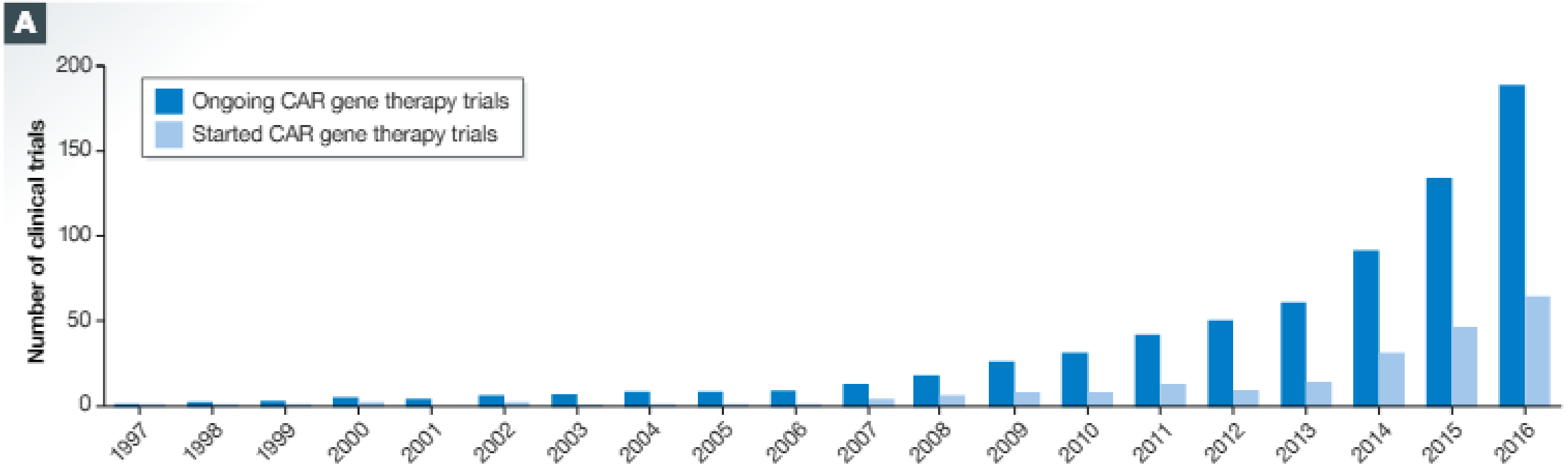
New therapies in the context of the Standards

Mr. Eoin McGrath
JACIE Operations Manager
EBMT

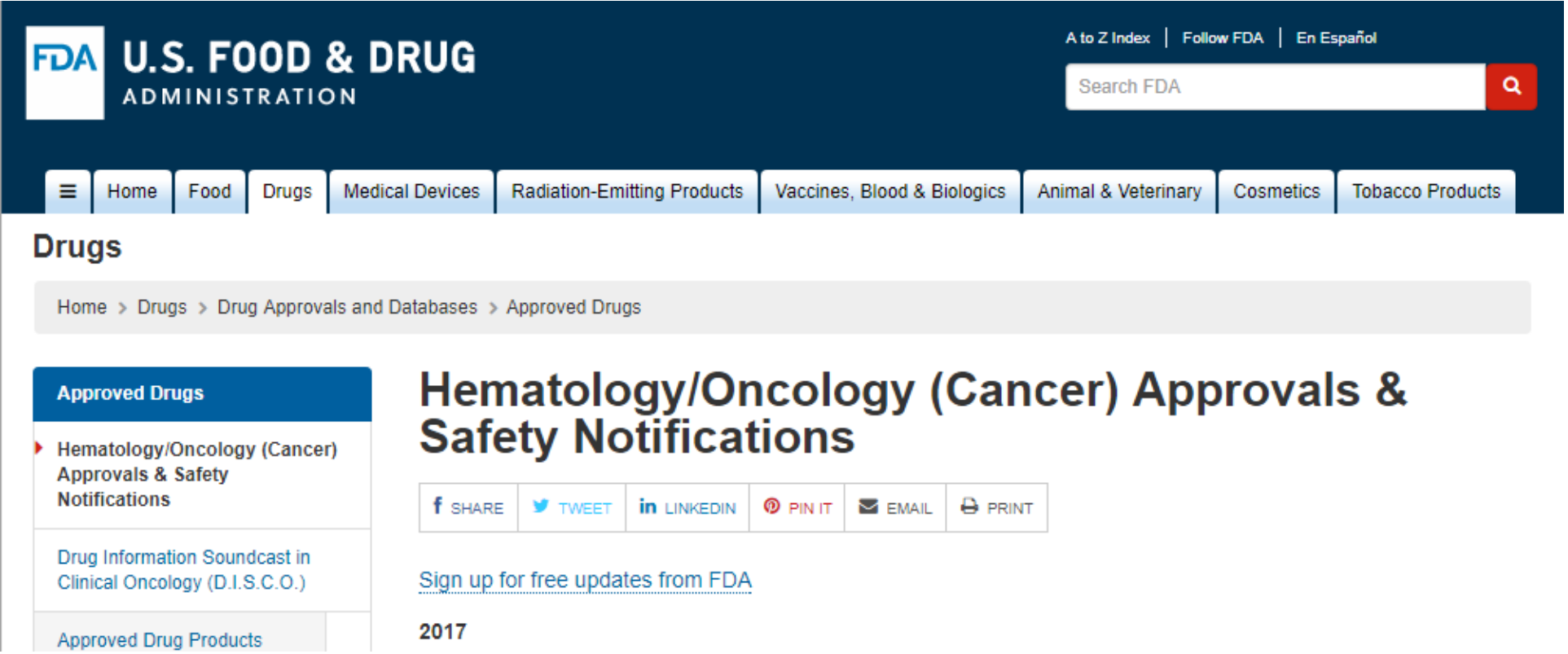
Cancer CAR T cell trials growth

EMBO Molecular Medicine Report on current CAR T cell trials *Jessica Hartmann et al*



Timeline of cancer CAR T cell trials as listed in Datasets EV1 and EV2 distinguishing between ongoing number (dark blue bars) and newly initiated trials in the indicated year (light blue bars)

http://onlinelibrary.wiley.com/doi/10.15252/emmm.201607485/epdf



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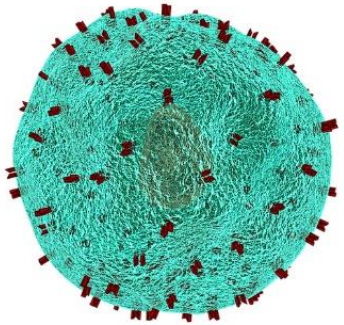
- 2017 – First CART therapies approved in USA
- 2018 – First approvals expected in EU



https://www.the-scientist.com/?articles.view/articleNo/50231/title/First-CAR-T-Cell-Therapy-Approved-in-U-S-/

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Concerns: Toxicity, Efficacy, Complexity and Costs

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Bone Marrow Transplantation (2017) **52**, 1588–1589

www.nature.com/bmt

EDITORIAL

CAR-T cells: the narrow path between hope and bankruptcy?

April 26, 2018

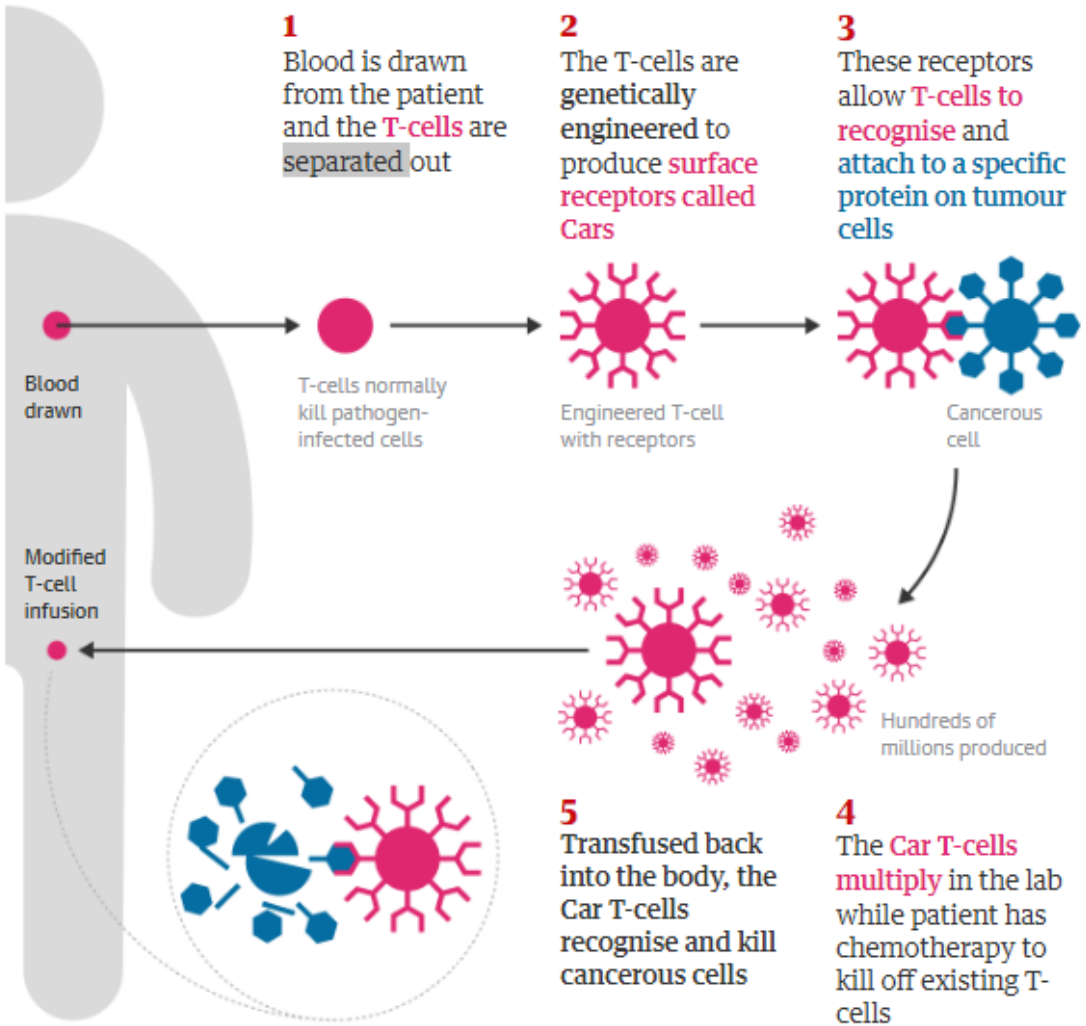
Non-Drug Costs of CAR-T Cell Therapy May Exceed $50,000

News > Medscape Medical News > Oncology News

What's the Total Cost of One CAR T-Cell Treatment?

Nick Mulcahy
April 26, 2018

T-cell cancer therapy: How engineered immune cells can kill tumours



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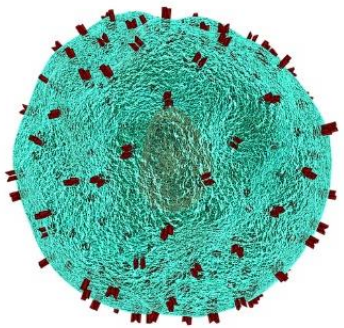
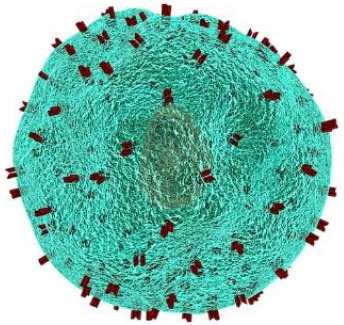
COMPLEXITY INCREASES RISK



Example of complexity

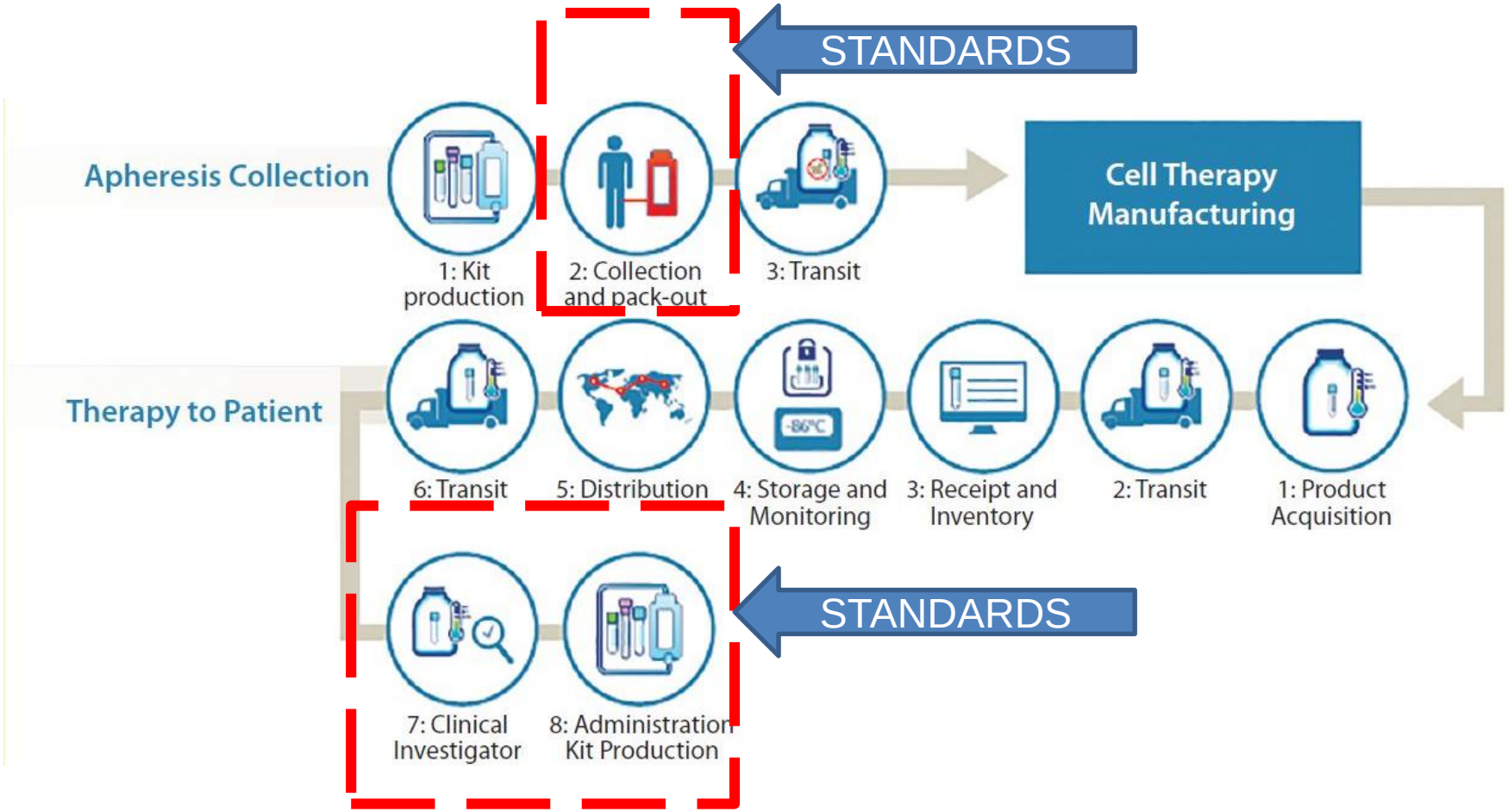
- “151 process steps, of which 54 are decision points which need to be captured and documented, and that’s just for one dose” Martin Lamb, TrakCel

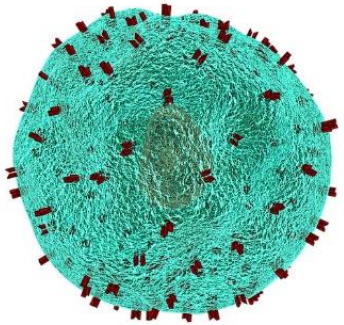
http://carat-horizon2020.eu/



https://www.regmednet.com/users/3641-regmednet/posts/19953-why-the-fda-s-car-t-approval-sends-strong-signal-to-cell-therapy-industry-an-interview-with-martin-lamb#!/feeds/564b8d51-674b-4576-8a8b-b31e272f76c1?open=false

Logistics complexity of an autologous cell therapy





Author: Dan O'Donnell http://www.bioprocessintl.com/wp-content/uploads/2015/10/13-9-sup-ODonnell-F11.jpg

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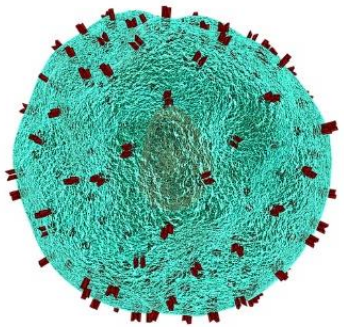
Challenges in the leukapheresis center

- Scheduling and coordination of care with autologous and normal donors and other clinical indications
  - Front-loaded weeks for mobilized stem cell products
  - Temporary placement of apheresis catheters
    - Coordinating for early-morning interventional radiology procedues
  - Coordinating with cell-processing lab for (processing and) shipping apheresis products to the central manufacturing facility
- Are the settings and equipment optimized for collection of lymphocytes (as opposed to stem cells?)

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

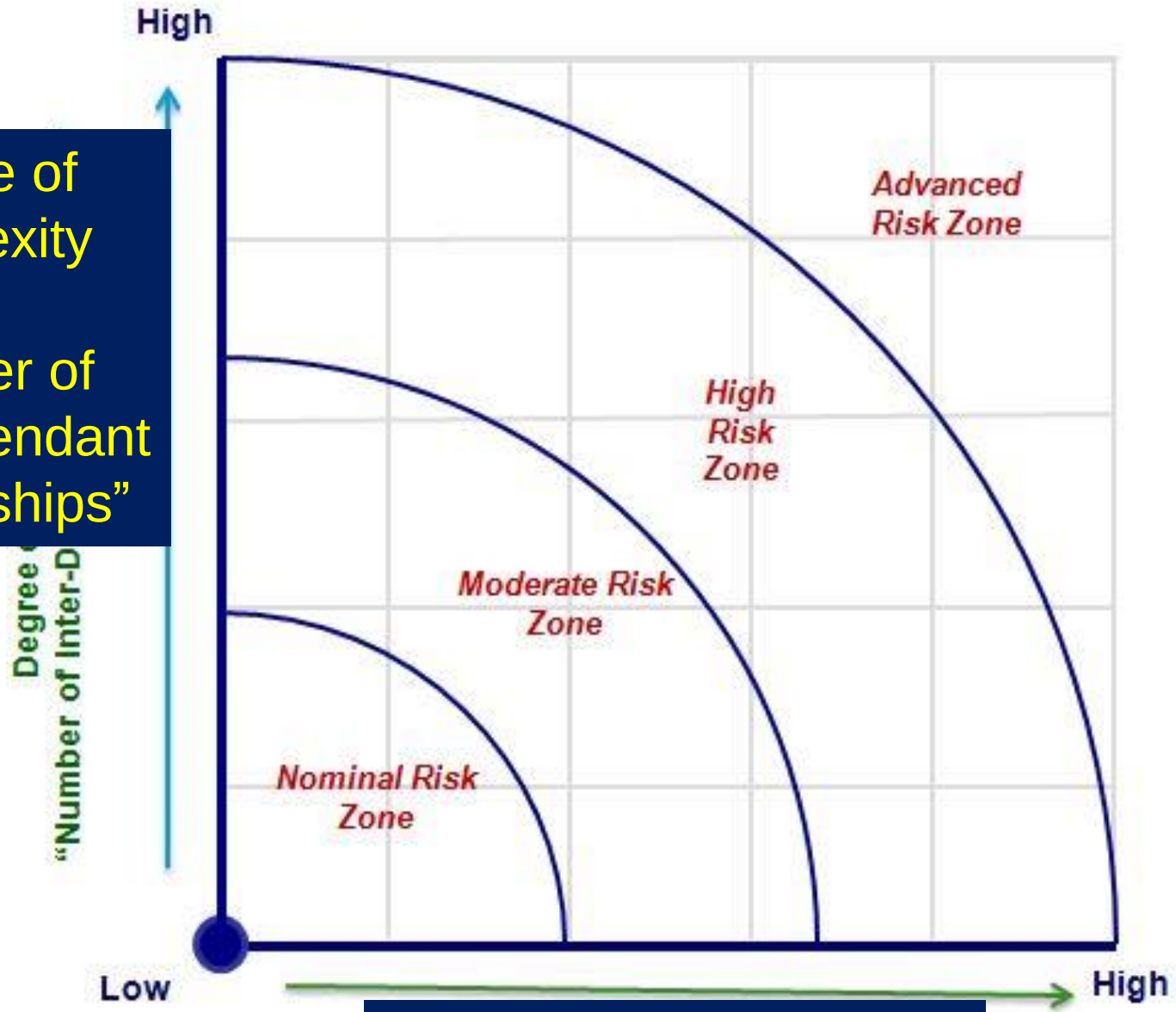
mark flower @markflower · May 3

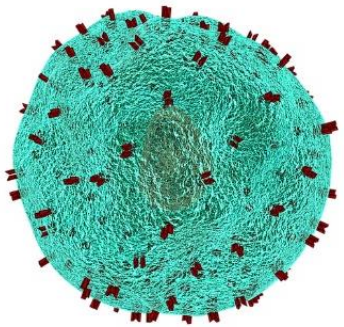
Dr Marcela Maus gives voice to challenges in apheresis centers - collecting the critical starting material for CAR T products #ISCT2018 #CAR-T



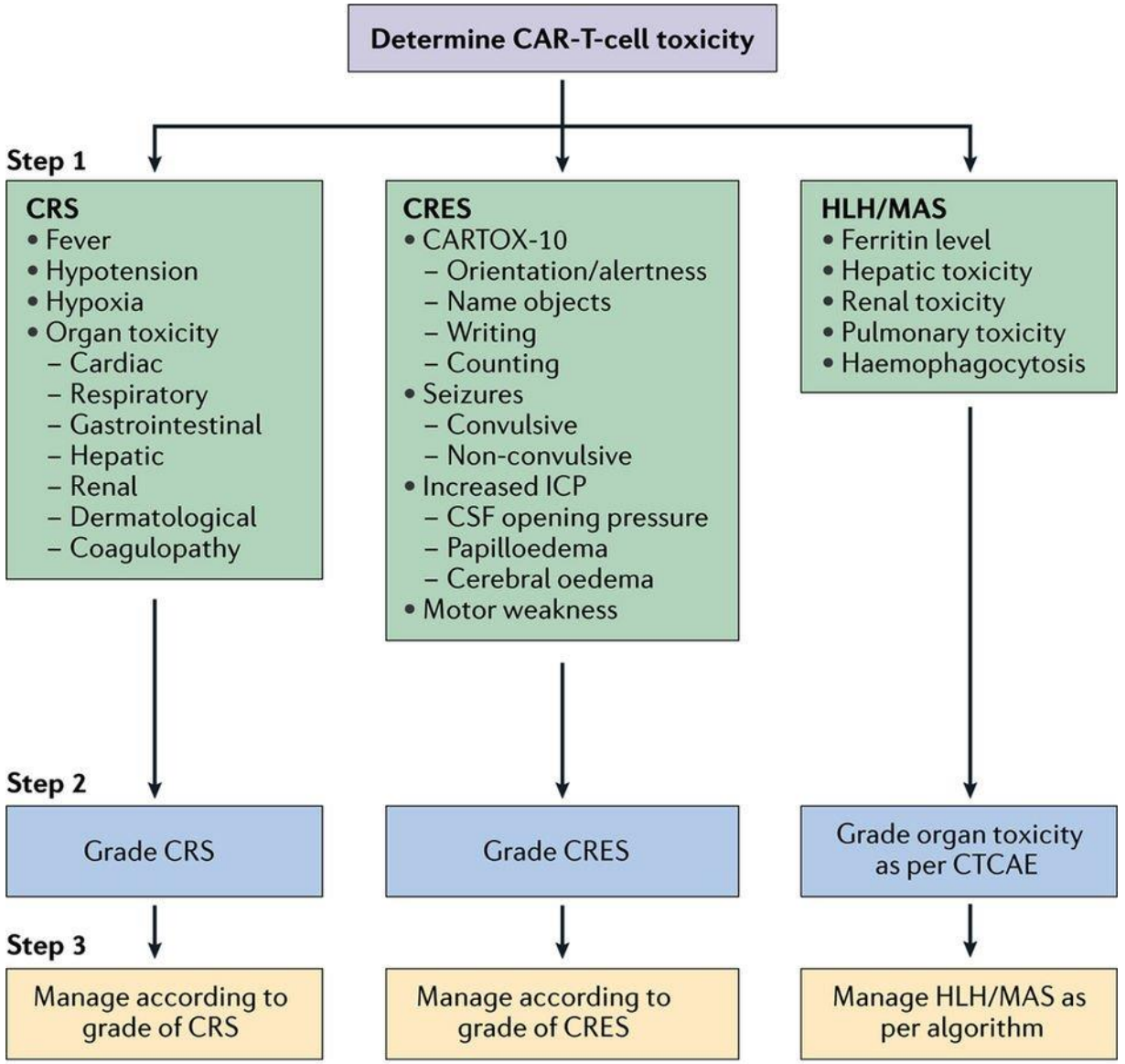
Degree of Complexity

"Number of Inter-dependant Relationships"

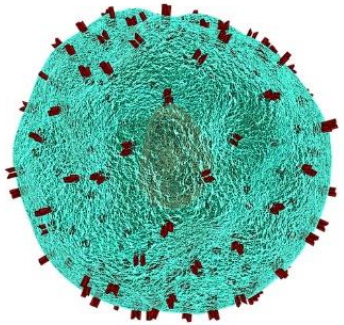




Degree of Uncertainty
"Number of Unknowns"

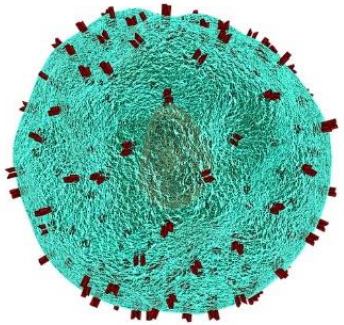


Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. *Nat Rev Clin Oncol*. 2017;



WHAT WILL THE STANDARDS DO FOR THESE COMPLEX THERAPIES?

RESPONSE IN STANDARDS



Terminology used in the Standards

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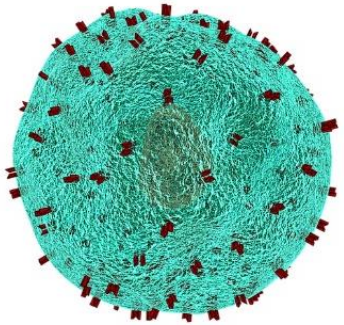
"SHALL"

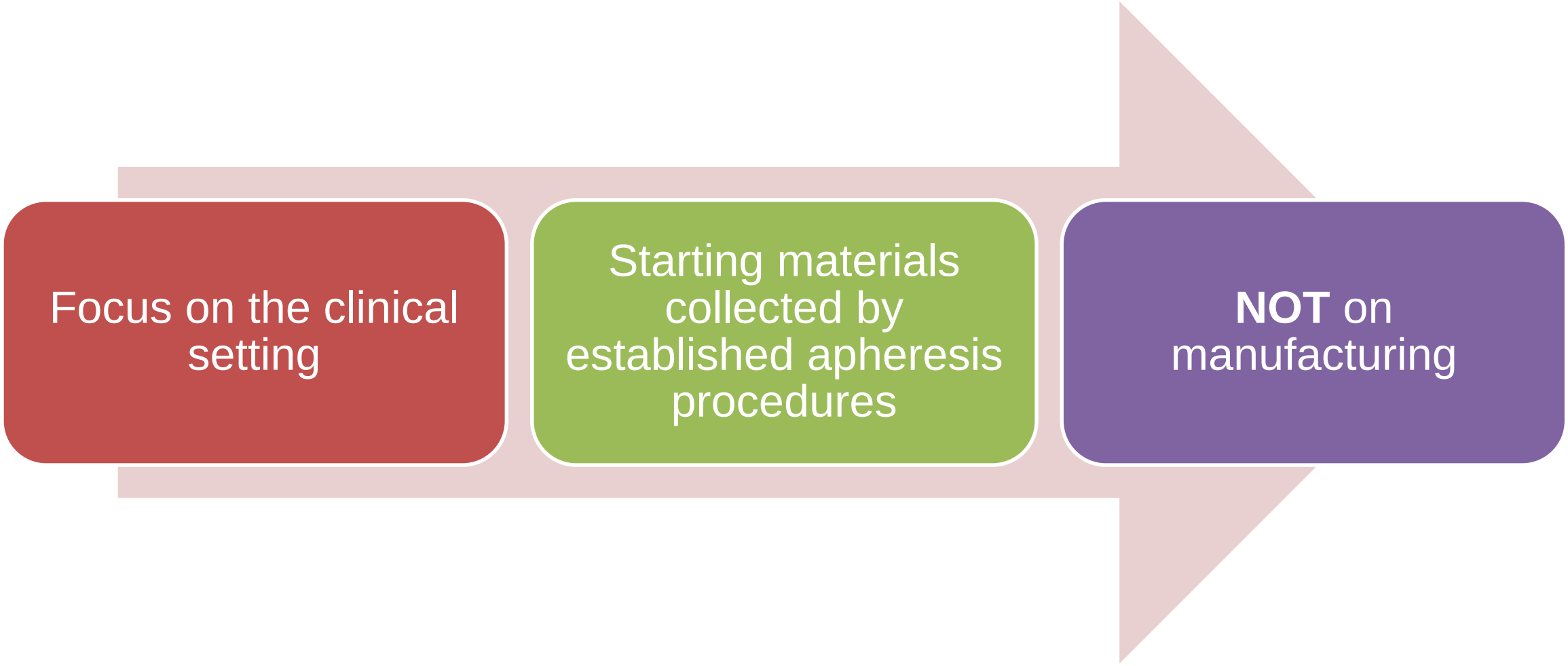
- Compulsory

"SHOULD"

- Strongly recommended but not compulsory



Standards: Features

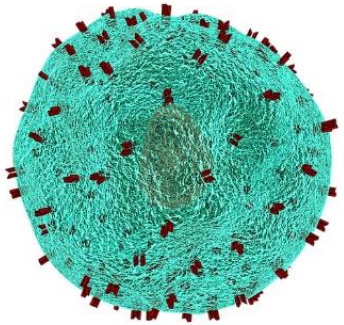


Standards: Aims

Highlight unique aspects of administration and toxicities of immune effector cells

Specify the clinical and quality infrastructure to facilitate safe administration of immune effector cells

Formalize subsequent monitoring and reporting of patient outcomes to enable continual process improvement



Standards apply to:

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- novel cellular therapy products
- manufactured by a third-party
- routed through an external facility

Origins

- Standards intended to promote quality in administration of immune effector cell products
- Standards initially developed by the FACT Immune Effector Cell Task Force and then JACIE experts invited to contribute


INTERNATIONAL STANDARDS FOR HEMATOPOIETIC CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION

Sixth Edition
Version 6.1

NOTICE

These Standards are designed to provide minimum guidelines for programs, facilities, and individuals performing cellular therapy or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a program, facility, or individual should implement if the standard of practice in the community or applicable governmental laws or regulations establish additional requirements. Each program, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with these Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations.

The Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee – ISCT and EBMT expressly disclaim any responsibility for setting maximum standards and further expressly disclaim any responsibility, liability, or duty to member programs, directors, staff, or program donors or patients for any such liability arising out of injury or loss to any person by the failure of member programs, directors, or staff to adhere to the Standards or related guidance.

STANDARDS

If your centre does not administer IECs then the standards simply do not apply

These standards for Immune Effector Cells (IECs) are contained within the Hematopoietic Ceullar Therapy Standards.

Standards: Third-party provider

- Third party : a facility separate from the facilities primarily involved

- e.g. pharmaceutical company, central state manufacturing facility

Standards: Third-party provider

- B1.2.1 If the Clinical Program or an intermediary facility receives cellular therapy products directly from a third-party provider, the following responsibilities shall be defined, at a minimum, by a written agreement:

Standards: Third-party provider

Traceability and chain of custody of cellular therapy products.

Cellular therapy product storage and distribution.

Verification of cellular therapy product identity.

Review and verification of product specifications provided by the manufacturer, if applicable.

Readily available access to a summary of documents used to determine allogeneic donor eligibility.

Documented evidence of allogeneic donor eligibility screening and testing in accordance with applicable laws and regulations.

Standards

Chain-of-custody documentation should include:

- Dates
- Times
- responsible parties for
  - distribution and receipt
  - storage
  - release for administration.

Clinical Programme should

Define and verify	• distribution conditions
Designate	• space • suitable equipment for receiving and storing CT products
Product ID	• confirmed by two professionals
Compare product with	• written physician order • patient ID

Standards

B2.8 Written guidelines for:

- Communication
- Patient monitoring
- Transfer of patients to ICU, ER / equivalent

Standards: Pharmacy

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- B2.11.1 Pharmacies shall have access to medications adequate to treat expected complications of immune effector cell administration, including cytokine release syndrome.

http://victoryoncology.com/wp-content/uploads/2015/11/pharmo.jpg

Standards: Physician knowledge

- B3.3.3.12 Diagnosis and management of veno-occlusive disease of the liver and other causes of hepatic dysfunction.
- B3.3.3.13 Management of thrombocytopenia and bleeding, including recognition of disseminated intravascular coagulation.
- B3.3.3.14 Management of hemorrhagic cystitis.
- B3.3.3.15 Management of mucositis, nausea, and vomiting.
- B3.3.3.16 Monitoring and management of pain.
- B3.3.3.17 Graft versus host disease.
- B3.3.3.18 Cytokine release syndrome
- B3.3.3.19 Tumor lysis syndrome.
- B3.3.3.20 Macrophage activation syndrome.
- B3.3.3.21 Cardiac dysfunction.
- B3.3.3.22 Renal dysfunction.
- B3.3.3.23 Respiratory distress.
- B3.3.3.24 Neurologic toxicity.
- B3.3.3.25 Anaphylaxis.
- B3.3.3.26 Infectious and noninfectious processes.

Standards

B3.7.3.4 Care interventions to manage cellular therapy complications, including, but not limited to:

- cytokine release syndrome
- tumor lysis syndrome
- cardiac dysfunction
- respiratory distress
- neurologic toxicity
- macrophage activation syndrome
- renal and hepatic failure
- disseminated intravascular coagulation
- Anaphylaxis
- neutropenic fever
- infectious and noninfectious processes
- Mucositis
- nausea and vomiting
- pain management.

Standards: Nurses

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- B3.7.4 There shall be written policies for all relevant nursing procedures, including, but not limited to:
  - B3.7.4.7 Detection and management of immune effector cellular therapy complications including, but not limited to, those listed in B3.7.3.4.
  - **Should also be associated education/training**

Oncology Nurses Must Watch for CAR T-Cell Therapy Side Effects

By Bryant Furlow

Tuesday, May 9, 2017

Conferences › ONS 2017 Hematologic Malignancies Oncology Nursing

http://www.cancernetwork.com/ONS-2017/oncology-nurses-must-watch-car-t-cell-therapy-side-effects

Standards: Pharmacists

Training shall include:

- B3.8.2.1 An overview of haematology/oncology patient care, including the cellular therapy process, cytokine release syndrome, and neurological toxicities.
- B3.8.2.3 Therapeutic drug monitoring, including, but not limited to, anti-infective agents, immunosuppressive agents, anti-seizure medications, and anticoagulants.

- B3.8.3 Designated Pharmacists shall be involved in the development and implementation of guidelines or SOPs related to the pharmaceutical management of transplant cellular therapy recipients.

Standards: Pharmacists

- B3.8.4.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and cytokine release syndrome and neurological toxicities resulting from cellular therapies.
- **Minimum of 10 hours per year**

Standards: Quality Manager

- B3.10.2 / C3.3.2 / D3.3.2 The … Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.
  - Avoid conflicts of interest

Standards: Quality Management

- B4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:
  - B4.7.3.2 For immune effector cells, an endpoint of clinical function as approved by the Clinical Program Director.

- B4.7.3.3 Overall and treatment-related morbidity and mortality at
  - thirty (30) days
  - one hundred (100) days,
  - one (1) year

  after transplantation cellular therapy product administration.

Standards: Quality Management

- B4.8.3 Audits shall include, at a minimum:
  - B4.8.3.1 Periodic audit of the accuracy of clinical data.
  - B4.8.3.2 Annual audit of safety endpoints and immune effector cellular therapy toxicity management.

Standards: Quality Management

- B4.10 Policies and procedures for occurrences:

Errors	Accidents	Deviations
Serious adverse events	Serious adverse reactions	Complaints

Standards: Quality Management

Including the following activities at a minimum:

– B4.10.2 **Investigation**.

- B4.10.2.1 A thorough investigation shall be conducted by the Clinical Program in collaboration with the Collection Facility, Processing Facility, and other entities involved in the manufacture of the cellular therapy product, as appropriate.

Standards: Quality Management

- B5.1 Establish and maintain policies or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in B4. These documents shall include all elements required by these Standards and shall address at a minimum:
  - B5.1.10 Management of cytokine release syndrome and central nervous system toxicities.

Standards: Policies for Recipient Care

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Procedures for administration

Consultation to review goal and plan

Regular assessment of recipient to detect complications

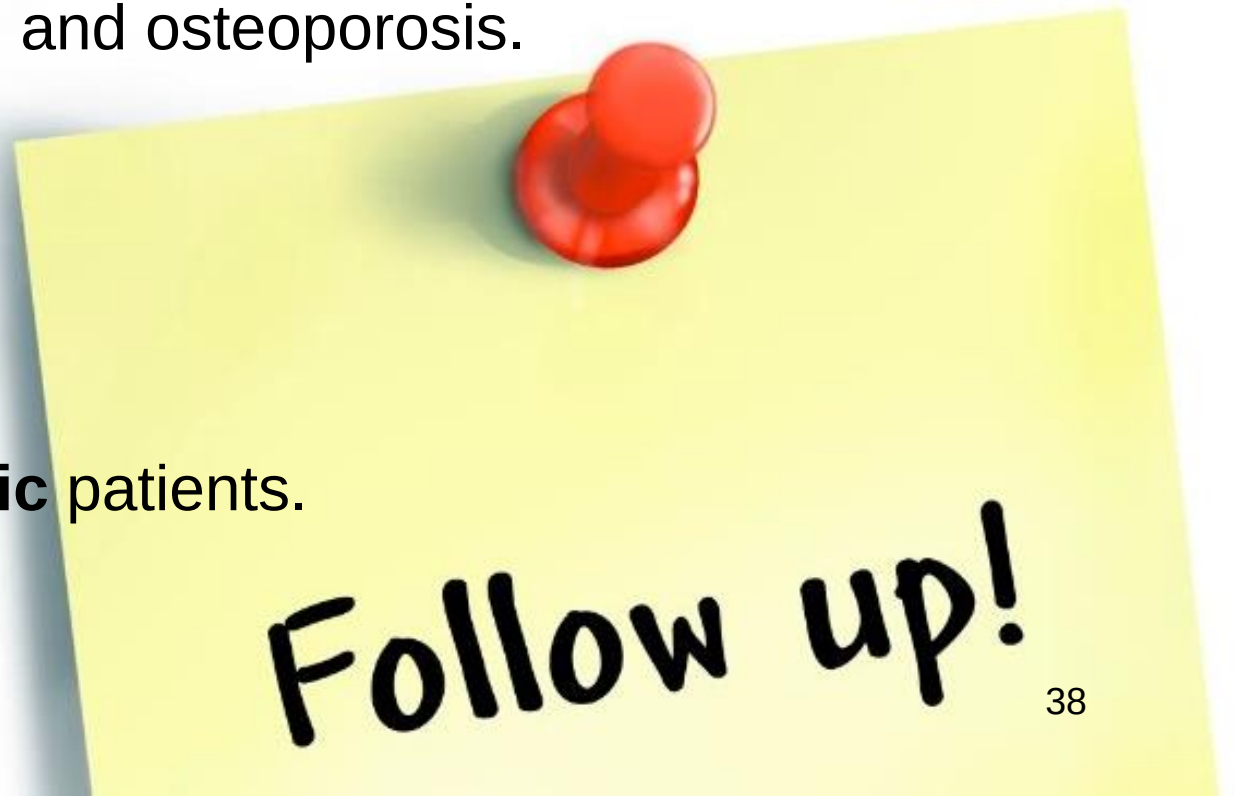
Written plan to rapidly escalate care

Timely communication to clinical staff and other services

Procedures for management of complications

Standards: Long term follow-up

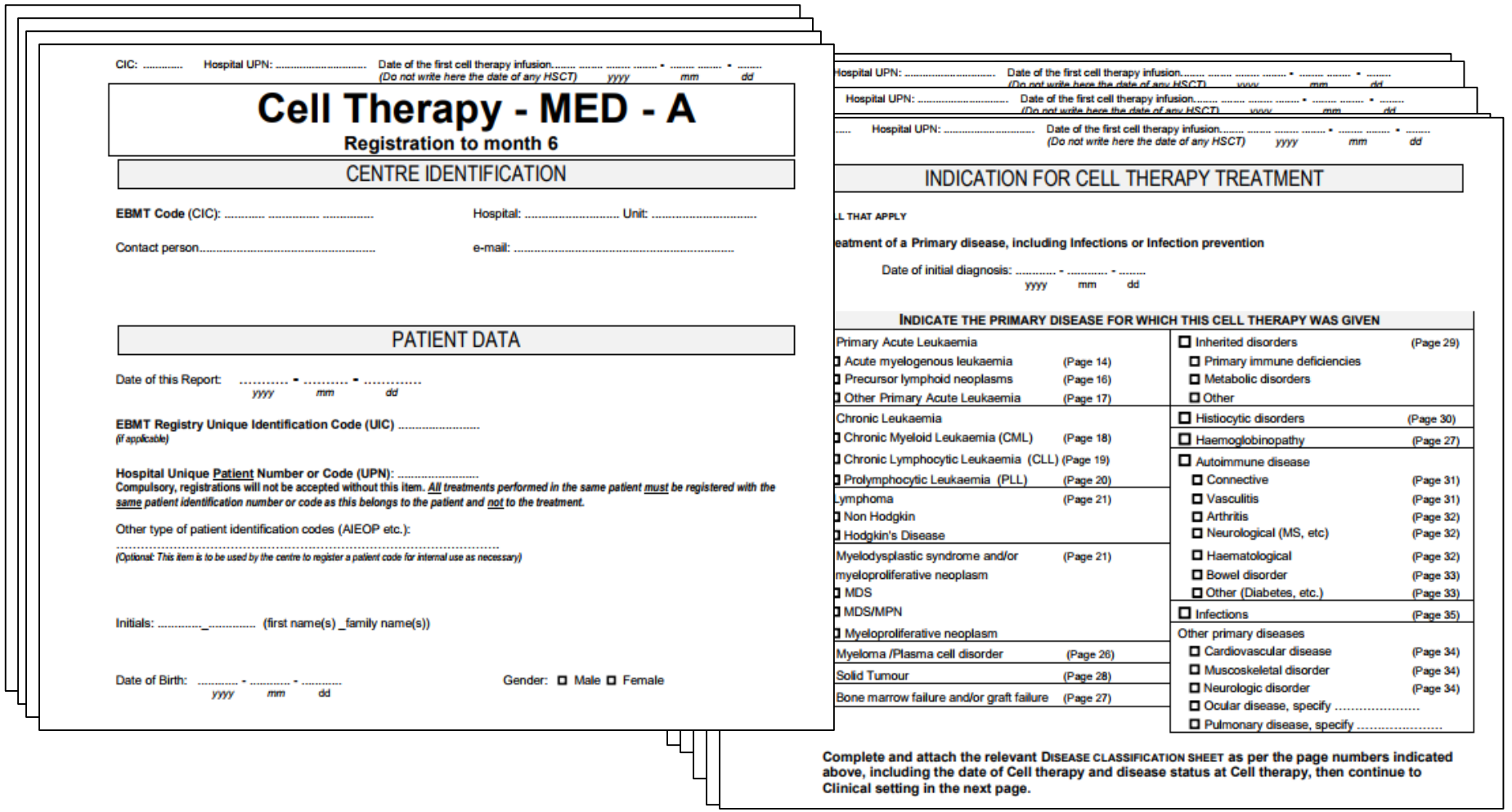
- B7.12.1 Policies or Standard Operating Procedures for monitoring by appropriate specialists of recipients for post-cellular therapy late effects, including at a minimum:
  - Endocrine and reproductive function and osteoporosis.
  - Cardiovascular risk factors.
  - Respiratory function.
  - Chronic renal impairment.
  - Secondary malignancies.
  - Growth and development of **pediatric** patients.



Standards: Research

- B8.1.2 There shall be a process to manage investigational cellular therapy products.

Data reporting



CIC: ..... Hospital UPN: ..... Date of the first cell therapy infusion..... - ..... - .....
(Do not write here the date of any HSCT) yyyy mm dd

Cell Therapy - MED - A

Registration to month 6

CENTRE IDENTIFICATION

EBMT Code (CIC): ..... Hospital: ..... Unit: .....

Contact person..... e-mail: .....

PATIENT DATA

Date of this Report: ..... - ..... - .....
yyyy mm dd

EBMT Registry Unique Identification Code (UIC) .....
(if applicable)

Hospital Unique Patient Number or Code (UPN): .....
Compulsory, registrations will not be accepted without this item. *All* treatments performed in the same patient *must* be registered with the *same* patient identification number or code as this belongs to the patient and *not* to the treatment.

Other type of patient identification codes (AIEOP etc.):
.....
(Optional: This item is to be used by the centre to register a patient code for internal use as necessary)

Initials: ..... (first name(s) _family name(s))

Date of Birth: ..... - ..... - .....
yyyy mm dd

Gender: ☐ Male ☐ Female

Hospital UPN: ..... Date of the first cell therapy infusion..... - ..... - .....
(Do not write here the date of any HSCT) yyyy mm dd

INDICATION FOR CELL THERAPY TREATMENT

LL THAT APPLY

eatment of a Primary disease, including Infections or Infection prevention

Date of initial diagnosis: ..... - ..... - .....
yyyy mm dd

INDICATE THE PRIMARY DISEASE FOR WHICH THIS CELL THERAPY WAS GIVEN

Primary Acute Leukaemia		☐ Inherited disorders	(Page 29)
☐ Acute myelogenous leukaemia	(Page 14)	☐ Primary immune deficiencies	
☐ Precursor lymphoid neoplasms	(Page 16)	☐ Metabolic disorders	
☐ Other Primary Acute Leukaemia	(Page 17)	☐ Other	
Chronic Leukaemia		☐ Histiocytic disorders	(Page 30)
☐ Chronic Myeloid Leukaemia (CML)	(Page 18)	☐ Haemoglobinopathy	(Page 27)
☐ Chronic Lymphocytic Leukaemia (CLL)	(Page 19)	☐ Autoimmune disease	
☐ Prolymphocytic Leukaemia (PLL)	(Page 20)	☐ Connective	(Page 31)
Lymphoma	(Page 21)	☐ Vasculitis	(Page 31)
☐ Non Hodgkin		☐ Arthritis	(Page 32)
☐ Hodgkin's Disease		☐ Neurological (MS, etc)	(Page 32)
Myelodysplastic syndrome and/or myeloproliferative neoplasm	(Page 21)	☐ Haematological	(Page 32)
☐ MDS		☐ Bowel disorder	(Page 33)
☐ MDS/MPN		☐ Other (Diabetes, etc.)	(Page 33)
☐ Myeloproliferative neoplasm		☐ Infections	(Page 35)
Myeloma /Plasma cell disorder	(Page 26)	Other primary diseases	
Solid Tumour	(Page 28)	☐ Cardiovascular disease	(Page 34)
Bone marrow failure and/or graft failure	(Page 27)	☐ Muscoskeletal disorder	(Page 34)
		☐ Neurologic disorder	(Page 34)
		☐ Ocular disease, specify	
		☐ Pulmonary disease, specify	

Complete and attach the relevant DISEASE CLASSIFICATION SHEET as per the page numbers indicated above, including the date of Cell therapy and disease status at Cell therapy, then continue to Clinical setting in the next page.

39 pages

Conclusion

Existing standards offers good framework

Focus on ensuring patient safety

‘Work in progress’

Recommended reading

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Joint Accreditation Committee
ISCT | EBMT

Maus and Nikiforow *Journal for ImmunoTherapy of Cancer* (2017) 5:36
DOI 10.1186/s40425-017-0239-0

Journal for ImmunoTherapy of Cancer

COMMENTARY Open Access

The Why, what, and How of the New FACT standards for immune effector cells

Marcela V. Maus[1,2*] and Sarah Nikiforow[3,4]

Maus M V., Nikiforow S. The Why, what, and How of the New FACT standards for immune effector cells. *J Immunother Cancer*. 2017;**5**:36.

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Thank you