Challenges in Capturing Long Term Follow up of Recipients of Genetically Modified Cells

Cell Therapy Liaison Meeting

January, 2018

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

Outline

- Development of the Cellular Therapy Registry
  - Standardized Data Collection Platform
  - Data Standards and Sharing
  - Considerations for capturing long term follow up.
- Recommendation vs. Interpretation for Commercial Genetic Modified Products.
- Approaches to optimize follow up.
- Overview and recommendations.

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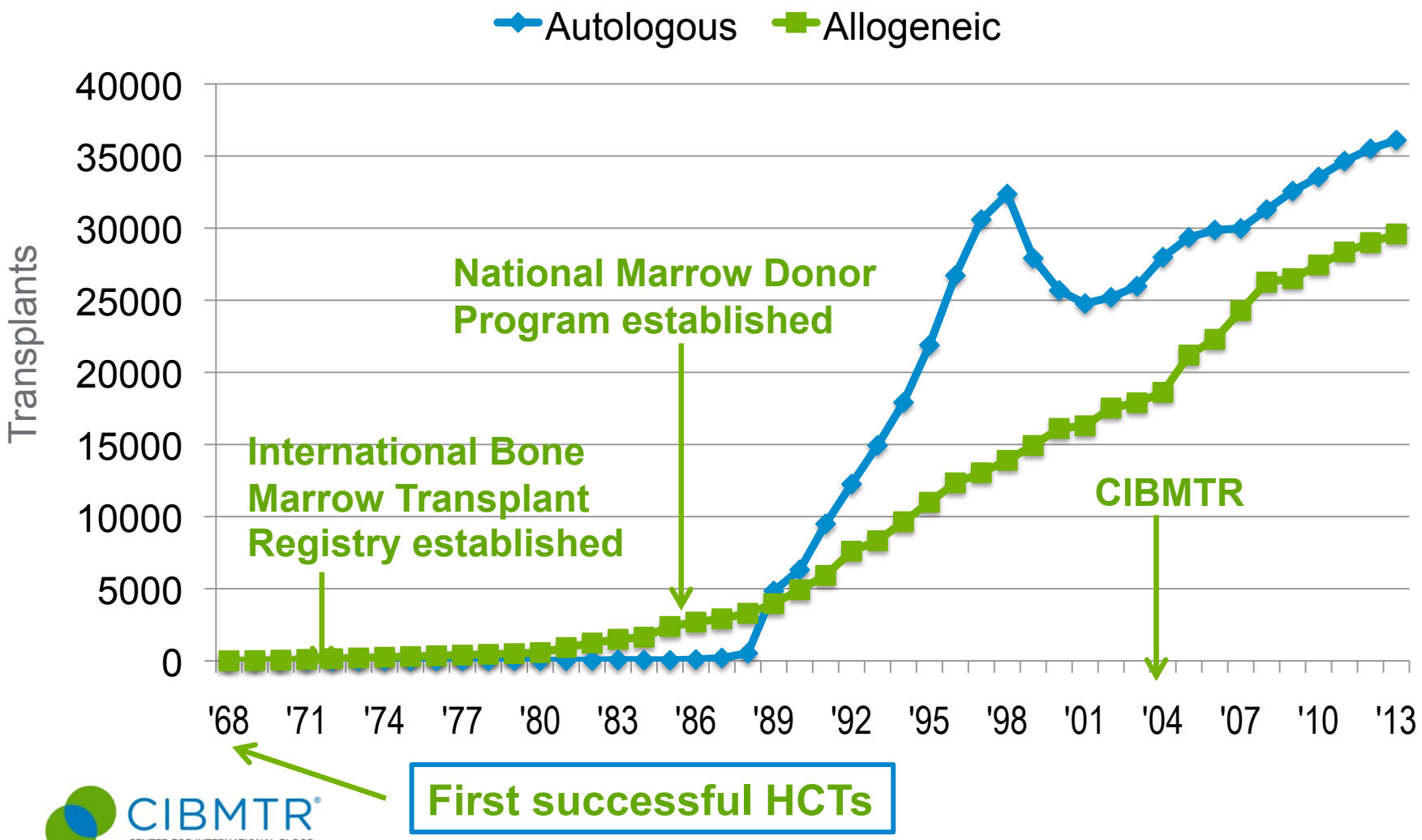
A Little History: We Have Been Around for a Very Long Time



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NMDP/Be The Match

Established outcomes registry and research repository in 1986

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Medical College of Wisconsin

Established outcomes registry in 1972; NIH funded since 1985

The CIBMTR is a research collaboration between **NMDP/Be The Match** and the **Medical College of Wisconsin**

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Characteristics of HCT Registry Data

- Population-based
  - Population defined by receipt of a specific type of therapy
  - No other eligibility criteria (i.e. do not need to be in a specific clinical trial or in a certain kind of center)
  - Requirement for consecutive reporting
- Longitudinal
  - No specific end date for follow-up
  - Depends on ability of treating physician/center to maintain contact
- Variable dataset

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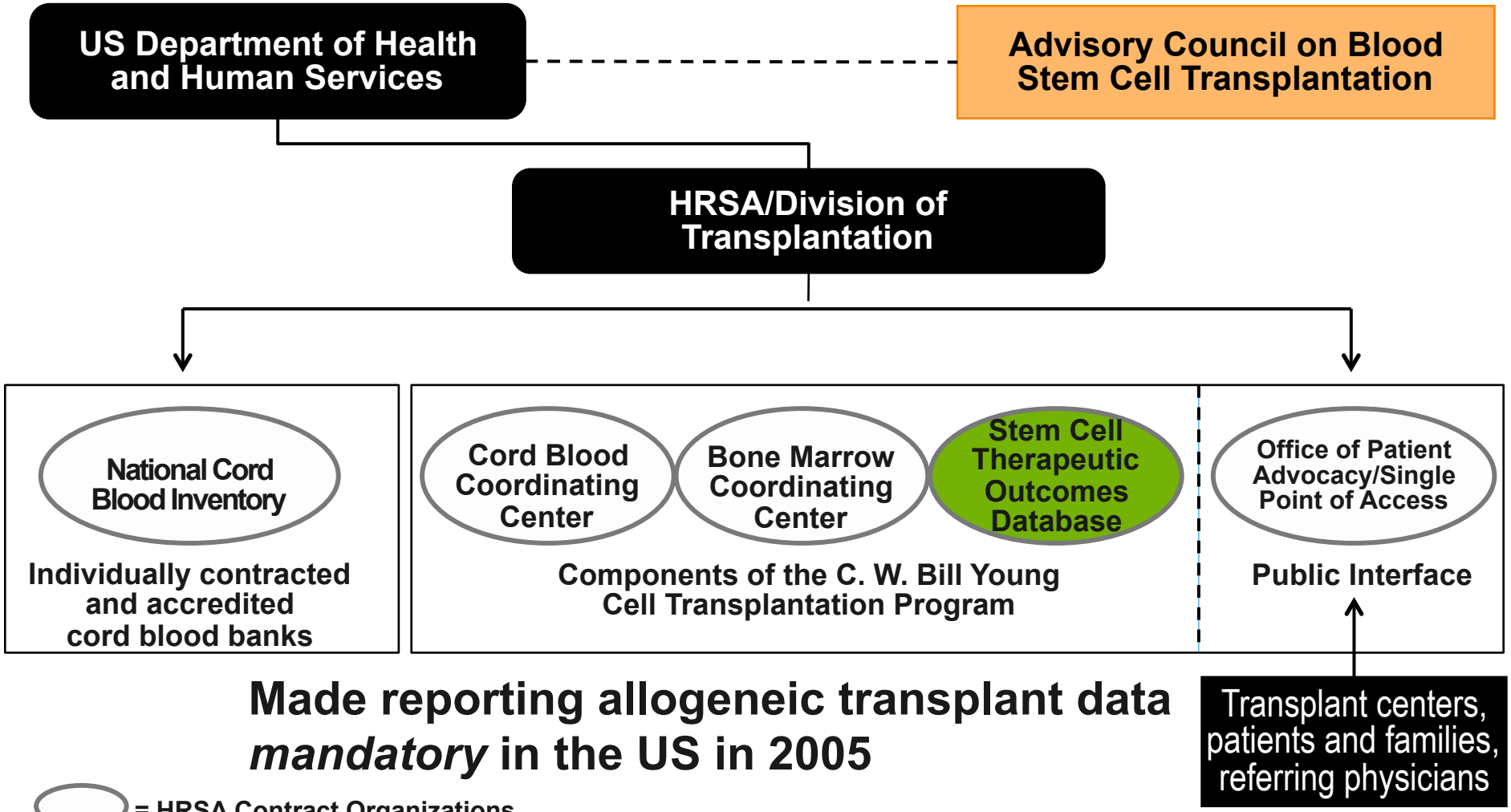
C.W. Bill Young Cell Transplantation Program*



Made reporting allogeneic transplant data *mandatory* in the US in 2005

= HRSA Contract Organizations

= Other New Organizations or Relationships

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* Created by the Stem Cell Therapeutic and Research Act of 2005 and the Stem Cell Therapeutic and Research Reauthorization Act of 2010

Requirements of SCTOD

- Collect data
  - Outcomes of allogeneic HCTs performed in the US or performed outside the US with US grafts
  - **Other therapeutic applications of blood stem cells**
    - **Regenerative medicine**
    - **Cellular therapy of malignant disease**
  - Quality of life
- Disseminate data
  - Multiple Users, Formats
- Analyze data
  - Center-specific outcomes
  - Wide Range of Research
- Research Repository

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CIBMTR Cellular Therapy Initiative - Objectives

- To study therapies using cellular products for indications other than hematopoietic replacement or recovery.
- To provide an infrastructure to allow long-term follow-up of patients treated with genetically manipulated cellular therapy products.

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CIBMTR Cellular Therapy Initiatives - History

- **1990s-Jan 2017**: Donor lymphocyte infusions to treat post-transplant relapse/infection capture on HCT forms
- **2006- June 2016**: SCTOD mandate to collection data on non-HCT uses of blood stem cells
  - Outreach to disease specialist
  - Simple registry of activity
- **July 2016-current**: Revamp the Cellular Therapy Registry with the launch of CTED forms.
  - Expanded fields on indications, product manufacturing and complications, **long term follow up mechanism**
  - Converge all cellular therapies, including DCIs in one track.
  - NCI Pilot Project

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CIBMTR Cellular Therapy Initiatives - History

- **2014-2017**: active initiative to understand the community's needs and to develop an infrastructure to meet those needs
  - CIBMTR Advisory Committee/Advisory Council presentations
  - Forum of wide range of stakeholders in 2015, 2016 and 2017
  - Series of meetings with industry and international registries
- Summer 2016: new Cellular Therapy Registry forms launched in FormsNet

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CTED Pilot

- NCI-funded 1 year project to “Beta” test the CTED forms.
- Launched in July 2016
- Direct input from centers at two in person meetings
- Data harmonization and input from international partners (EBMT and JHSCT)
- Input resulted in the release of revised forms July 2017.
- Time studies are ongoing to determine reporting burden and appropriate reimbursement rates

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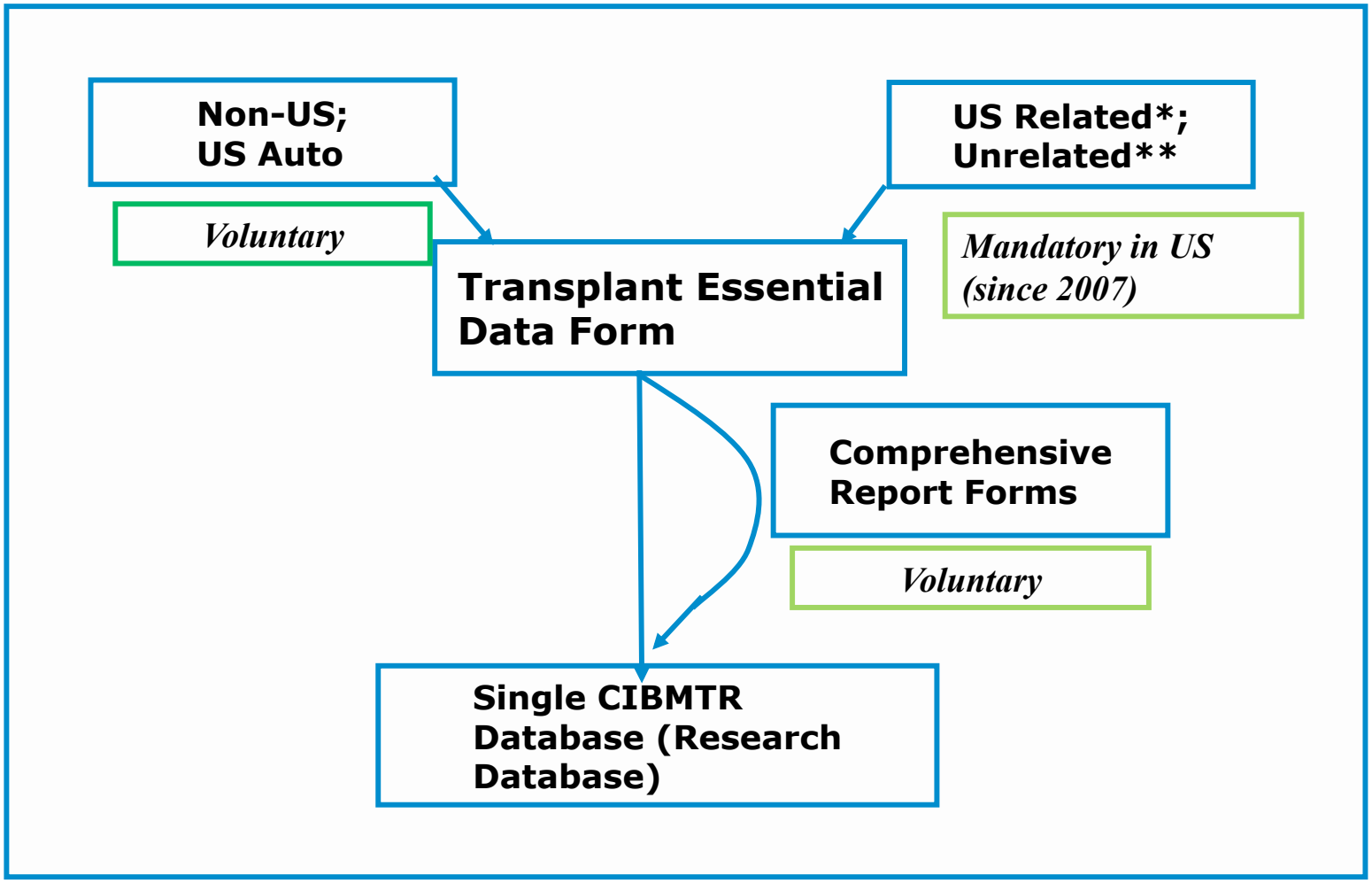
Data Flow – Transplant



*Donor outcomes routinely collected
**Donor outcomes collected on subset

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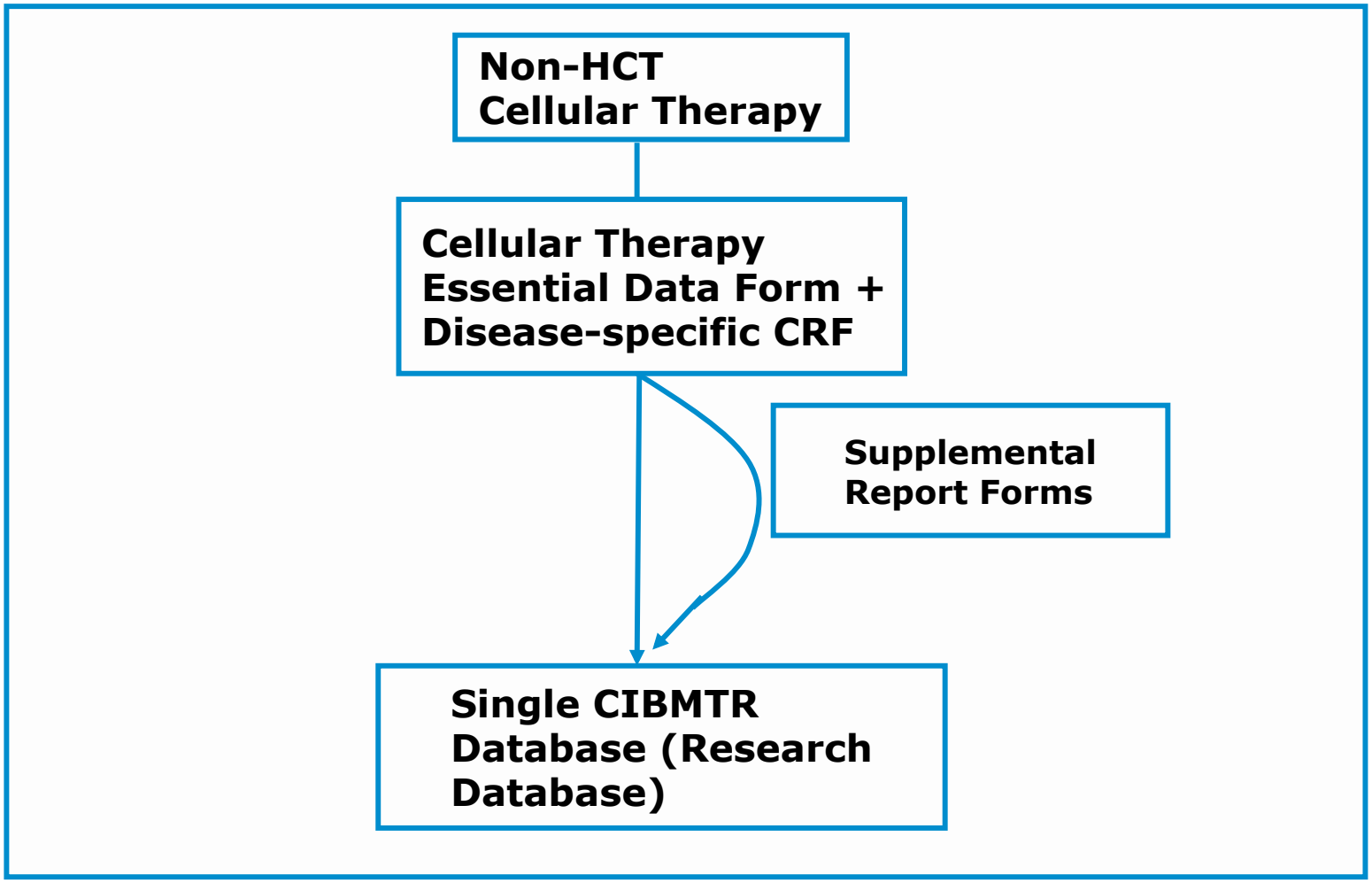
Data Flow – Cellular Therapy



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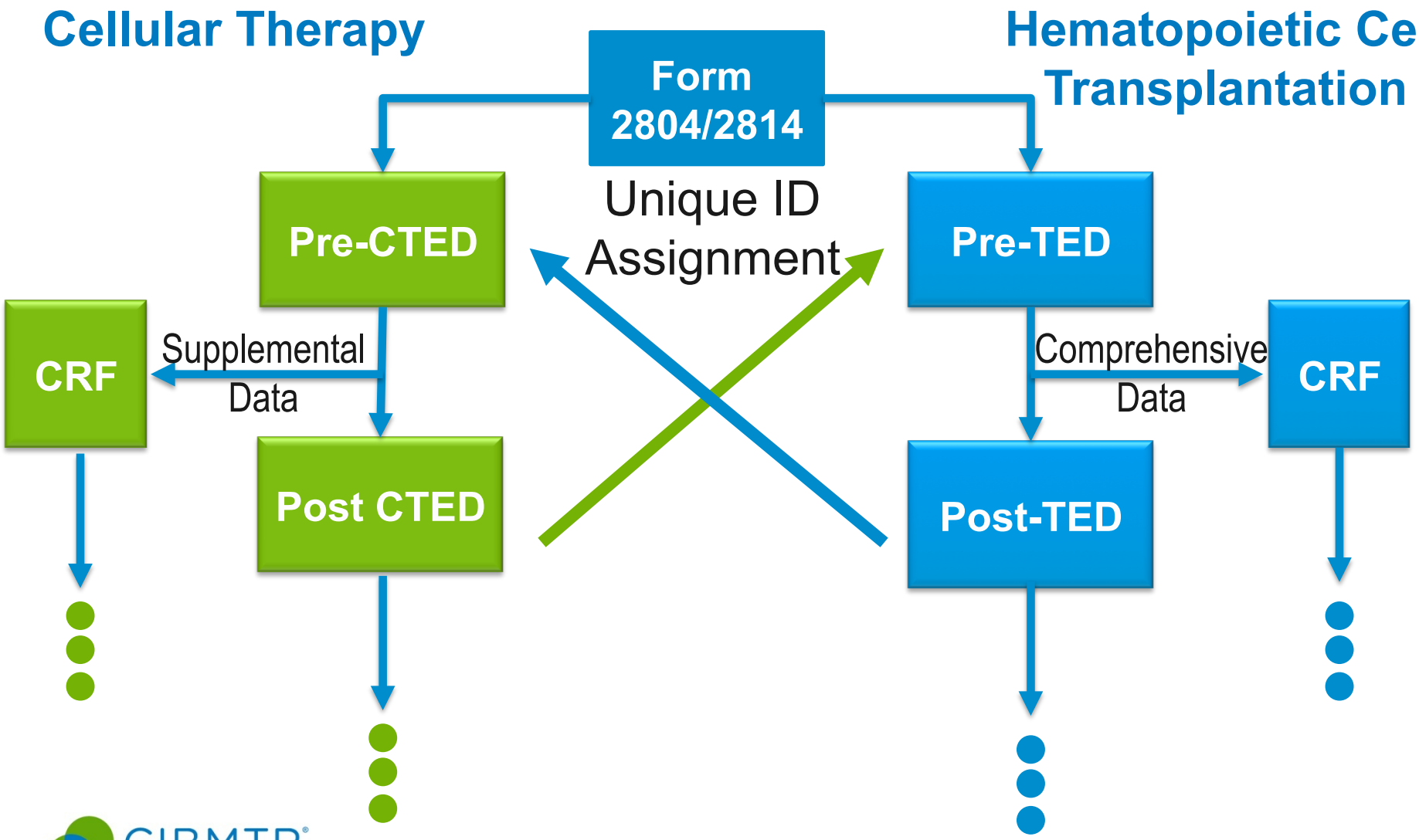
Integrated Data Flow



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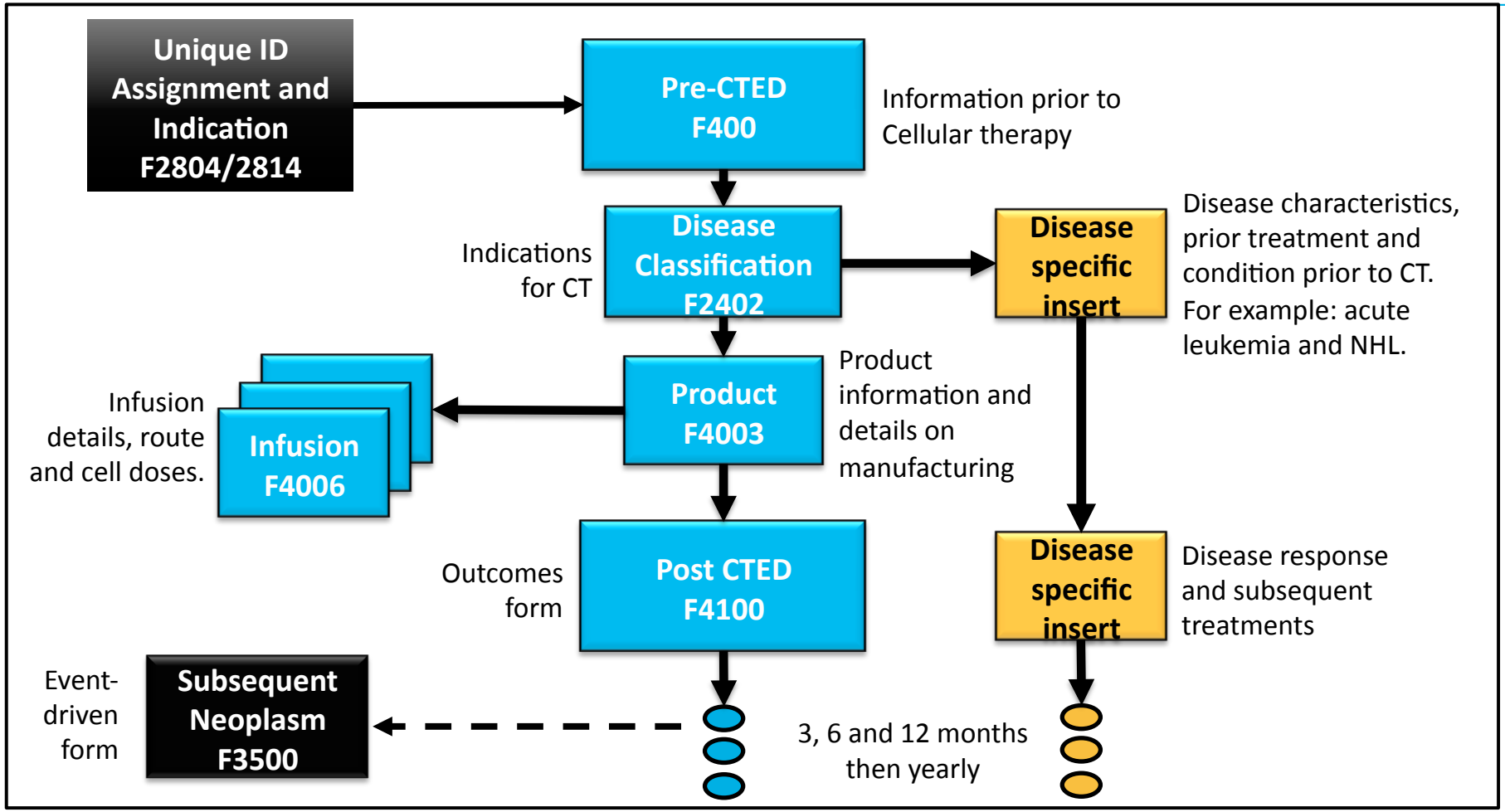
Cellular Therapy Registry Data Flow



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Product Form – Form 4003
How to Define a Cell Product? Example CD19-CAR

Donor — Autologous

Tissue Source — Peripheral Blood

Cell Type — Lymphocytes: CD8+ cells

- Specific Commercially Available Product
- Capture the name of the product
- Product ID
- Clinicaltrials.gov Number for the Protocol

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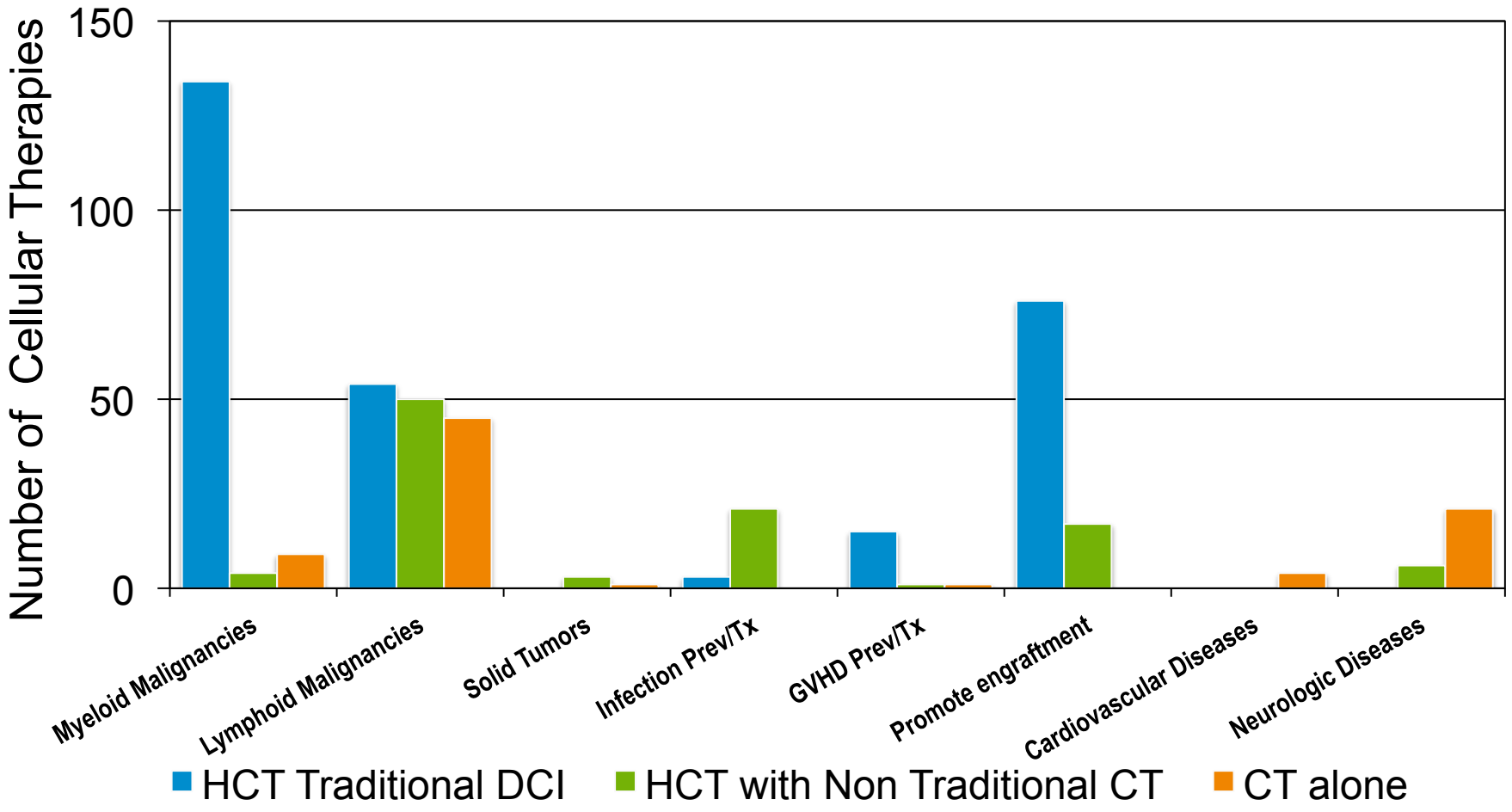
Cellular Therapy Specific Data

- Treatment description
  - Lymphodepleting chemotherapy and adjuvant treatment (e.g. immune checkpoint inhibitor)
- Cytokine Release Syndrome:
  - Capture all signs and symptoms to adapt to any grading system.
  - Treatment and resolution
- Other important outcomes
  - Neurotoxicities, other toxicities, infections, hypogammaglobulinemia, cytopenias, GVHD, subsequent neoplasms, death.
- Persistence of cell product.

Indications for Cellular Therapy, 2016-2017 – CTED Pilot (N=475)



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Cellular Therapies for Treatment of Malignancies – Excluding DLI – July 16' to November 17'

Characteristics	N=149
Centers	**50**
Indication	
Acute Lymphocytic Leukemia	**62**
Acute Myeloid Leukemia	**2**
Hodgkin Disease	**6**
Multiple Myeloma	**10**
Non Hodgkin Lymphoma	**61**
Other Hematologic Malignancy	**2**
Solid Tumors[1]	**6**
Genetically Modified Cells[2]	**114**

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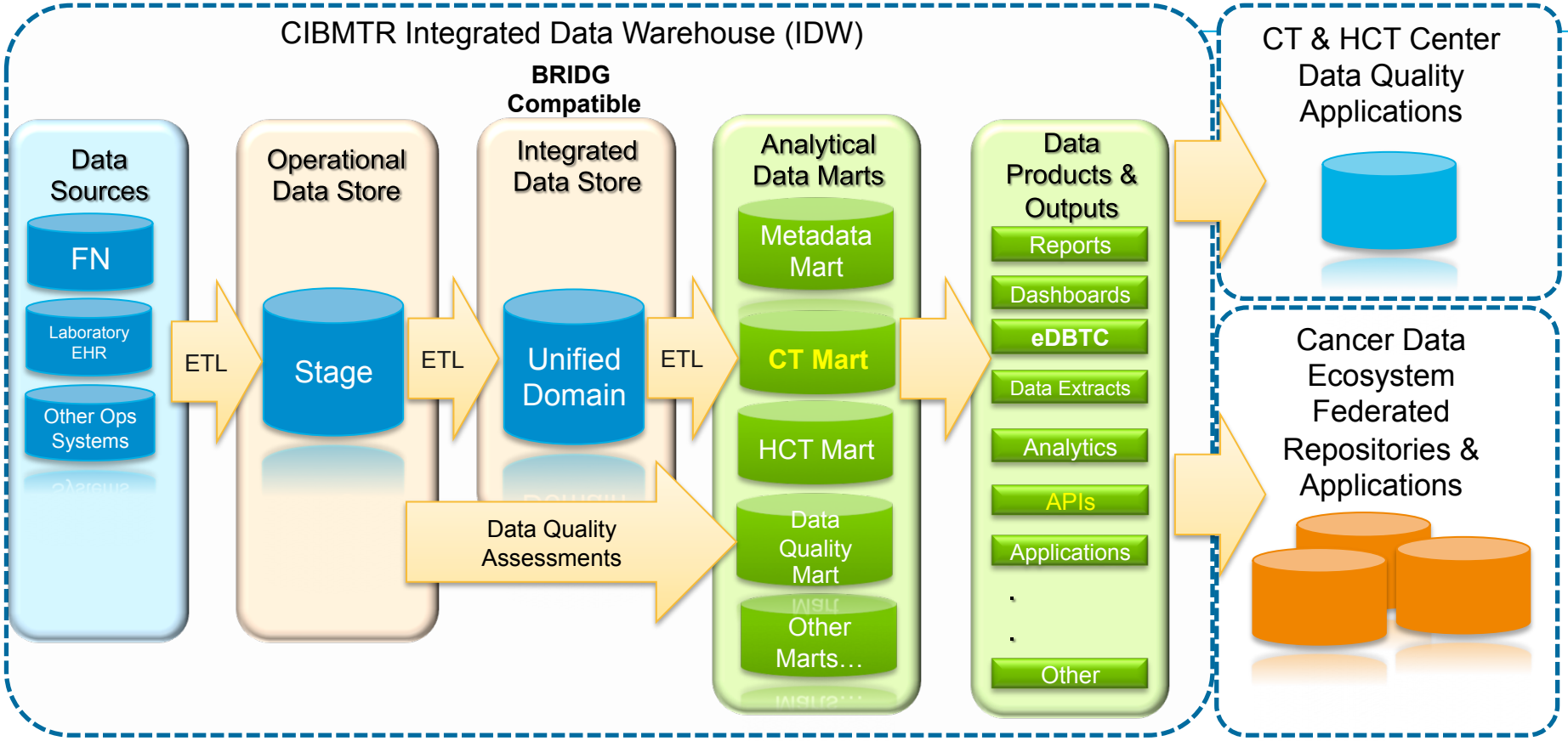
[1] GBM, Neuroblastoma and Sarcoma [2] CAR: BCMA, CD19, CD22, CD30, CD16v, CD123 and CD171; Ny1-ESO.

Data Processing, Quality and Sharing



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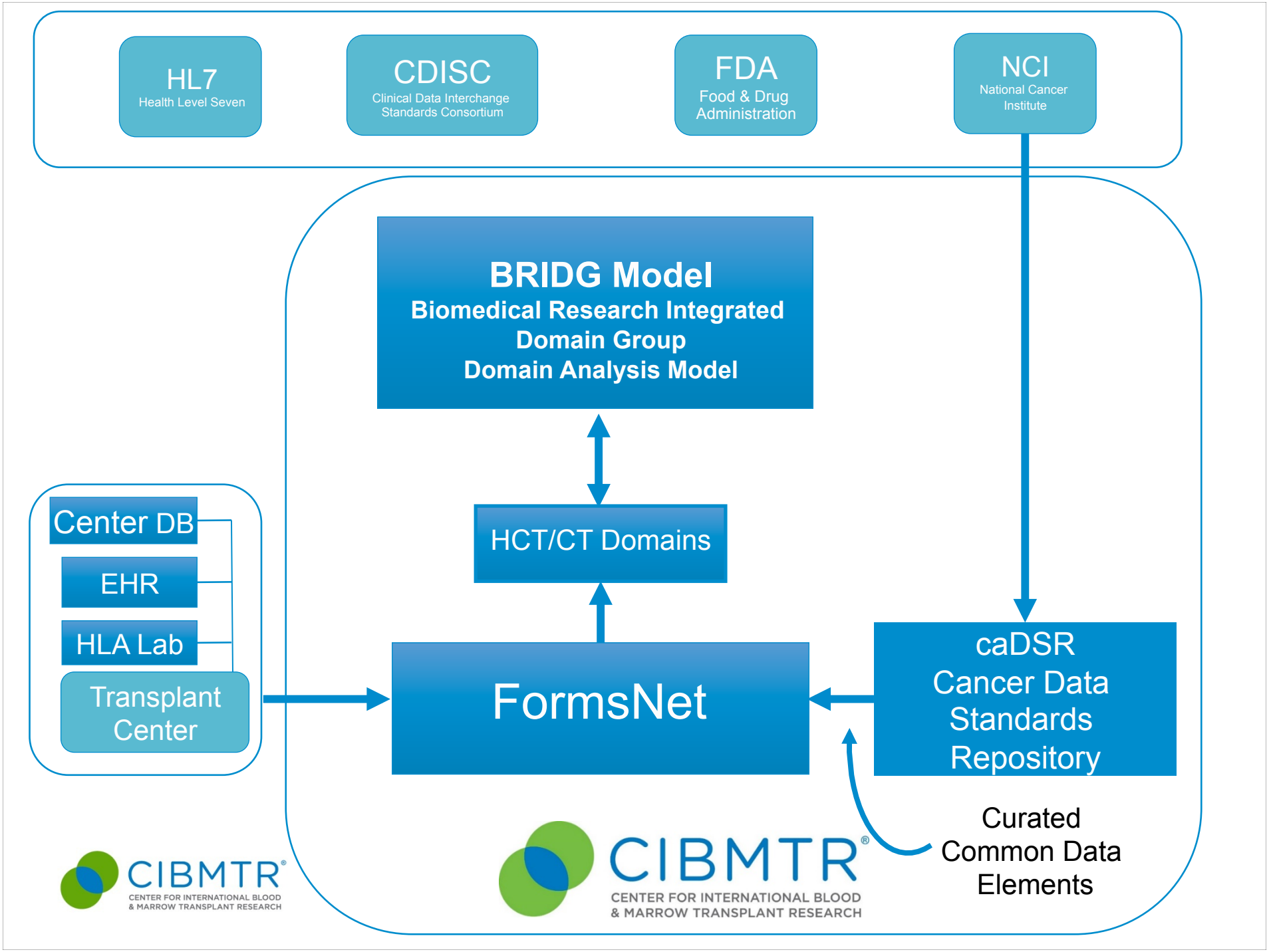
HL7
Health Level Seven
CDISC
Clinical Data Interchange Standards Consortium
FDA
Food & Drug Administration
NCI
National Cancer Institute
BRIDG Model
Biomedical Research Integrated Domain Group
Domain Analysis Model
HCT/CT Domains
Center DB
EHR
HLA Lab
Transplant Center
FormsNet
caDSR
Cancer Data Standards Repository
Curated Common Data Elements
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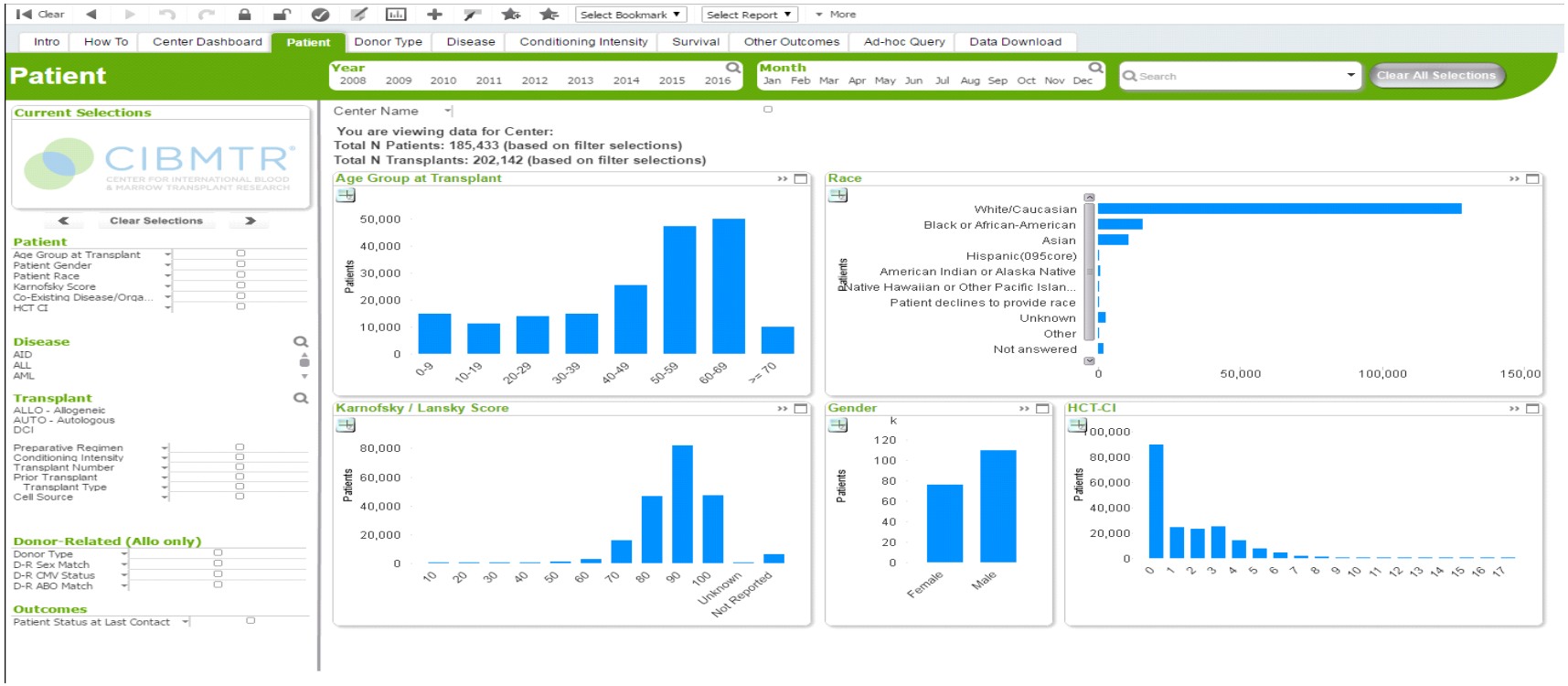
eDBtC Patient Level Data



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Follow up Structure

Type of cells	Time points	Follow up
HCT	3m, 6m, 1 year, yearly up to 5 years then every 2 years	Until death
Genetically Modified Cells	3m, 6m, 1 year, yearly	15y
Third Party CTLs	3m, 6m, 1 year, yearly	2y then HCT
Unmanipulated donor lymphocyte infusions	3 m	HCT
Mesenchymal stem cells	3 m	HCT

Issues Pertinent to Cellular Therapy Follow-up – Multiple treatments and centers

- Consider Jane Doe:
  - 12 year with early relapse of ALL
  - CAR-T-cell therapy #1 – no response
  - CAR-T-cell therapy #2 – different construct, different institution - response
  - HCT – third institution
    - *Viral-specific T-cell therapy post-transplant*
- Who reports what to where? How does the data *flow?*

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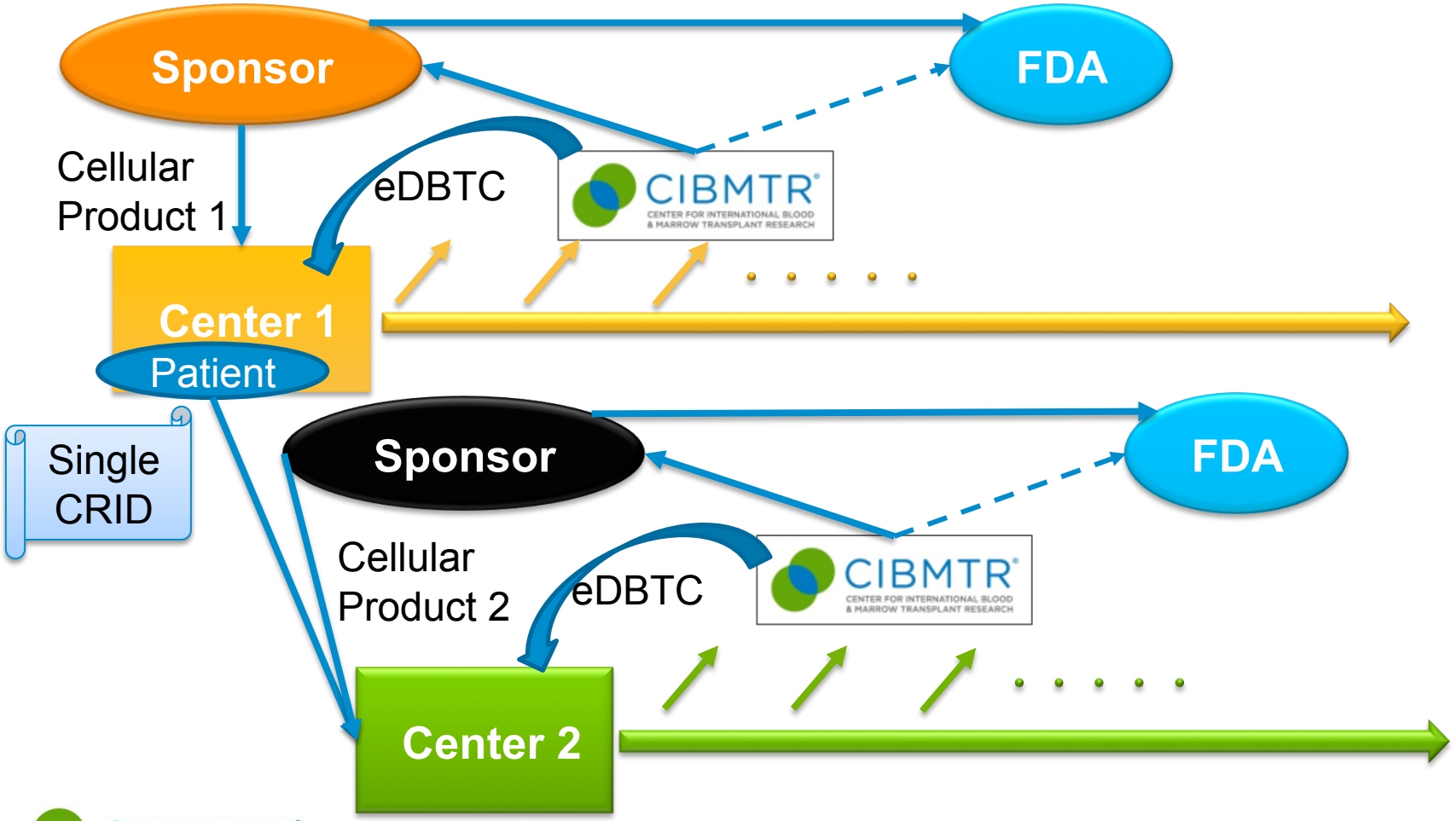
CT Model for Long Term Follow up



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eDBCT=Enhanced
Data Back to Centers

Issues Pertinent to Cellular Therapy Follow-up – 15 years

- Optimize follow up and patient tracking through ePRO.
- Patients consent to allow the CIBMTR to directly contact them.
- Dedicated coordinator group responsible to communicate with patients.
- Data from this mechanism would be available to centers through eDBtC similar to clinical data.

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Issues Pertinent to Cellular Therapy Follow-up – Pregnancy

- Outcome forms capture pregnancies after CT and outcomes.
- Capture information of health of the baby is challenging.
  - Rely on center to report
  - Direct patient contact
  - Request for pediatricians' notes and growth charts through the ePRO system.

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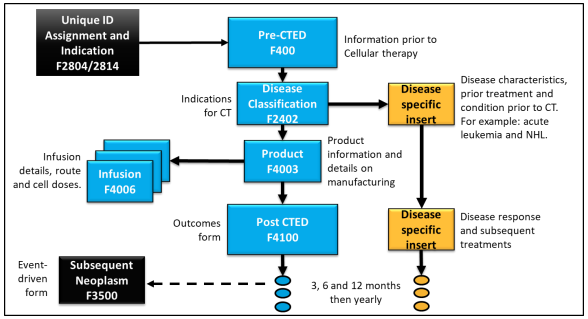
Commercial CAR-T cell: Current Status

CTED Modifications:

- Additional supplemental data
- Follow up every 6 months for 15 years

CTED



CTED with same schedule Modifications:

- Mechanism to collect samples from patients who develop subsequent neoplasms

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Conclusions and Recommendations

- Standardized database will be important to the field.
  - Minimal set of data elements required;
  - Avoid having multiple databases for each company and for similar cellular products.
- Recommendation of minimal follow up schedule to avoid increasing the burden of data collection and maximizing efficiency.
- Promote innovative approaches for patient tracking and follow up.

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