Operational Considerations For Implementing an Immune Effector Cell Program Using Manufactured Off-site Products

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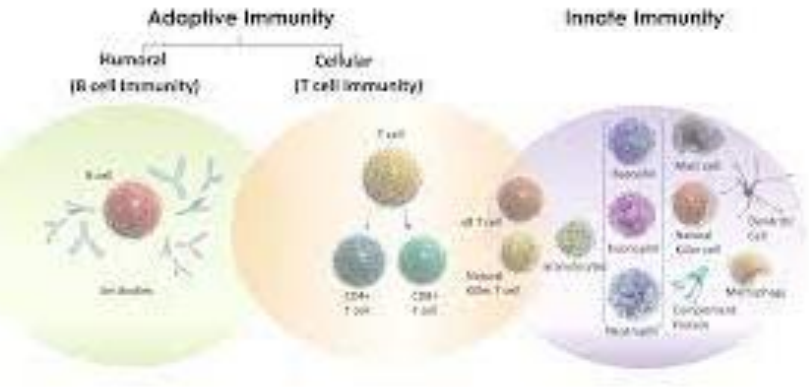
- Dana-Farber Cancer Institute
- Connell & O'Reilly Families Cell Manipulation Core Facility

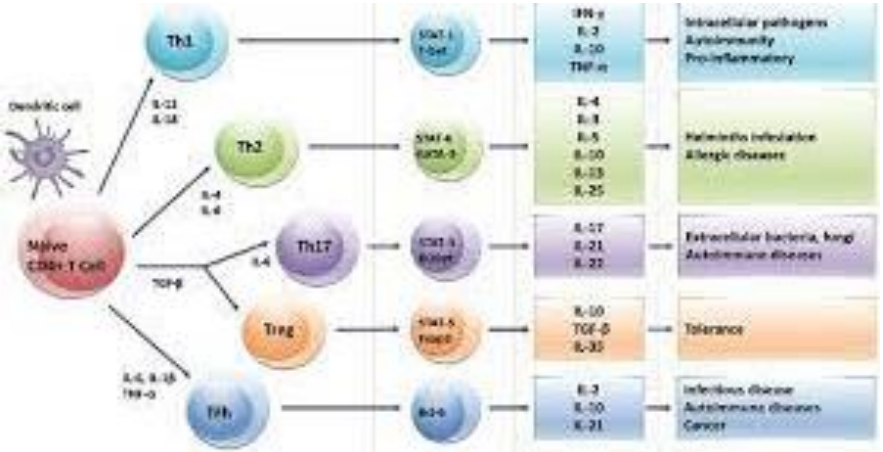
Objectives

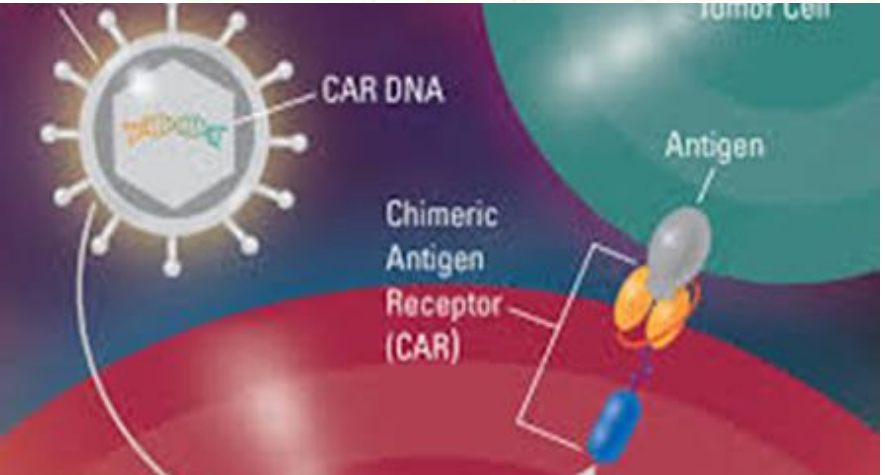
Understand the importance of reviewing a study for feasibility from a logistical & regulatory perspective

Learn how various institutional teams work together to onboard IEC treatments

Become familiar with the overall operational and logistical considerations when working with pharmaceutical/biotech companies.







Immune Effector Cells

- Cells that can initiate an immune response:
  - T cells, Plasma cells, B cells
    - Activated T cells target pathogens via cell-mediated response
    - Activated B cells secrete antibodies
  - Effector cells
    - Regulatory T cells (T_{reg})
    - Helper T cells (T_h)
    - Cytotoxic T cells
  - Engineered T cells to produce a specific response
    - Virus specific T cells
    - Effector cells target specific antigens / proteins to target cancer cells

Landscape of Cellular Therapies

Cell and Gene Therapies are undisputedly an area of important growth and potential for the future of oncologic and non-oncologic indications for pediatric and adult patient populations.

There is considerable investments being made across institutions for continued R&D, basic research, clinical trials, and commercial products, as well as capacity increases for the administration of these therapies.

Each institution will need a plan for managing the growth of this field and addressing what areas have the expertise, experience, facilities, and established relationships for to bring these therapies forward

High-Volume Cell Therapy Pipeline

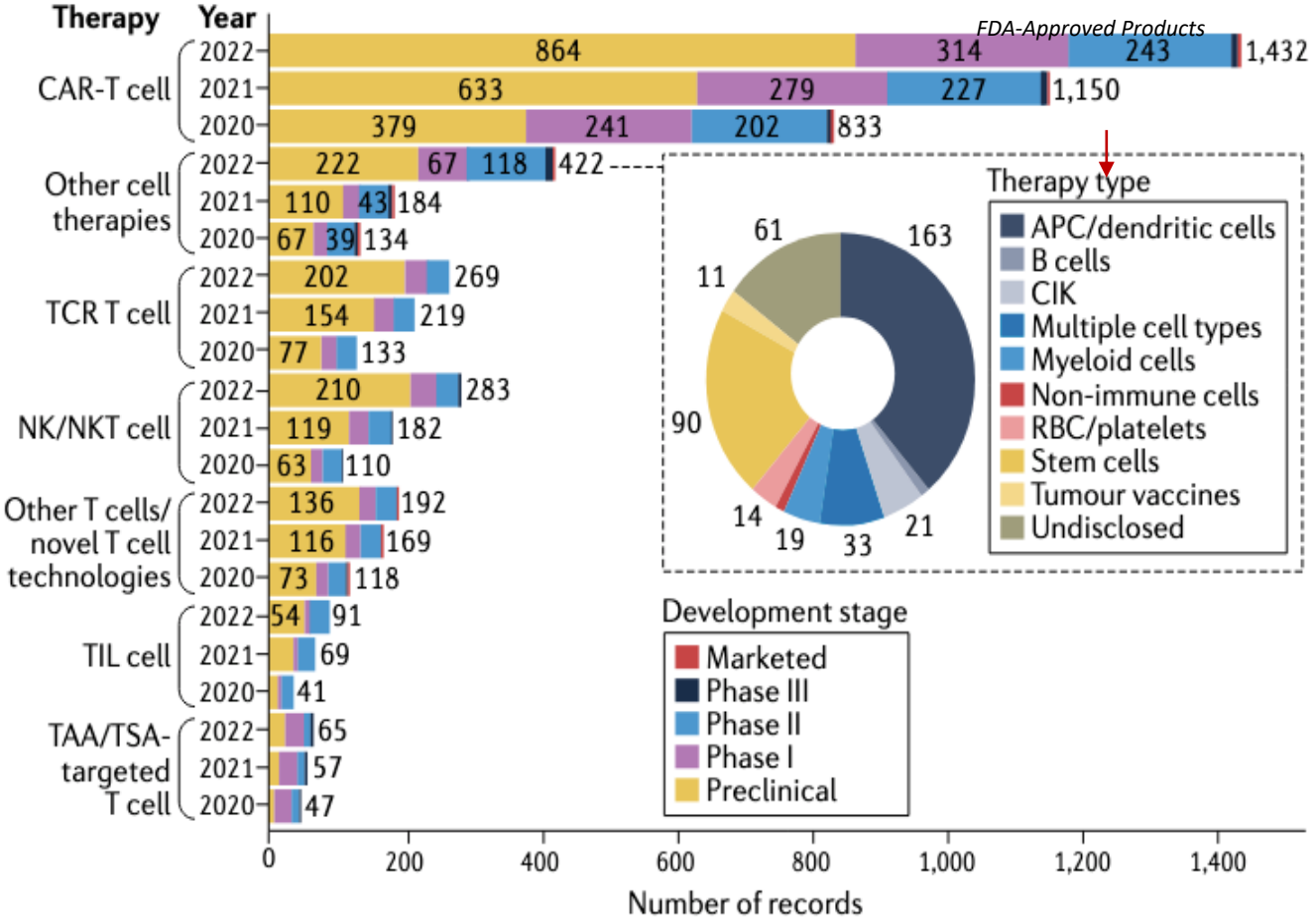


Fig. 1 | **Changes in the cancer cell therapy pipeline by therapy type and year.** Comparison of cell therapy agent development pipeline across various therapy types from 2020 to 2022. APC, antigen-presenting cell; CIK, cytokine-induced killer; NK, natural killer; RBC, red blood cell; TAA, tumour-associated antigen; TCR, T cell receptor; TIL, tumour-infiltrating lymphocyte; TSA, tumour-specific antigen. The pie chart shows the composition of the 'other cell therapies' category in 2022.

Landscape of cancer cell therapies: trends and real-world data; Nature; *doi: https://doi.org/10.1038/d41573-022-00095-1*

DF-CMCF Handles All Investigational and Licensed Cell Therapy Products

Investigational CT Products

- NeoVax
- NKG2D
- ProHema
- KTE-19 Zuma-1, Zuma-2, Zuma-3
- NY-ESO-1c259
- bbb2121
- NiCord
- Fate
- UCART123
- CARsgen CT053
- Adaptimmune
- Haplo CMIL NK
- CD30 CAR T
- TnMUC1 CAR T
- Eureka eTCR
- Poseida
- Kymriah SPt IND
- TCR αβ
- PBCAR191
- ACR101, 201
- CD37 CAR T
- TRQ15-01
- EBV-CTL
- Allovir ALVR106
- BK JC CTLS
- Fate
- UCART123
- PHE885 CAR T
- TILS
- Neximmune
- TEG002 eTCR
- Cartitude
- MB CART2019.1
- Triumvira TACO1-HER2
- GPRC5D CAR
- Axi-cel CAR T
- CD33 CAR
- GM HPC SCID
- GM HPC Sickle

Licensed CT Products

Oncology

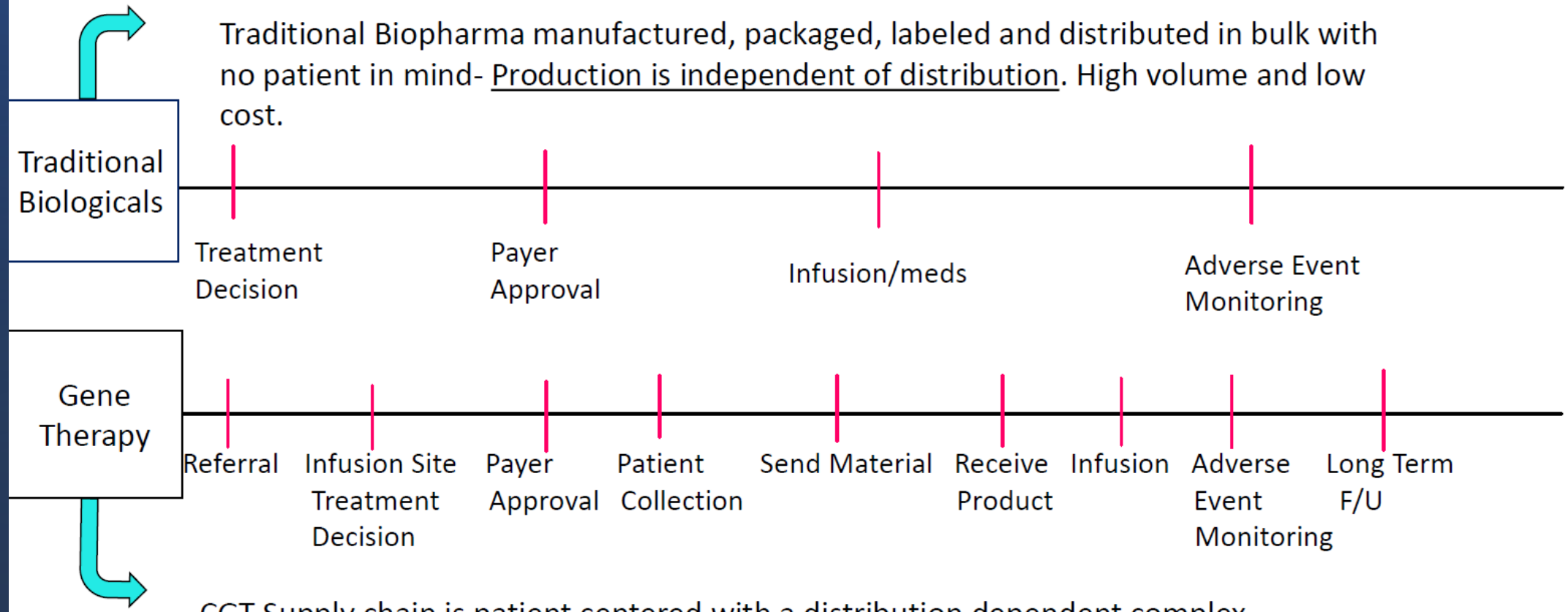
- (ABECMA) Idecabtagene Vicleucel
- (BREYANZI) Lisocabtagene Maraleucel
- (CARVYKTI) Ciltacabtagene Autoleucel
- (KYMRIAH) Tisagenlecleucel
- (PROVENGE) Sipuleucel-t
- (TECARTUS) Brexucabtagene Autoleucel
- (YESCARTA) Axicabtagene Ciloleucel
- Licensed HPC, Cord Blood

Non-Oncology

- (SKYSONA) Elivaldogene Autotemcel
- (ZYNTEGLO) Betibeglogene Autotemcel

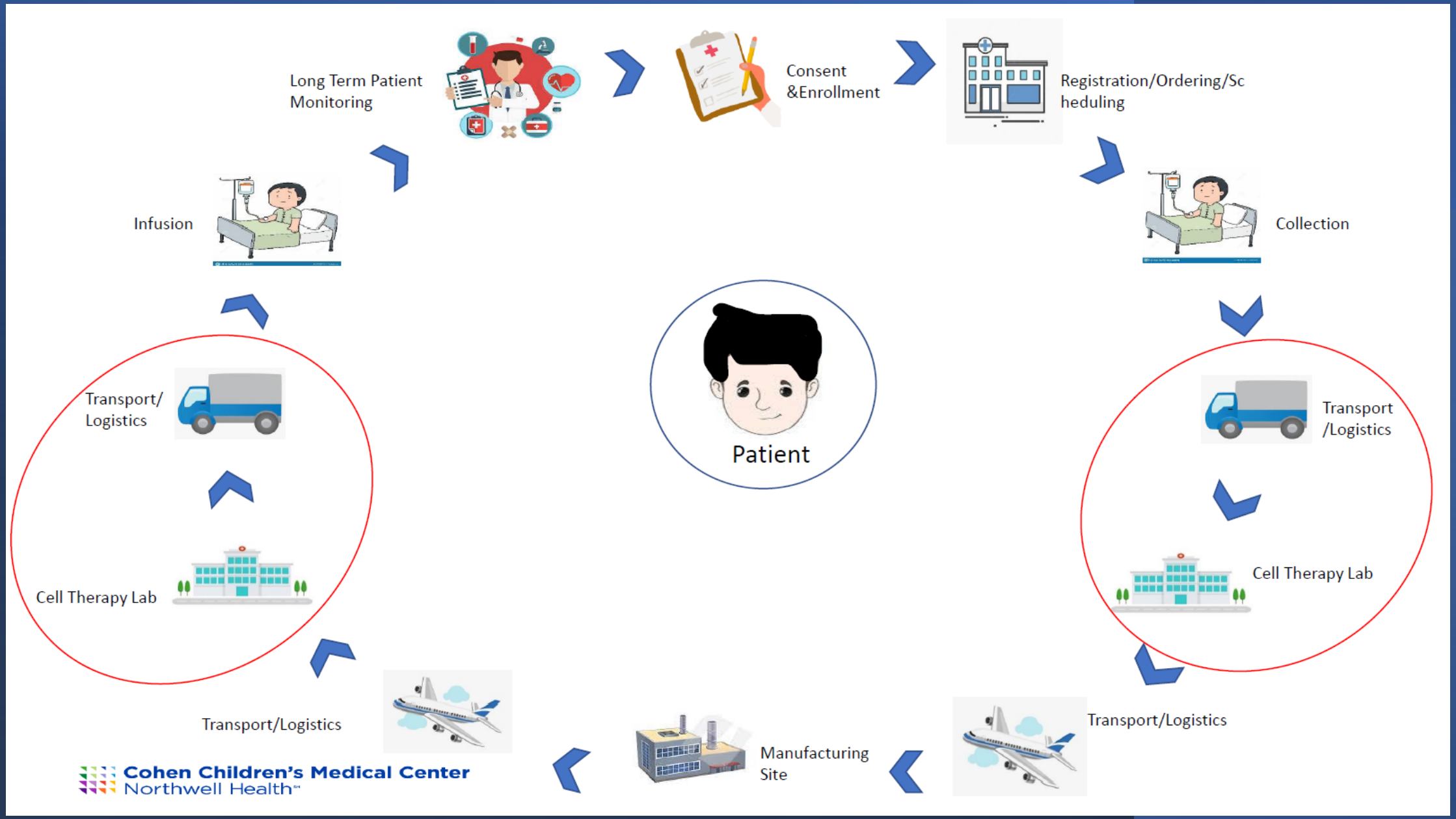
Shifting the Delivery System..

Traditional Biopharma manufactured, packaged, labeled and distributed in bulk with no patient in mind- Production is independent of distribution. High volume and low cost.

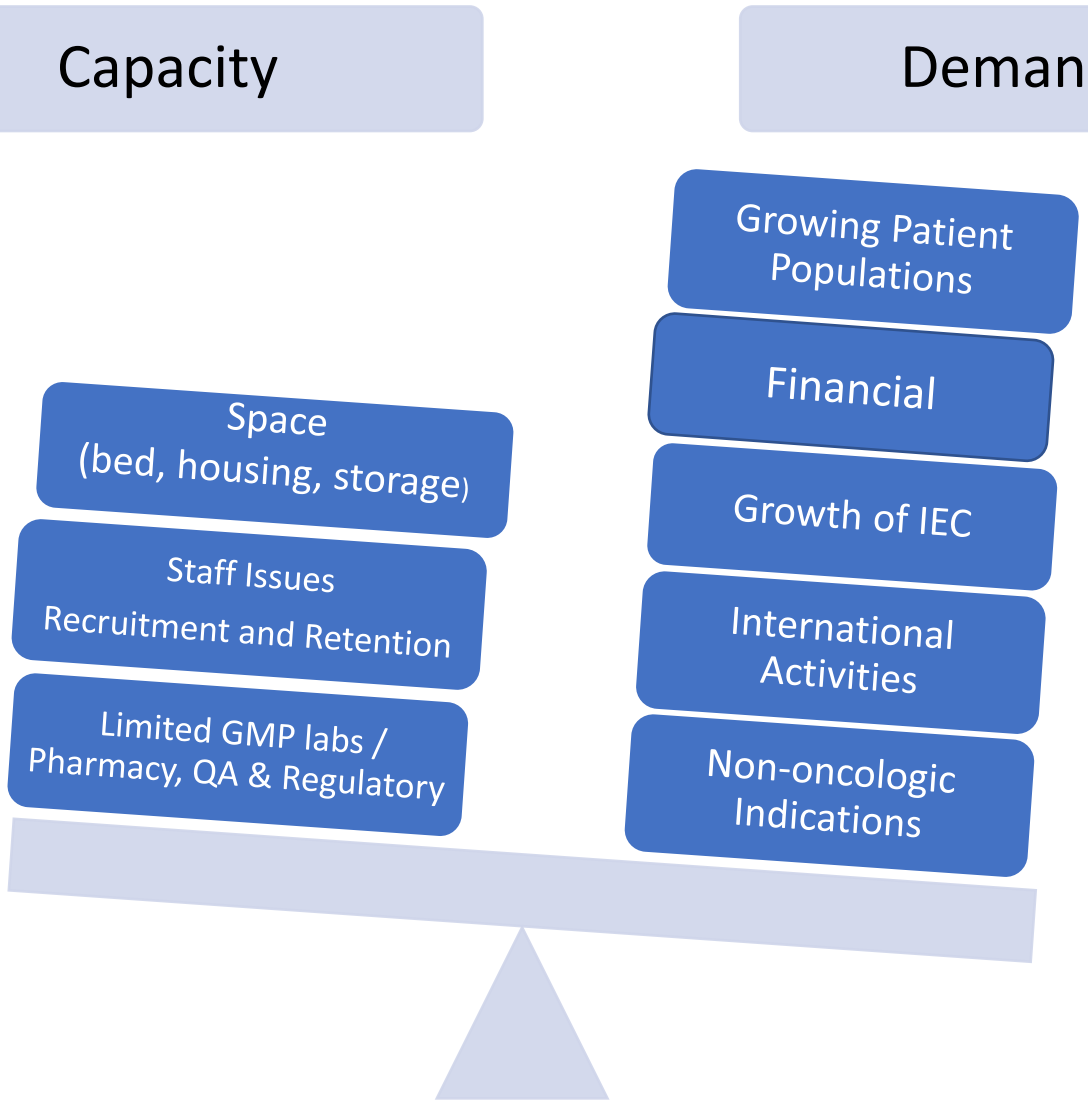


CGT Supply chain is patient centered with a distribution dependent complex manufacturing process Low Volume and high cost.

Cohen Children's Medical Center
Northwell Health


Long Term Patient Monitoring
Consent &Enrollment
Registration/Ordering/Scheduling
Collection
Transport /Logistics
Cell Therapy Lab
Transport/Logistics
Manufacturing Site
Transport/Logistics
Cell Therapy Lab
Transport/ Logistics
Infusion
Patient
Cohen Children's Medical Center
Northwell Health

Expected Demand Outweighs Capacity



It is expected that FDA will approve (License) 10-20 products per year for the next few years

Pipeline –
Which Products / Trials to Choose to be involved with

Clinical Team(s)

Heme, Solid Tumor, Non-malignant, etc.

Research Investigators

Who will manage the products?

Cell Therapy Lab,

Blood Bank, Pharmacy

Pharmacy

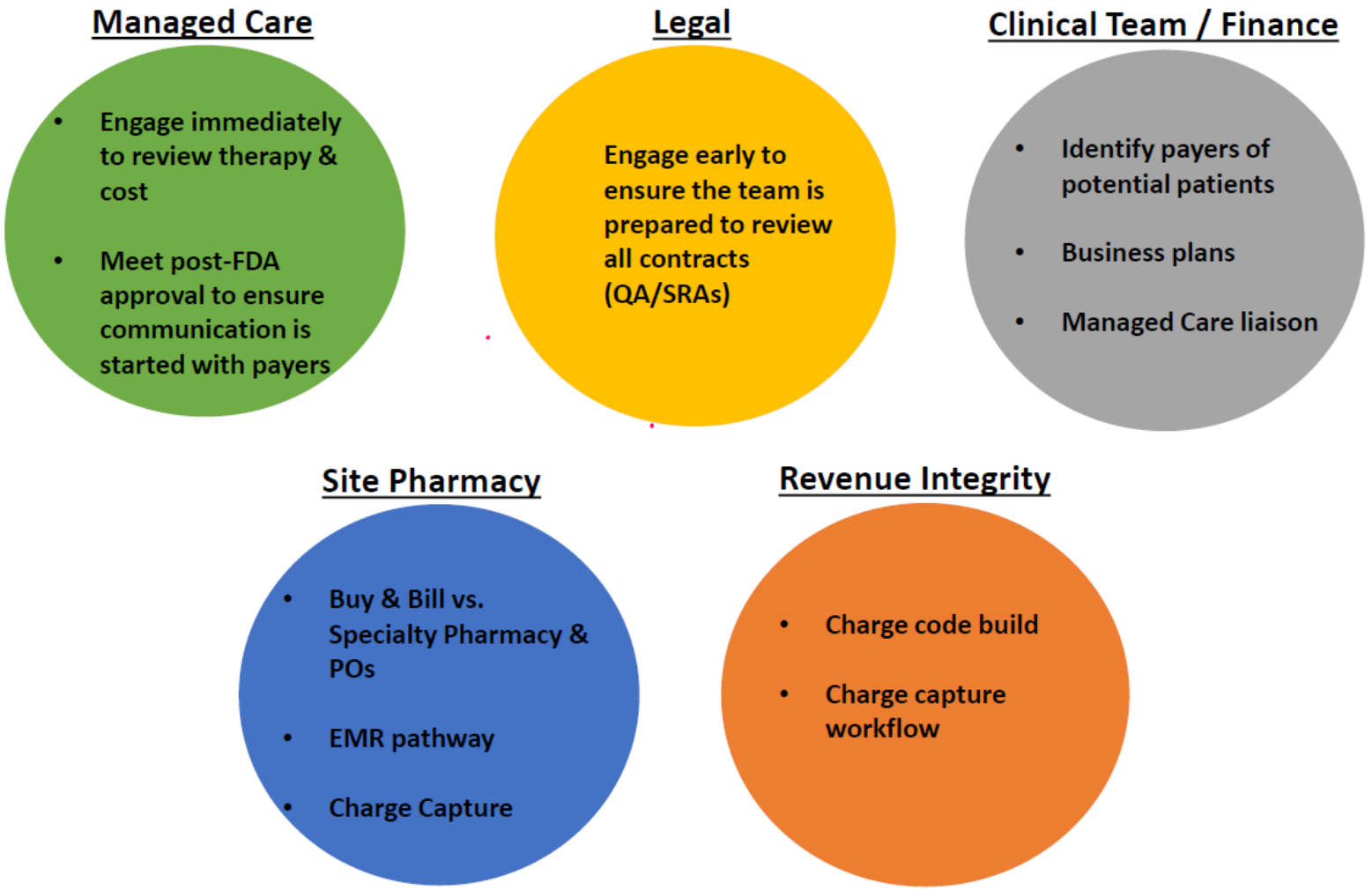
(On boarding special medications to treat CRS, etc.)

Administration

Finance, Legal,

Internal Review Board, Biosafety, Scientific Review, etc

Internal Work

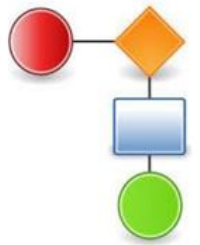


Clinical Trials and Licensed Product Handling Readiness

Clinical Trial Review

- Multiple Departmental Reviews
- Disease center interest – patient enrollment, feasibility,
- Costs - non reimbursable ancillary costs
- Department operational ability – Nursing, Pharmacy, Clinical Lab / Path, CT Lab, research coordinators, etc.
- Internal Review Board, Safety Review Committee, Scientific Review

Building workflows



Agreements

- Multiple Types and Departments Involved
- NDA – nondisclosure agreements / confidentiality agreements
- Clinical Trial Agreements
- Pharma contracts
- Quality Agreements
- Long Term follow-up agreements

Timeliness of review of contracts against clinical needs

Financial

- Trial product vs licensed products
- Alignment with payors
- Pharmacy vendor payment terms

Ancillary cost data capture and reporting,

Product ancillary cost – apheresis / raw material collection, handling (documents, labeling, PHI), storage and manufacturing)

Patient assistance

Alignment with payors/our site/pharma

Change Management – Sponsor Documents

Documents

- Protocols
- Apheresis manuals
- CT Lab manuals
- Research manuals
- Consents
- Forms (Data, product disposition,)

Change Controls

Need good communication with research staff to notify ancillary areas of pending changes

Version updates need to be submitted to IRB and approved

- May take 30+ days to be approved
- Need to be notified that they have been approved

Need to prepare for version changes and be ready to train and implement once approved by IRB

Agreements


Confidentiality Agreements
Clinical Trial / Service Agreements
Quality Agreements
Other (Banking, Lab Services, etc.)

Quality Agreements

- Scope of the Agreement
- Roles & Responsibilities
- Audits
- Communication
- Storage & Distribution
- Release documentation
- Complaints & Recalls
- Responsibility Matrix
- Responsible parties

EXHIBIT A

Item		Responsibilities	
		CMCF	COMPANY
1.0	Organization and Personnel	▪ Ensure CMCF personnel and subcontractors, in accordance with cGMP, have appropriate training, skills, knowledge and experience to perform services. ▪ Subcontracting is not permitted of any activities related to study products, with the exception of those cited in the agreement and IND, without prior written consent from COMPANY	▪ Confirm by audit.
2.0	Premises and Equipment	▪ Ensure premises, environment, utilities, equipment and computerised systems are properly designed, calibrated, maintained and validated in accordance with GXP.	▪ Confirm by audit.
3.0	Applicable GMP's	▪ As per 21 CFR 210, 211, 600 and 1271, ICH Q7	▪ Confirm by audit
4.0	Raw Materials and Packaging Materials	▪ Source raw materials. ▪ CMCF is responsible for auditing and maintaining a supplier qualification program for all raw material suppliers except those purchased directly by COMPANY.	▪ Confirm by audit. ▪ COMPANY shall approve specifications on raw materials.
5.0	Cells and viral vector stocks	▪ COMPANY will procure initial HCTP raw materials and CMCF perform manufacturing as detailed in SOP's.	▪ COMPANY shall provide appropriately tested viral stocks to CMCF to allow entry of the viral vector into cGMP areas.
6.0	IND Product Specification	▪ CMCF shall provide COMPANY with a Manufacturers Certificate of Analysis (CoA) in accordance with the defined IND product specifications.	▪ COMPANY shall define product specifications.
7.0	Master Controlled Documents	▪ CMCF shall prepare Batch Production Records (BPR's) and SOP's for manufacture of the IND product in accordance with cGMP's after completion of development / validation work ▪ Changes to these documents will be handled as outlined by Change Management SOP's.	▪ COMPANY shall provide CMCF with Process Flow Diagrams, equipment lists and other documentation indicating all critical process parameters and information to allow BPR's and SOP's to be drafted. ▪ COMPANY will review and approve all BPR's and SOP's prior to

Audits and Monitoring Visits

Initial Audits & Site Initiation Visits (SIVs)

- All inclusive Clinical, Lab & Collections, Pharmacy, Post Infusion Mgt.
- Quality Systems (GxP (GCP, GMP, GDP))
- Collection, Processing, Storage, Thaw, Dosing, Issue
- Chain of Custody (COC)
- Chain of Identity (COI)
- Environmental Monitoring

Monitoring Audits

Clinical Mgt Documentation

- Study enrollment
- CT Drug product documents – COC & COI
- Clinical documentation -
- Reporting of Adverse Events and other Outcomes

- Sponsor documents
- Accountability Logs

Chain of Custody and Chain of Identity

Ensuring Documented Hand-Offs

- Begins at initial patient / donor identification and testing (disease type and stage, HLA, etc.)
- Screening and eligibility testing
- Collection to Courier
- Courier to Manufacturer to Courier
- Courier to Clinical Port of Entry
- Preparer to Clinical team to Patient

Agreeing on Identifiers

- Most healthcare organization use:
  - Name, Medical Record #, DOB
- Most Clinical Trials use Subject ID
- BioPharma may use other identifies

STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

Standards Development in Action: Autologous Cell and Tissue Therapy Labeling Standards

CHALLENGE

With more than 1,000 clinical trials in progress, autologous cell and tissue therapies offer promising new avenues for treating life-threatening and chronic diseases and restoring the function of damaged organs and tissues. After donation, cells can travel across the globe and pass between dozens of different stakeholders before finally making it back to the original donor as a therapy. However, the **labeling standards for these products were originally designed for one-way donation processes** and do not account for the complexity of the autologous therapy supply chain. This fragmented process can result in the loss of information critical to product safety, as stakeholders often capture information in different ways at each step.

STANDARDS COORDINATING BODY

REGENERATIVE MEDICINE

Project: Chain of Custody/Chain of Identity

TYPE: STANDARDS ADVANCEMENT PROJECT

PARTNERS: ICCBBA AND THE SCB CELL THERAPY, GENE THERAPY, AND TISSUE ENGINEERING WORKING GROUPS

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and

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on

1. **Chain of Identity (COI)**
   The permanent and transparent association of a cell or gene therapy's unique identifiers from procurement of tissue or cells throughout the full product(s) lifecycle including post treatment monitoring.

2. **Chain of Custody (COC)**
   Concurrent, permanent, auditable documentation illustrating the guardianship of a cell or gene therapy product from its origin through its final disposition.

3. **Therapy ID (COI identifier)**
   A unique code used to discern a cell or gene therapy and the intended therapy recipient.
   The CoI identifier should be identical throughout the product chain, and on all related products.

STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

Working Group - Conclusion

From an industry perspective, we want to have a harmonized format for the Chain of Identity Identifier. We believe that for safety reasons the CoI identifier should be identical throughout the product chain, and on all related products.

This proposal defines the core CoI Identifier code format and supports assignment of the CoI identifier in a number of ways. In summary:

(a) the Collection Facility can create CoI identifier at the time of first collection

- ✓ 1st DIN can be used as part of CoI identifier

(b) the Sponsor/Manufacturer can assign CoI identifier prior to first collection

- ✓ e-Traceability system can be used
- ✓ Manual creation of sponsor/manufacturer unique sequence can be used

E.g. CIA999920123456 C

3rd party issuing agency ensures:

STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

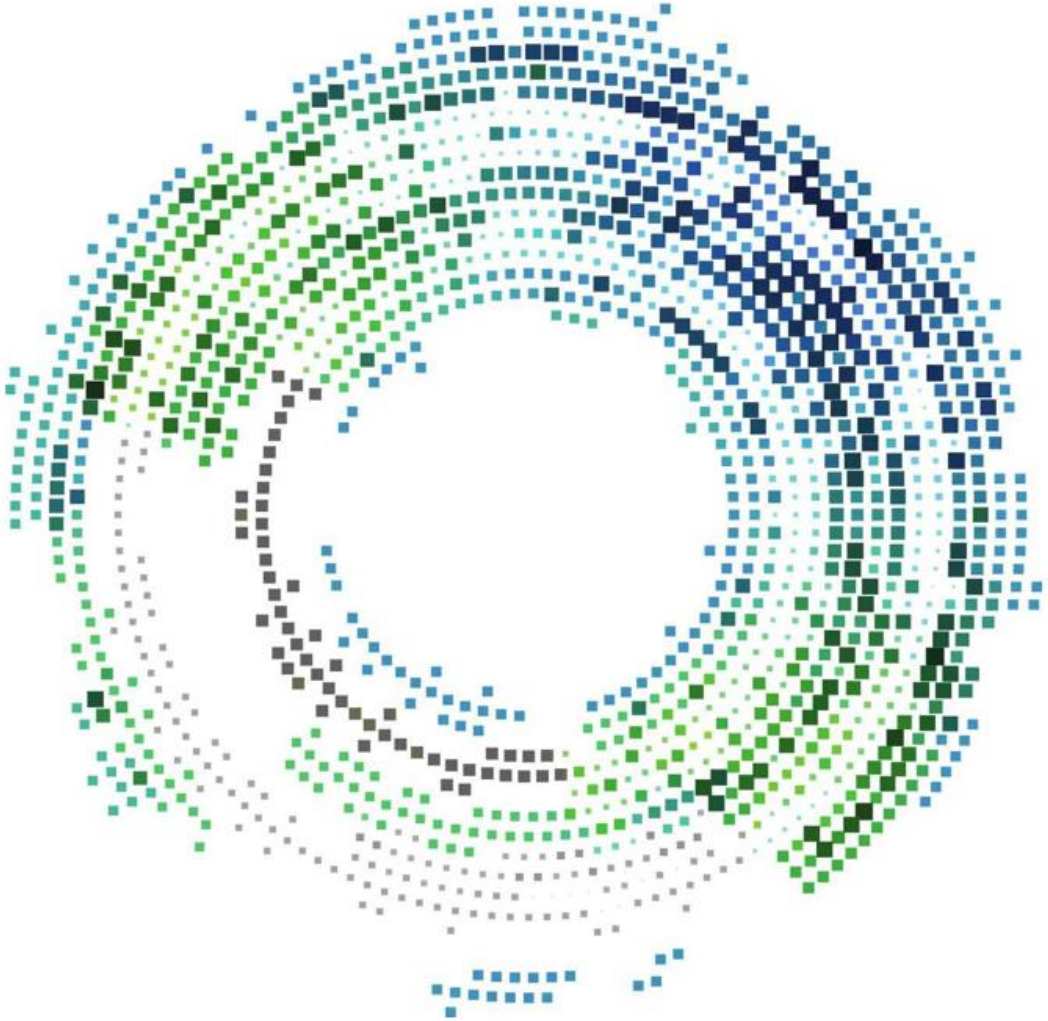
- **The COI Identifier is unique across all sponsors/manufacturers**
- **Uniqueness is global and guaranteed over a long time period**
- **The COI Identifier can be encoded in a standardized electronically readable format**
- **The COI Identifier in electronic format contains context information to distinguish it from any other identifier**
- **The COI Identifier has controls to limit the potential for human transcription error**

Informed Consent

- Make sure **Patients Know** that **PHI** will be **Shared** with Manufacturers and Testing Labs
- State how long their cells will be available and / or kept for use

Deloitte.

Leveraging FACT and/or AABB Accreditation To Meet Industries Need to Site Qualify & Audit



NextGen IWG
Site Certification Webinar

October 27, 2022

NextGen Industry Working Group (IWG)

Our Mission

Empower Collaboration among CGT Leaders to Share Best Practices

Harmonize Industry Standards

Develop Solutions for Patients, Providers & Relevant Stakeholders

Founding Members

LEGEND BIOTECH, Roche, Celyad, Kite A GILEAD Company, Johnson & Johnson, Kiadis pharma, Celgene, JUNO THERAPEUTICS, AgenTus THERAPEUTICS, Orchard therapeutics, RubiusTherapeutics, bluebirdbio

OUR MEMBERSHIP IS GROWING

Current Members

InstilBio, gamida cell, gentibio, TCR² THERAPEUTICS, Genentech, Bristol Myers Squibb, Takeda, allianceRx Walgreens PRIME, Roche, janssen, bluebirdbio, Pfizer, Kite A GILEAD Company, Catalent, Autolus, Lyell, VERTEX, Biogen, PACT, Celyad, CRISPR THERAPEUTICS, astellas, gsk GlaxoSmithKline, Orchard therapeutics, talaris THERAPEUTICS, AgenTus THERAPEUTICS, ArsenalBio, kyverna, Johnson & Johnson, SAREPTA THERAPEUTICS, Kiadis pharma, AVROBIO, Intellia THERAPEUTICS, RubiusTherapeutics, GINKGO BIOWORKS, AstraZeneca, NOVARTIS, LEGEND BIOTECH, change FOODS

IN COLLABORATION WITH INDUSTRY STAKEHOLDERS

fact, aabb, ASFA, BE THE MATCH, ICCBBA, STANDARDS COORDINATING BODY REGENERATIVE MEDICINE, ASGCT American Society of Gene + Cell Therapy, EBMT

Leveraging Accreditation versus Site Audits

The following are real-life examples of requirements that were addressed in accreditation standards in response to industry feedback. Feedback was provided via comparison of audit checklists, review of industry nonconformances, and multistakeholder discussions. Note that different companies often have different priorities, which present opportunities for industry standardization.

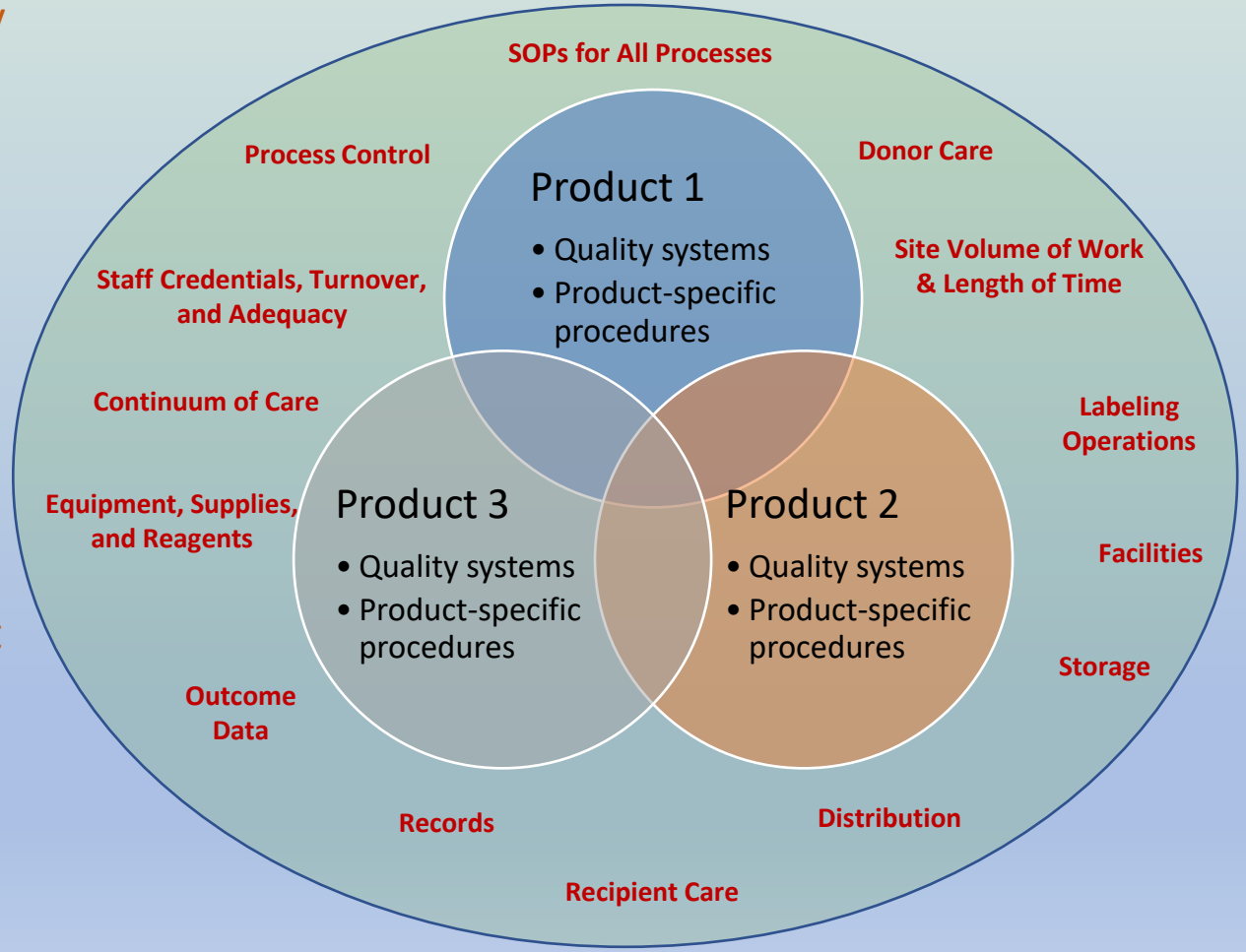
GMP Training.	GMP not always required, but GTPs and others often are.	Require GxP applicable to activities.
Qualification of software updates.	Implied by qualification requirements.	Specified software in qualification standard.
Temperature monitoring post-collection.	Many effective methods; insufficient data proving one over another.	Require risk assessment to evaluate need for continuous monitoring.
REMS.	Not all products will require REMS or same strategies.	Written to be more high-level.

- Compliance assessed during each inspection.
- Deficiencies are specifically cited in accreditation reports when cited.

Accreditation Standards Require Robust Infrastructure

A majority of the concepts audited by manufacturers are already covered by accreditation standards. Furthermore, manufacturing and administration of cellular therapies is complex. Participation of multiple entities is required, unlike traditional pharmaceuticals. Accreditation fills many gaps in what industry can control.

- Cellular therapies routinely involve more interdisciplinary groups (e.g., health care specialties, treatment settings, brick and mortar vs mobile services).
- Patient care, manufacturing schedules, and chains of identity and custody are more challenging.
- Good Tissue Practices (GTP; 21 CFR 1271 in the U.S.) are always required.
- Good Manufacturing Practices (GMP; 21 CFR 210, 211, 600s) may be required post-collection.
- A robust infrastructure is required to administer the right IECs to the right patient, at the right time, with the right management and supportive care available and implemented.
- Patient follow-up will be required; Risk Evaluation and Mitigation Strategies (REMS) may be required for products with significant or unusual toxicities.



SIV and Audits

- Negotiate! Negotiate!

- Audits and visits
- Data ownership & sharing
- Define what is in scope

Reporting Outcomes and Adverse Events

Outcomes

- **Disease progression or remission status**
- **Side Effects**
- Endocrine and reproductive function and osteoporosis, Cardiovascular risk factors, Respiratory function, Chronic renal impairment, Secondary malignancies.
- **Growth and development of pediatric patients.**
- **Long Term Follow-up -** 15 years

Adverse Events

Policies to manage AEs

- Routine / Expected Outcomes
  - Fevers, chills, etc.

Serious AEs

- CRS - Cytokine Release Syndrome
- Neurologic dysfunction

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

CIBMTR Data Reporting

Cellular Therapy Initiatives

In addition to receiving data on transplant recipients, CIBMTR receives data about patients who received other cellular therapies. Most activity is focused on the use of chimeric antigen receptor (CAR)-T cells for hematologic cancers. CIBMTR receives these data via a suite of CTED forms and continues to work with international registries to review and harmonize data collection globally.

Cellular Immunotherapy Data Resource (CIDR)

CIBMTR receives funding from the National Institutes of Health (NIH) to serve as the CIDR to collect outcomes of patients receiving non-transplant cellular immunotherapies to support observational studies and inform prospective studies and clinical trials. The Immuno-Oncology Translational Network (IOTN) supports the Cancer Moonshot℠ initiative to accelerate cancer research to make more therapies available to more patients.

Cellular Therapy Product

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Registry Use Only

Sequence Number:

Date Received:

CIBMTR Center Number: ___ ___ ___ ___ ___

CIBMTR Research ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Event date: ___ ___ ___ ___ – ___ ___ – ___ ___
YYYY MM DD

Product Identifiers

NMDP cord blood unit ID: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Registry donor ID: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Non-NMDP cord blood unit ID: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Global Registration Identifier for Donors (GRID): _

Donor DOB: ___ ___ - ___ - ___
YYYY MM DD

Donor age: ___ ☐ Months *(use only if less than 1 year old)*

☐ Years

Donor sex: ☐ Male ☐ Female

CIBMTR Center Number: ___ ___ ___ ___ ___ CIBMTR Research ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Cellular Therapy Product Identification

If more than one type of cell therapy product is infused, each product type must be reported separately on a new F4003.

1. Name of cellular therapy product
   - ☐ Axicabtagene ciloleucel (Yescarta®) – ***Go to question 2***
   - ☐ Brexucabtagene autoleucel (Tecartus™) – ***Go to question 2***
   - ☐ Ciltacabtagene autoleucel (JNJ-4528) – ***Go to question 2***
   - ☐ Idecabtagene vicleucel (Abecma®) – ***Go to question 2***
   - ☐ Letetresgene autoleucel (brand name will go here when approved) – ***Go to question 2***
   - ☐ Lisocabtagene maraleucel (Breyanzi™) – ***Go to question 2***
   - ☐ Orvacabtagene autoleucel – ***Go to question 2***
   - ☐ Tisagenlecleucel (Kymriah®) – ***Go to question 2***
   - ☐ Other product – ***Go to question 3***
   - ☐ No product name – ***Go to question 3***

2. Is the product out of specification? *(only for commercially available products)*
   - ☐ Yes
   - ☐ No

Cell Product Source

3. Date of cell product collection
   - ☐ Known - ***Go to question 4***
   - ☐ Unknown – ***Go to question 5***

4. Date of cell product collection: ___ ___ ___ ___ - ___ ___ - ___ ___
   YYYY MM DD

5. What is the tissue source of the cellular product? *(check all that apply)*
   - ☐ Bone marrow (BM)
   - ☐ Cord blood unit (CBU)
   - ☐ Peripheral blood
   - ☐ Adipose tissue
   - ☐ Amniotic fluid
   - ☐ Cardiac tissue
   - ☐ Hepatic tissue

Summary : There are many factors to consider when deciding to bring on a new CT product:

- **Clinical need** and patient population
- **Financial** considerations for institution and patient
- **Capacity** – beds, lab, staffing, Treatment Location
- **Technical & Operational Expertise** -
  - clinical staff (ADE, REMS),
  - lab processing, (COI,COC, Handling)
  - Pharmacy (Role, Contracts, Meds)
- **Administrative and Regulatory**
  - IRB, Safety Board,
  - Data capture reporting, management and mining
  - Audits
  - Operational logistics
- **Long term follow-up**