendor. Whenever possible, the inclusion of photos depicting key steps should be included.

Whatever methods are deployed for external site training, it is critical that dry runs with the external site are performed as a final step. These practice runs can identify issues not apparent during training. For example, the external site might discover an inability to download the Cryologger software to local computers because of configuration or local information technology policies. Identification and resolution of such issues prior to having a cell product in hand are key to smooth operations at an external site.

Shipping of Starting Materials

After collection from a patient, starting materials, such as apheresis product or whole blood, must be adequately labeled, packaged and shipped to the manufacturing site. Personnel at sites participating in a multi-center clinical trial must be adequately trained on trial-wide SOPs to ensure the correct packing and shipping of starting materials. Procedures should include confirmation of all addresses and labeling requirements before the package leaves the shipping site. Pre-printed shipping labels, provided by the trial, may also help to minimize errors. Effective and prompt communication between the collection site (remote clinical site) and the manufacturing site is likewise essential to ensure that the manufacturing site is ready to receive and process the material when it arrives. Therefore, each site's trial coordinators must understand the importance of (i) prompt communication with the manufacturing site about patient enrollment and schedules, (ii) completion of all chain of custody documentation and (iii) packing of material into the shipping container according to common SOPs. In the authors' experience, a common source of manufacturing deviations is inadequate labeling or incorrect packing of starting materials by local trial coordinators or shipping personnel. Such errors can lead to more serious deviations such as out of specification temperature readings due to incorrect placement of temperature probes or cold packs during packing.

There are a number of courier services capable of transporting cryopreserved or fresh cell products, including legacy logistics companies like FedEx, more focused logistics companies like World Courier and U.S. Xpress and, finally, cell therapy-specific courier services like Cryoport and QuickSTAT. The courier service should be selected by the manufacturing site and must take into account the specific requirements of a trial. For example, trials that require shipments and deliveries over the weekend or on holidays must use a courier

Infusion Site Qualification Questionnaire

INFUSION SITE QUALIFICATIONS	Mark the column that best describes your company			
	Yes	No	N/A	Comments
Are you FDA registered? If yes, please provide a copy of your FDA registration.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Are you FACT (Foundation for the Accreditation of Cellular Therapy) Accredited? If yes, please provide a copy of your FACT accreditation.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Do you have a formal quality plan?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Do you perform self-assessments to assess your level of process control and regulatory compliance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Do your employees participate in a formal current Good Manufacturing Practice (cGMP) or current Good Tissue Practice (cGTP) training program?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Do you have a space to store 2- to 5-mL cryovials in a liquid nitrogen freezer?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Do you have written procedures to receive and store cryopreserved product?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
We will provide our "Thawing and Infusing CTL IND Products" SOP* and a link to a training video along with this questionnaire. Once you have read and understood the SOP and watched the training video, please complete the attached training log and answer the following questions:				
• Are you comfortable following this procedure?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Do you require any additional training? If yes, please explain.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Is there an SOP detailing the viability testing?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Is there an SOP detailing the sterility testing?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Is your sterility testing method validated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Do you have a written procedure for positive sterility notification in case of a positive sterility result for an IND product ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Positive sterility notification MUST be reported to study sponsor and manufacturing site (Children's National Medical Center) within 24 hours . Are you comfortable following this procedure?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

*Attachments – SOP D01 Thawing and Infusing CTL IND Products and Training Log
Completed by:

Print Name	Title	Signature	Date
Print Name	Title	Signature	Date

All qualifications questionnaires are considered PROPRIETARY INFORMATION and will not be used or disclosed outside of Children's National Medical Center, except under written agreement.

Figure 2. Qualification questionnaire for infusion sites. An example questionnaire that is used to qualify cell therapy sites for infusion. CTL, cytotoxic T lymphocyte; IND, investigational new drug; N/A, not applicable.

service that is available during those times. Likewise, some services can navigate the vagaries of international shipments and relevant customs barriers (e.g., shipments to and from Canada), whereas others cannot. When travel distances are short—for example, between two affiliated institutions in the same metro area, or even in the same state—personal transport of starting materials by clinical trial staff may be faster and more reliable than using a courier service. Even so, there may be liability concerns associated with this approach, and these should be considered appropriately. Additionally, some courier services are willing to participate in completing chain of custody documentation, and others will use only their proprietary tracking systems to document when packages are picked up and delivered. FDA regulations must always be followed, but some states also have specific requirements and registrations that must be completed prior to shipping to the state.

Selection of a shipping container must accommodate the size of the product, the temperature at which it is shipped and desired features, such as built-in continuous temperature monitoring and Global Positioning System tracking of the shipper. FACT common standards (C10) [9] set out requirements for shipping starting materials. In particular, these standards require that the material be placed in a sealed secondary container to prevent leaks, that the temperature be controlled and continuously monitored and that the container be validated for the shipping task. Packaging of starting materials commonly involves several different materials inside a shipper, including a sealed biohazard bag, an absorbent sheet, cold packs, padding/bubble wrap and an additional outer container (such as a cardboard box).

Common commercially available shippers include the Crêdo series 4-248, manufactured by Pelican BioThermal; evo 2–8°C smart

shipper and evo CRT (15–25°C) smart shipper, manufactured by SAVSU Technologies; and STP-320, manufactured by Saf-T-Pak/Inmark. At one consortium site, the approach to validation includes testing to determine how long the shipper maintains an acceptable internal temperature when exposed to extreme temperatures. The goal is to show that the shipper can maintain the desired temperature for up to 36 h since shipping from any location in North America is generally completed in this time frame. To perform these validations, staff place sample starting material in different primary containers (such as vacutainers or a blood bag) in the shipper and then place the shipper in an environment at different temperatures: –20 to –30°C, 0 to +8°C, +18 to +25°C and +32 to +37°C. Staff then record the temperature at intervals using a probe next to the sample material to identify the point at which the temperature is out of range. In addition to validation at specified external temperatures, performance qualification is done to test the shipper under conditions comparable to the shipment of starting material. Performance qualification involves shipping sample material to different locations and determining if the material stays within the desired temperature range. An example of data collected from such a performance qualification for the evo CRT smart shipper is shown in [Table 3](#).

Given the many potential points of failure during the shipping of starting material, regular tracking and trending of deviations using paper-based and in-person audits of the packing and shipping process are essential components of a quality assurance program. Repeated out-of-temperature deviations in particular should alert the manufacturing site to potential problems with the starting material shipping process.

Receiving the Final Product at Remote Clinical Sites

Selecting a date

In the experience of the consortium, there is typically little flexibility when choosing a shipment date for receipt of cellular therapy products. Usually, the clinical research team works with the attending physicians to determine the optimal date of delivery and infusion. The clinical research team then contacts the remote clinical site's processing laboratory to confirm staff are available for receiving the delivery. It is critical that the remote clinical site's clinical team, the manufacturing site and the remote clinical site's processing lab communicate effectively to ensure seamless delivery and infusion of the product to the patient. Across the consortium, it is common to avoid Friday delivery. Most laboratories are not open on weekends, so should there be a delay in shipping or a lost item, there would not be staff available to receive the product or investigate lost shipments.

It is important that the type of shipper and study storage requirements be factored into receipt. For some studies, the product is required to remain in the shipper until time of infusion. If the study is using a Cryoport shipper, the shipper is typically validated for 7 days from when the liquid nitrogen charge occurred. Once charged by Cryoport, it is shipped to the manufacturing site for product packing and then shipped to the remote clinical site's processing laboratory so that by the time the shipper is dispensed from the manufacturing site it has already been charged for 2 days and only 5 days of the validated charge remain.

For these types of shipments, one consortium site, for example, usually coordinates to have the product delivered on the day of infusion. If the shipper is coming via a company such as FedEx, it may go through the hospital receiving dock. The product will then get routed through the normal mail delivery process, which can delay receipt and infusion, especially on days that the product arrives the same day as infusion. To more efficiently handle the receipt, the remote clinical site implemented a process to ensure that all deliveries are processed through the receiving dock. Once the itinerary is determined and tracking information is received, laboratory staff forward that information to the receiving dock and send a reminder the day before delivery. The receiving dock is then able to expedite the processing and delivery of the shipper. If the shipment is to be guaranteed for a 10:00 AM delivery, the receiving dock can then have it to the laboratory by 10:30 AM. During this time, laboratory staff are able to prepare paperwork, check calculations, call for pre-medication of the patient and be ready for an 11 AM infusion, the preferred infusion time of many remote clinical sites.

Although same-day infusions are possible, as previously outlined, most laboratories prefer the cells to arrive the day before infusion, which gives ample time to review all the paperwork and double check calculations; however, as mentioned, most laboratories do not have complete control over the scheduling. A consortium remote clinical site process laboratory once had a product arrive with an incorrect dose on the study dosing form. The dosing directions were followed, which led to an incorrect dose being infused, per the study form. Since then, a calculation verification system has been implemented as a part of the standard processing worksheet. It should be noted that some studies may not give enough pertinent information to complete the dose confirmation. Thus, early deliveries are strongly recommended to ensure ample time to review all the documents, prevent deviations and allow time for staff to clarify any questions with the sponsor.

Some studies allow for products to be relocated to the liquid nitrogen storage tank of the remote clinical site's processing laboratory. In this case, the laboratory requires the arrival date, type of storage container (vials, cassettes) and number of products for receipt. Staff can verify that space is available (a FACT standard) and store the product indefinitely, until infusion or product expiration. On rare occasions, products will be shipped fresh. In this case, the product is likely to be received on the day of infusion.

Processing laboratories typically have limited involvement in scheduling of infusions beyond confirming if staff are available to receive the shipment. To best prepare for upcoming shipments and infusions, staff attend weekly referral meetings with the clinical site team for updates about patient status, product delivery dates and proposed infusion dates. The clinical team of the remote clinical site also provides the laboratory with a final ship date, all the corresponding shipping information and the infusion date. Although management and supervisors are typically responsible for coordinating patient processing and scheduling shipments, email groups have been created that include entire laboratories on all notifications. This group email is used for all scheduling information, so laboratory and clinical teams are aware of upcoming deliveries and infusions. These emails help disseminate information, prevent bottlenecks and create redundancies for when staff take vacation, are sick or are too busy to respond. Some laboratories in the consortium also have staff

Table 3
Qualification of a cell transport container.

Test start date	Shipped from San Francisco to:	Evo ID	Unique shipment ID	Temperature range over 36 h	Time in transit (h:min)	Disposition
9/13/17	Arlington Heights, IL	2235	796	20.8°C to 21.4°C	23:21	PASS
9/13/17	Denver, CO	2452	795	20.8°C to 21.8°C	24:04	PASS
9/13/17	Albuquerque, NM	2172	794	20.3°C to 20.9°C	24:45	PASS

Acceptance criteria: payload temperature range of +15.0°C to +25.0°C for 36 h. ID, identifier.

available at night, so if inquiries come in on the group email, the response time is quicker than just having one contact for studies.

Some protocols require the remote clinical site to download temperature monitoring information once the product is removed. Prior to receipt, confirm with the manufacturing site which software is needed for downloading temperature monitoring. As mentioned earlier, mock runs are a great way to test software and data logger access prior to receiving a real patient product.

After the product has been removed, the dewar/shipper will need to be returned. The shipper can be returned by FedEx (ground) or by a courier, depending on the protocol. If the courier is going to take the shipper after it is emptied, you will need to determine if they will be waiting for you to unpack or if they will return at a scheduled time. Dewars may be old, with locks that do not securely close the lid. The authors utilize zip ties to keep the lids closed in cases where the fastener is loose.

Chain of custody

According to the new FACT and immune effector cell standards [10], the chain of custody (COC) for immune effector cells must travel with the product from collection through infusion. In the experience of the consortium, few shipping companies have a designated COC form designed to meet this new standard. If COC documentation is not adequate, each site should create a form and work with each sponsor to implement an acceptable compliant process. This form should be prepared prior to arrival of the product and would then start the COC at product receipt, as the courier would sign for release of the product to the cell process laboratory. If there is more than one type of product in the delivery (e.g., CD8+ and CD4+ cells), two COC forms would be prepared, one for each product/infusion.

For COC traveling with the product from collection to infusion (across multiple sites), it is important to know where the document is and to ensure the courier signs before they leave. COC can be found in plastic pockets on the outside of the delivery container or in a sleeve inside the container.

Forms

The manufacturing sites have forms that must be completed to document receipt and infusion. If possible, it is best practice to get copies of those forms before product delivery (should be available during training or mock runs). As discussed earlier, it is best practice to conduct a mock run for delivery (either with the manufacturing site or on your own). An additional consideration when filling out forms from sponsors is to use the specified dating practice, as some sponsors have requested European dating.

Infusion of product

Each protocol has specific instructions for product infusion. Is the product thawed at bedside? Is the product thawed and reconstituted in the laboratory? Is the product infused fresh? Although these questions are common and should be addressed prior to the mock shipment, unanticipated situations do occur in practice. To identify how often deviations occur during these multi-center clinical trials, data were analyzed from three consortium institutions with experience shipping manufactured products to external clinical sites. In total, there were five shipping and/or handling deviations out of 129 shipments (3.9%). Of these deviations, no more than two happened at any one manufacturing site, and despite the deviations from procedure, solutions were identified that allowed for all products to be infused. Although a 3.9% incident occurrence is low, especially for three unique manufacturing sites, it does illustrate that shipping and handling deviations will occur and will require real-time attention and

mitigation strategies, even from experienced manufacturing sites interacting with highly trained remote clinical sites.

Learning from the aforementioned experiences and additional experiences from within the consortium, the authors have listed examples of incidents that have occurred within the consortium and how they were addressed:

- (i) A fresh product arrived in a single port bag for infusion. The port was not compatible with institutional supplies, and the nursing staff was unable to spike the bag at bedside. The principal investigator and laboratory medical director were engaged, and they immediately called the manufacturing site and discussed a resolution. Cell processing staff took the bag back to the cell processing laboratory. Staff attached a coupler and syringe and transferred the product to a new infusion bag. The original bag was rinsed with Plasma-Lyte and added to the product for infusion. The entire product was returned to the unit for infusion with no further issues. It is best practice at first product administration to have the cell processing technician stay on the unit until infusion has begun successfully. It is also helpful to have the principal investigator available and manufacturing contact numbers on hand. This exemplifies the importance of practice runs using mock materials specific to the product/trial.
- (ii) A product arrived in multiple vials. The infusion dosing form instructed staff to thaw two vials to achieve the dose. Once the thaw was completed and reconstituted, a cell count determined the dose was below the prescribed dose (or study mandated dose). This was a first run, and the manufacturing site had not accounted for cell loss during thaw and transfer (there was no rinse as part of the protocol). The staff immediately contacted the manufacturing site for advice and were instructed to thaw an additional vial to achieve the prescribed dose.
- (iii) A product was shipped in a transport container, and the sponsor requested that the temperature data tracked during shipment be downloaded by the site and sent back to the sponsor. Despite a mock shipment being requested, it was never performed, and when the site tried to download the data from the data logger, it was determined that special software and a micro-universal serial bus adapter were required, so these were purchased for future products.

Based on our experience as a consortium supporting multi-center clinical trials, the authors offer the following suggestions related to successful shipping and receiving:

- Perform mock shipments until all parties are satisfied and comfortable with new products and clinical trials. Make these mock shipments as real as possible.
- Be prepared for things to go wrong.
- Have extra staff available for product receipt on new protocols.
- Have the contact information for responsible individuals at the manufacturing and distribution site readily available for each shipment and ensure that someone will be available at all times.
- Track all shipments closely and in real time.

Discussion

Expanding the number of clinical sites participating in cellular immunotherapy clinical trials is crucial given the rarity of many pediatric diseases and the need to provide access to these promising therapies to a larger and more diverse pediatric population. Specialized manufacturing sites are highly experienced in regulatory guidelines and the production of cell therapy products, and physicians at clinical sites are equipped to handle patient care. However, experience in the handling and shipping of starting material and final product manipulation is often overlooked during the planning stages of a clinical trial.

The authors stress that shipping and handling are complex and critical to the success of a trial and should be considered early and often in trial planning. Indeed, having representation by the manufacturing site, the clinical research team and the remote clinical site when planning new trials would be helpful. The authors' multi-institutional consortium has described shipping and handling best practices that meet regulatory guidelines, ensure operational effectiveness, provide proper training and highlight problems and incidents encountered and approaches taken to overcome these challenges.

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Declaration of Competing Interest

PJH has patents related to cellular therapies and is a co-founder and consultant of Mana Therapeutics and serves on their board of directors. PJH also serves on the board of directors of the Foundation for the Accreditation of Cellular Therapy.

Author Contributions

Conception and design of the study: CL, PJH. Acquisition of data: CL, AL, JA, JT, NZ, JHE, PJH. Analysis and interpretation of data: CL, AL,

JA, JT, NZ, JHE, PH. Drafting or revising the manuscript: CL, AL, JA, JT, NZ, JHE, PH. All authors have approved the final article.

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