Setting up a CAR-T Centre

Dr Michael Dickinson
Haematologist
Lead- Aggressive Lymphoma

Clinical Haematology

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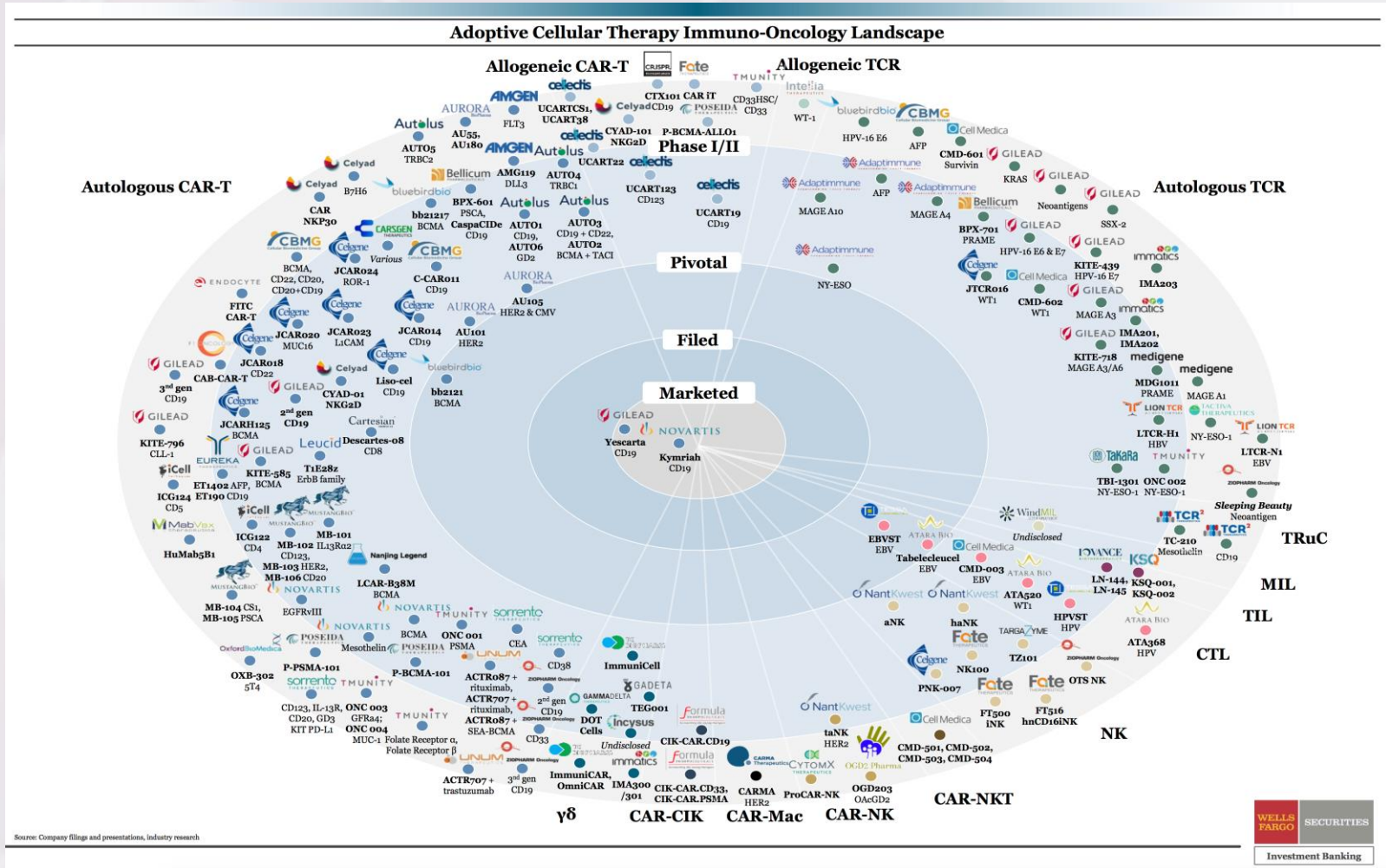
The Royal
Melbourne Hospital

T-cell activity 2019

291 CAR-T products in development, 161 in trials



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Most of us just want to give our patients the best treatment options.

Is giving CAR-T really so difficult?

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Overview

Manufacturing

Clinical Delivery

Trials

SOC

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GROUP LEADER

A/PROF MICHAEL KERSHAW

HEAD: CANCER IMMUNOLOGY PROGRAM; GROUP LEADER, SENIOR FACULTY

PROF JOSEPH TRAPANI

joe.trapani@petermac.org

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Manufacturing at Peter Mac

A strategic investment in 2003 to establish a cell therapy manufacturing capability and fit out a facility at our East Melbourne site. We invested over $10 million in these facilities – supported by Peter Mac and philanthropy.

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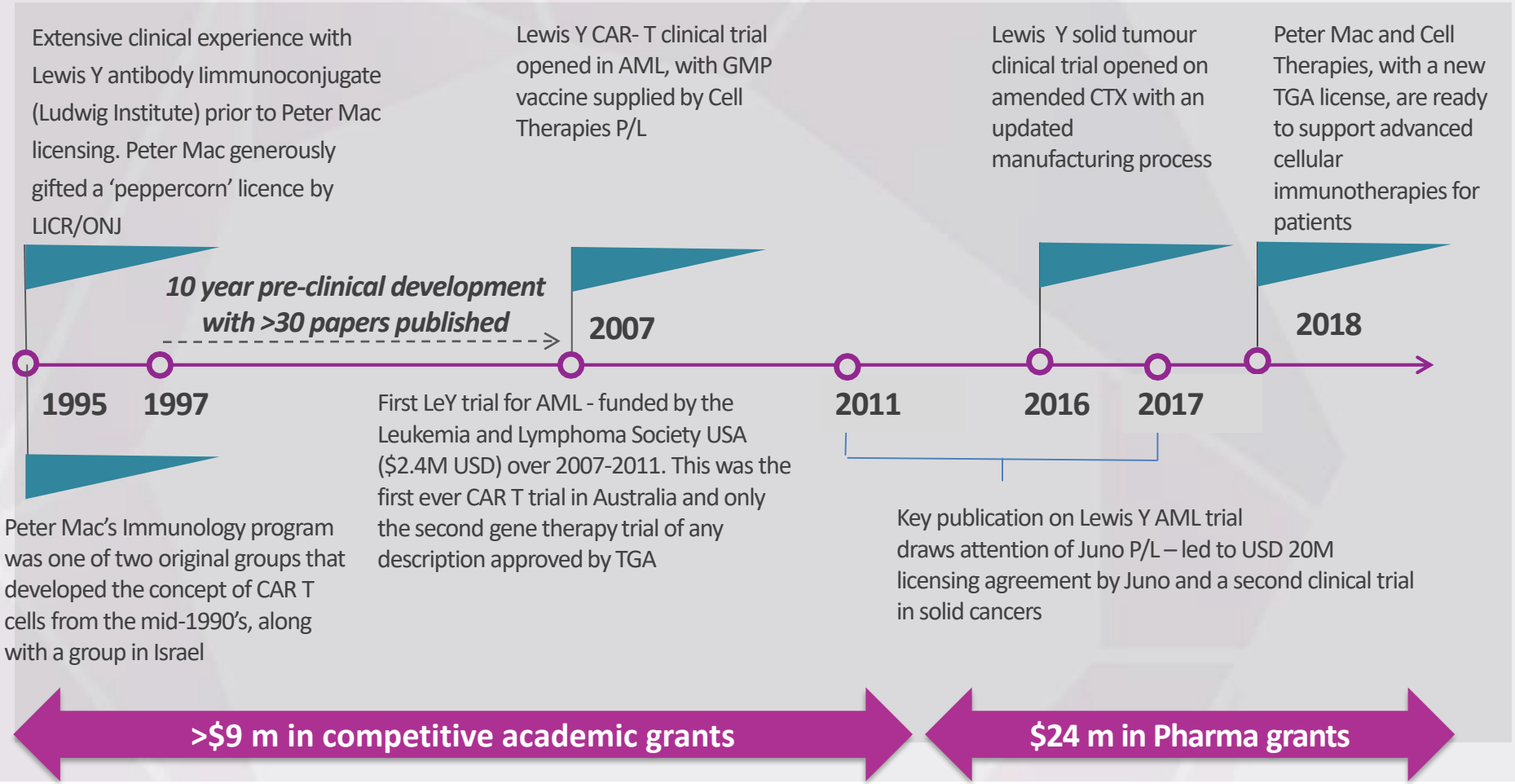
Long run-way to the clinic. We were ultimately reliant on philanthropy and a Pharma to get to the clinic.



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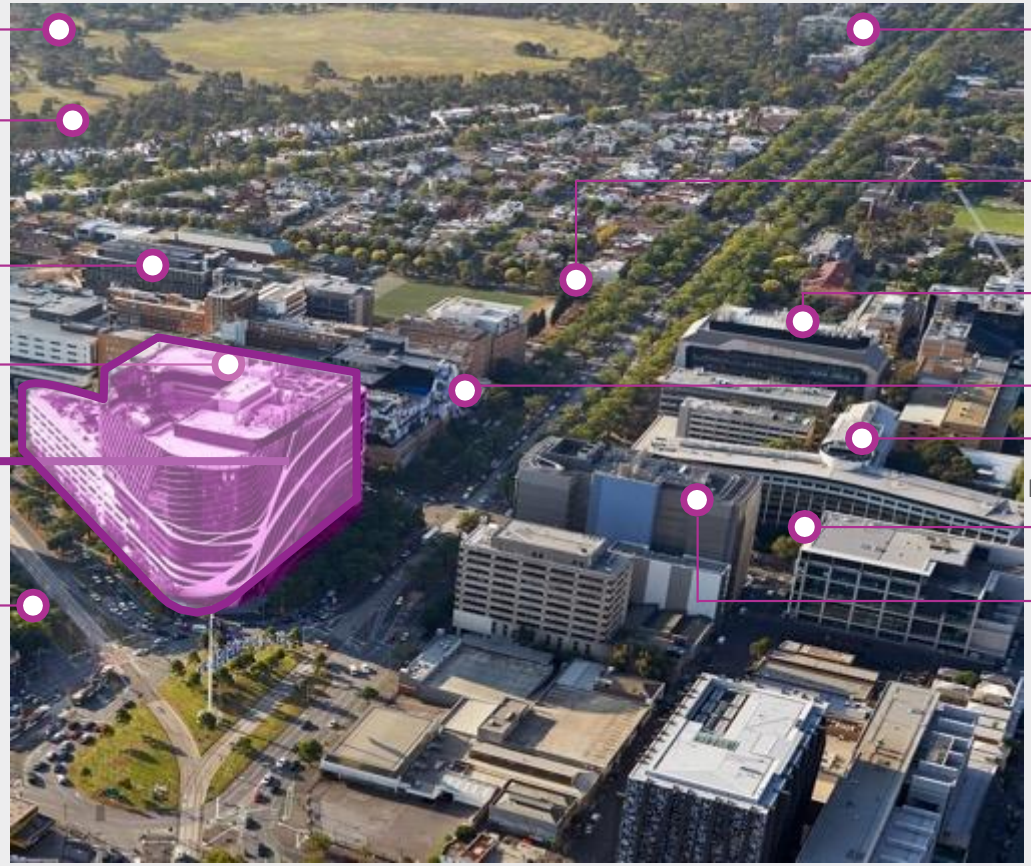
At the heart of Melbourne's Biomedical Precinct



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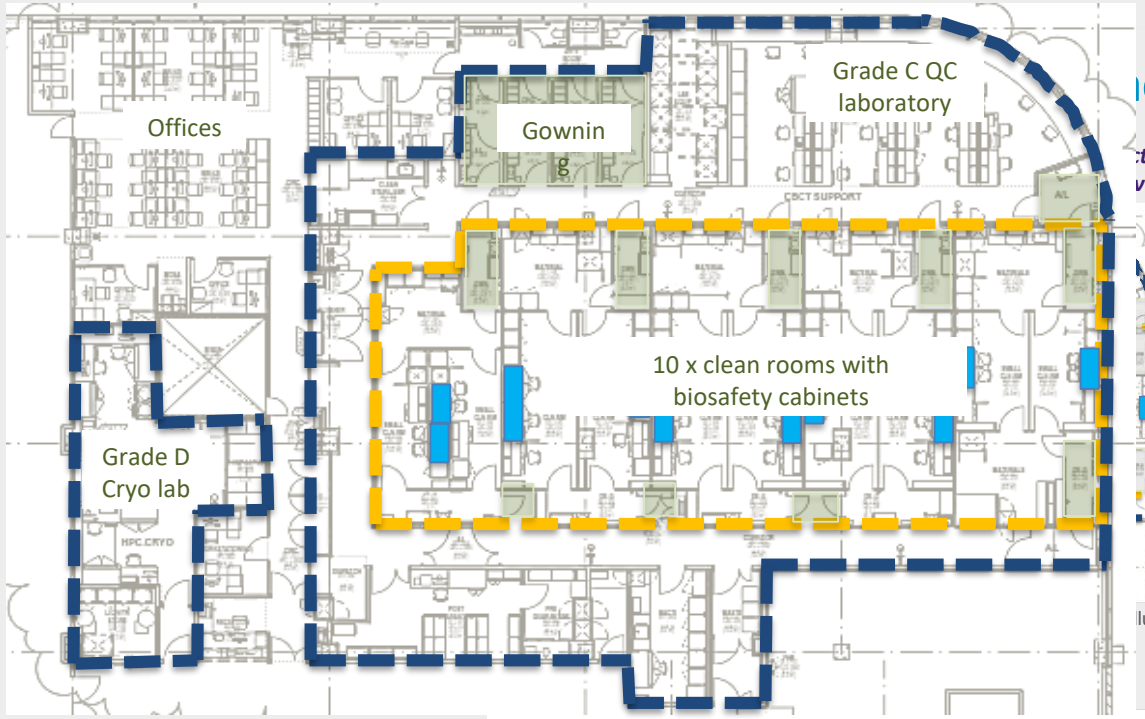
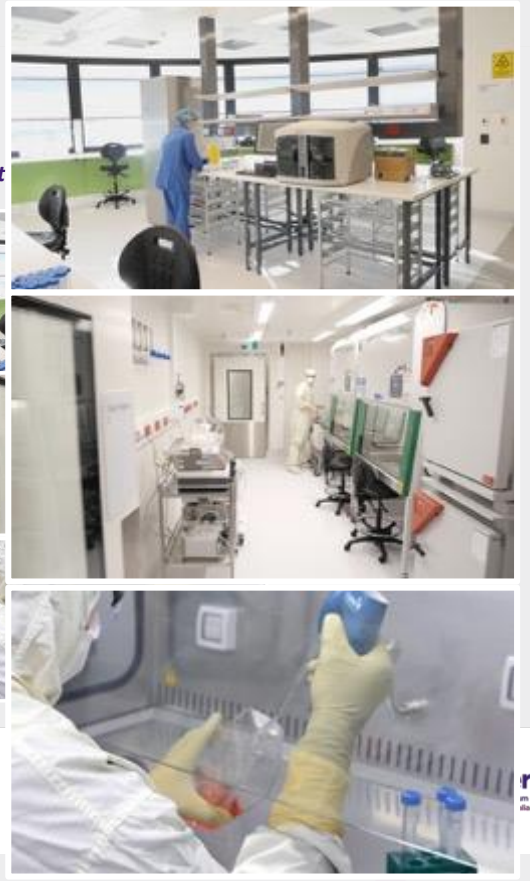
Manufacturing at Peter Mac

Over $16 million to build a new facility at Parkville. The manufacturing opportunity before us is seismic. Facility costs are significant representing ~20% of revenue





- TGA-licensed BL2 10 x clean room facility on level 9 of the Peter MacCallum Cancer Centre
- Specialising in closed-system, automated cell processing
- QC laboratory with FACS, BAC-T, ELISA and other systems

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Clinical trials at Peter Mac

From 2 clinical trials in 2016 to potentially 7 +++ in 2019

Challenge for:
- Physical capacity/ infrastructure
- Logistics management - over 10hrs per patient
- Releasing clinician time
- Research nurses

Current CAR-T clinical trials at Peter Mac

Phase	Clinical indication
Phase 1	Lung cancer – LeY target
Phase 2	Follicular lymphoma single arm relapsed refractory
Phase 3	Diffuse Large B cell Lymphoma
Phase 3	CART cells versus blinatumomab/inotuzumab in relapsed / refractory B cell ALL in adults
First in Human phase 1	Diffuse Large B cell Lymphoma
Phase 1	Myeloma

Pipeline of CAR-T clinical trials at Peter Mac

Number	Phase	Clinical indications
There are **currently 12** trials are in our pipeline	• First in human trials • Phase 1 • Phase 2 • Phase 3	• Myeloma • Lymphoma • Multiple Myeloma • Chronic Lymphocytic Leukaemia

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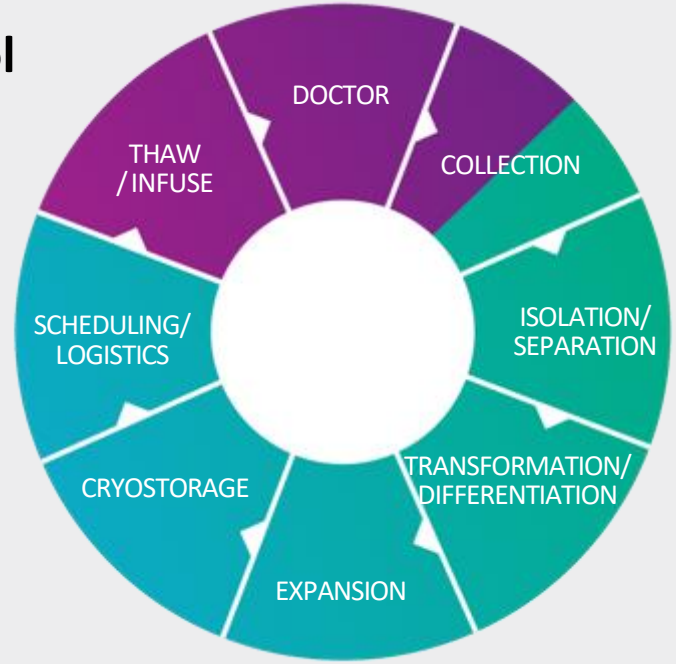
Apheresis Quality – critical to supply chain

Needle-to-needle process control and deep clinical integration



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Apheresis Service Offering- Overview

Initial Site Contact

What?

- Organisational structure & capability
- Apheresis platform(s); staffing; collection & cryo experience
- Analytics – flow cytometry, standard lab testing, serology

How?

- Questionnaire – relevant experience, documentation, etc.
- Accreditation & certification status (regulatory agencies, FACT/JACIE)

Site Establishment

What?

- Procedures
- Documentation
- Training
- Traceability
- Apheresis collection run data review
- Communication plan – site/client/CRO

How?

- On-site audit
- Gap analysis & CAPA
- Remediation (on-site or remote)
- Additional training
- Use sponsor protocols, SOP's and training materials

Ongoing Support & Management

What?

- Apheresis collection troubleshooting
- Oversight and communication
- Regular reporting back to sponsor

How?

- Remote collection support
- Remediation – as directed
- Ongoing Training – as directed
- Strong network linkages

Continuous Quality Improvement

What?

- Proactive site monitoring
- Collection optimisation
- Site standardisation across network

How?

- Establish CQAs & performance limits
- Tracking and trending of site collections
- Deviation & corrective action management
- Benchmark sites and operators
- Site feedback

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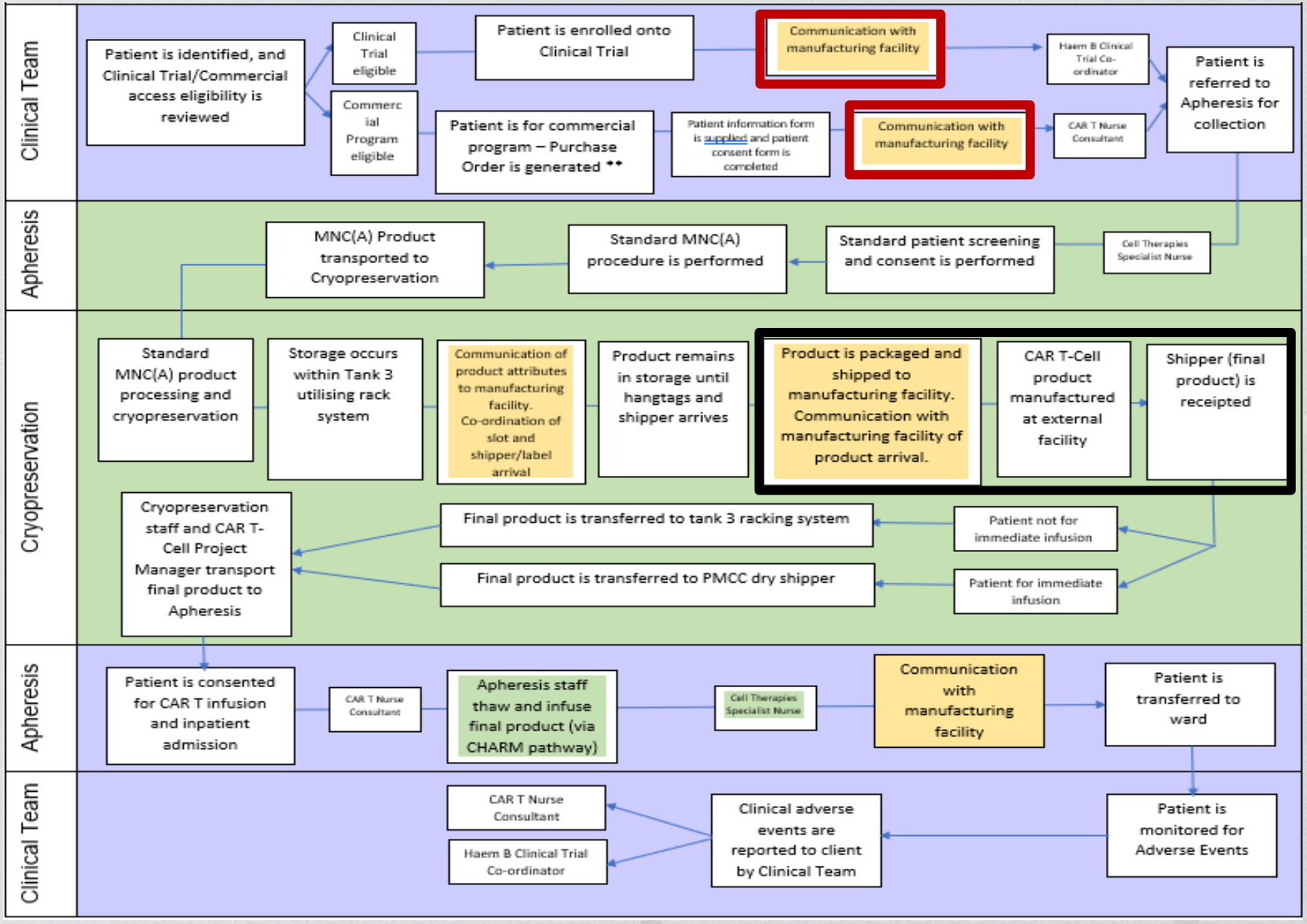
Cryopreservation Process and Variables

Multiple sources of variability and risk:

- **High variability in starting material**
- **High sensitivity of cells to cryopreservation and thawing, especially exposure to cryo-protectants and freeze rates**
- **Operator variability**
- **Microbial contamination risks**

CAR T-Cell complex logistics



CAR-T PATIENT JOURNEY

1. Referral

Triage by Disease Stream Lead

pre Tele-Health review

2. Enrolled in CAR-T program

Medical work up completed, education and psychosocial screening and referral by nursing team

3. Apheresis collection

PMC Day Apheresis Unit

4. Lymphodepleting chemotherapy

PMC Day Therapy Unit

5. Day 0 reinfusion

PMC Day Apheresis Unit with admission to inpatient haematology ward following

6. Alert Strategy to key areas

Broadcast email to key clinical areas, notifying of CAR-T reinfusion
HAT, ICU, pharmacy, haematology nursing and medical, bed access coordinators

7. Patient Monitoring

Day 1-7
?IP admission to haematology ward or **daily** review

OP monitoring in PMC day therapy unit on discharge, PMAC@H for weekend reviews

*Readmit as per deteriorating patient CAR-T triage pathway *

8. Transition Care to Referring Centre

D 28 Restaging and clinic review
Continue to monitor or transfer of care back to referring centre

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Resource utilisation

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Toxicity / Safety data crucial in understanding resource and service planning

AE	Tisagenlecleucel	Axicabtagene Ciloleucel
CRS – Any	Paediatric ALL : 79% Adult DLBCL:74% Median onset 3 days (1-51), duration 8 days	Adult DLBCL: 94% Median Onset 2 (1-12) days, duration 7 days
CRS – Gr 3-4	Paediatric:49% (Penn CRS) Adult DLBCL: 23%	Adult DLBCL: 13% (Lee criteria)
Tocilizumab usage	ALL: 39% DLBCL:15%	43% (DLBCL)
Neurological event – Any	Paediatric ALL: 72% Adult DLBCL: 58% Median onset 6d Duration 6d for ALL and 14d for DLBCL	Adult DLBCL: 87% Median onset 4d (1-43) days, median duration 17d
Neurological event – Gr III/IV	Paediatric ALL: 21% Adult DLBCL: 18%	Adult DLBCL: 31%
Unresolved cytopenia (D28)	Paedatric ALL: 37% Adult DLBCL: 44%	NR (38% Gr III/IV TCP and 78% neutropenia)

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CRS Management - Summary

	Fever	Hypotension	Hypoxia	Intervention
Grade 1	**T ≥ 38.0°c** **Not attributable to any other cause. If received anti-pyretic or anti-cytokine therapy, fever is no longer required to grade CRS severity	None	None	**Ward-based management**
Grade 2		**sBP < 90mmHg** Not requiring vasopressors	Low-flow nasal oxygen **(<6L/min)**	**HAT Team referral**
Grade 3		**sBP < 90mmHg** Requiring **1x** vasopressor (+/- vasopressin)	High flow nasal oxygen **(>6L/min),** non-rebreather mask, Venturi mask or face mask	**ICU admission**
Grade 4		**sBP < 90mmHg** Requiring **>1** vasopressor (excluding vasopressin)	Positive pressure (CPAP, BiPAP, intubation or ventilation)	

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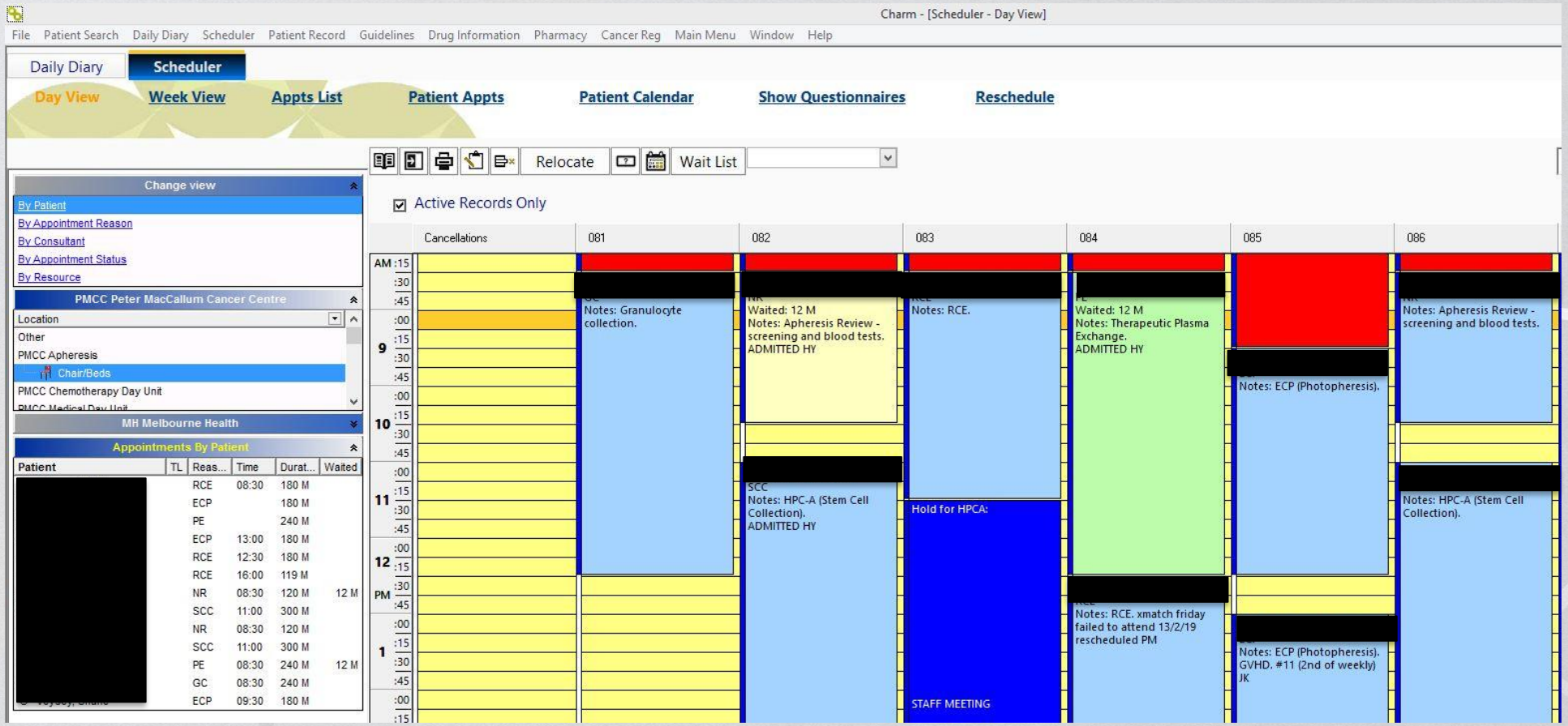
Outpatient scheduling – CHARM



Our experience of the Novartis product

- Juliet
- Trials currently in progress
- Commercial CART
- Training / TGA requirements

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ESTABLISH A REFERRAL MANAGEMENT PROCESS

Referral process follows established tumour disease practice

Triage responsibility by disease stream lead
Overall governance – Simon Harrison and John Seymour

REFERRAL CAR-T ELIGIBLE?

Pre consultation discussion between Consultant/ CAR-T Fellow/ Nurse Consultant and referring centre (not via a GP or other practitioner)

NOT ELIGIBLE

Ineligible Patient
referred back to referring centre

ELIGIBLE AND APPROPRIATE

Outpatient review of patient by CAR-T team with appropriate work-up

ELIGIBLE AND APPROPRIATE

Patient presented for discussed in Haematology MDT. Note: a peer haematologist from referring centre will be involved for bridging therapy management locally

Clinical prioritisation committee to be established with external physicians

Enrol in CAR-T program

Peter Mac members	**Non-Peter Mac members**
Simon Harrison	TBC
John Seymour	
Michael Dickinson	
Ashish Bajel	
Con Tam	
David Ritchie	
Apheresis nurse manager	
CAR T program nurse	

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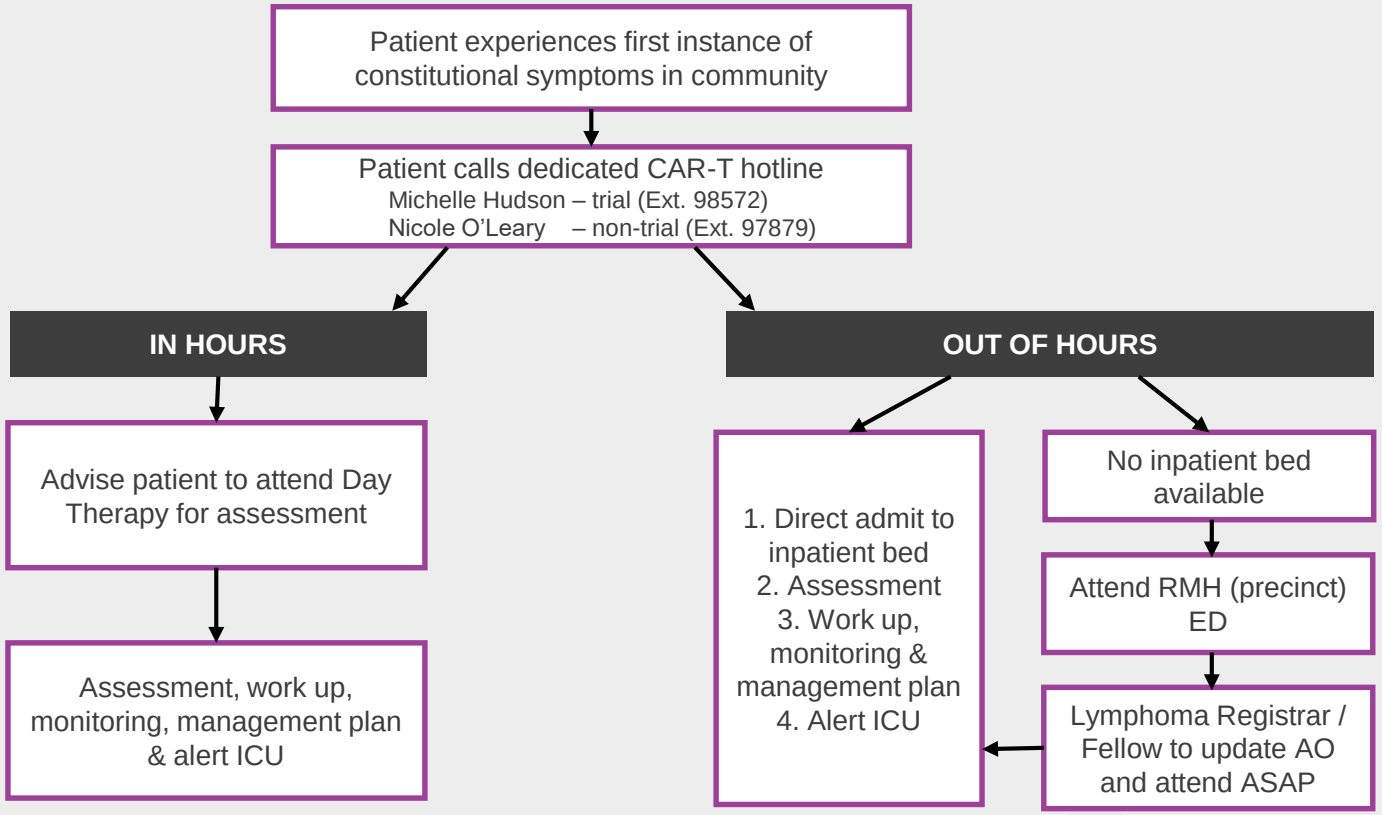
CAR-T Deteriorating Patient Pathway



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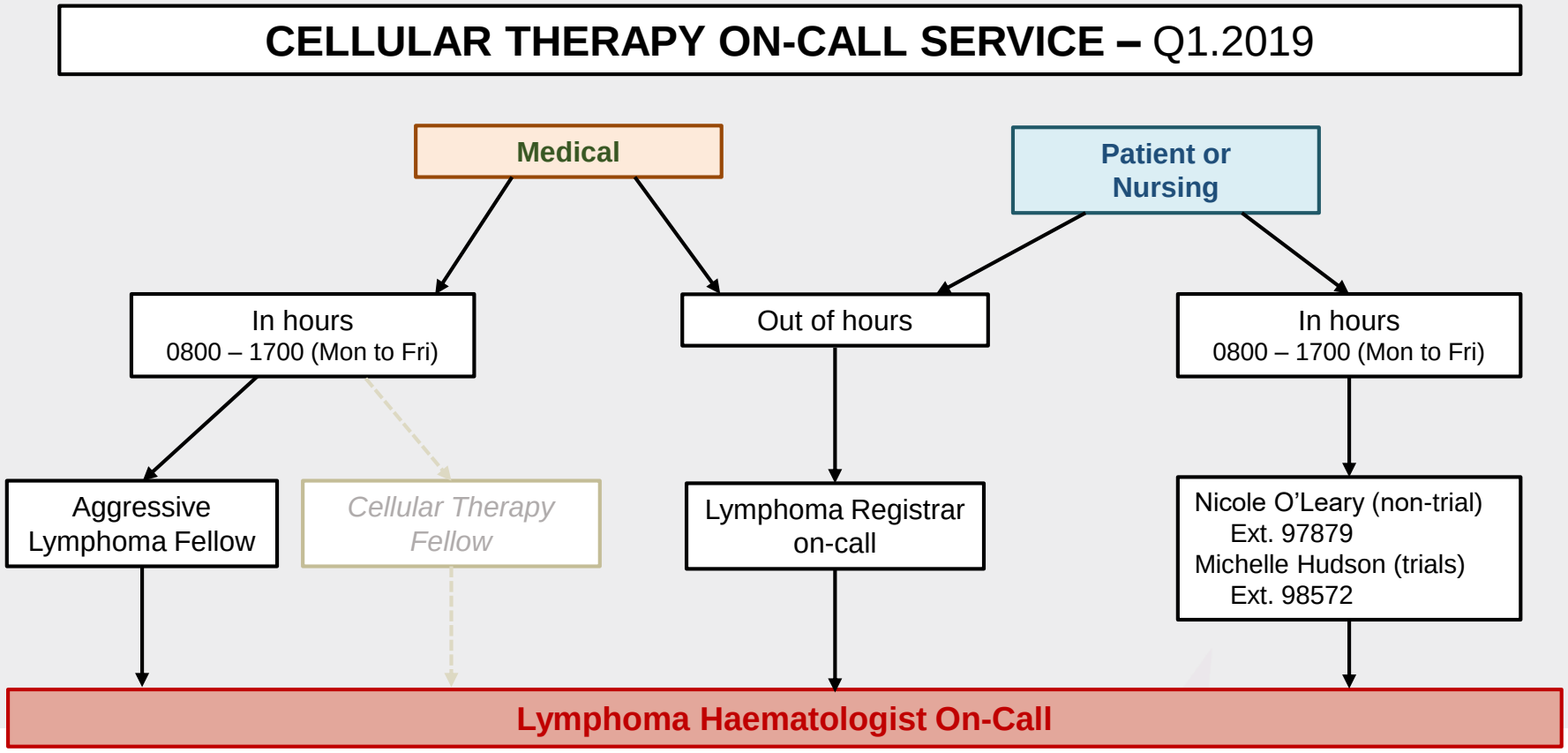
CAR-T On-call Service - PMCC



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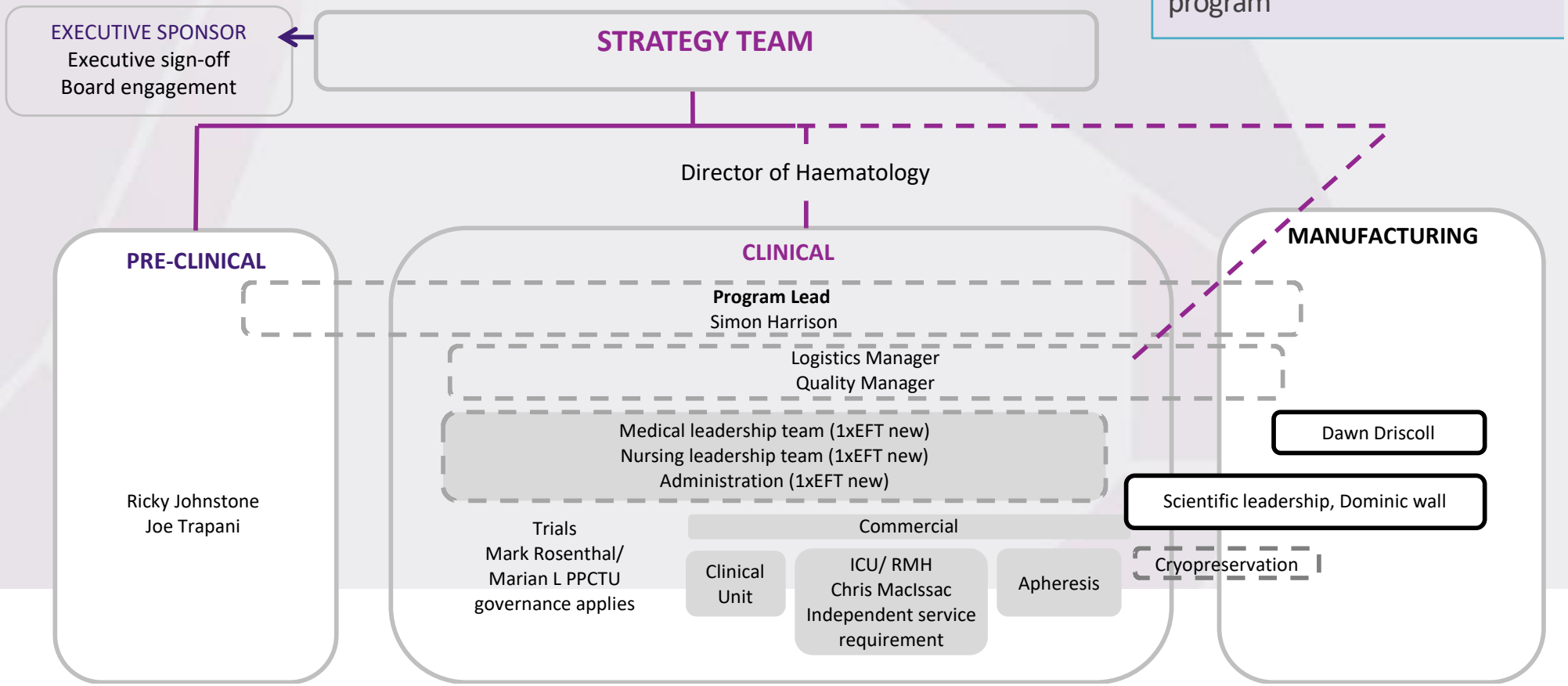
NEW GOVERNANCE AND MANAGEMENT WITH EXECUTIVE SUPPORT
A NEW CELLULAR IMMUNOTHERAPY PROGRAM

Peter Mac has already self funded over ~$1m in the program



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What is the current situation

AUSTRALIAN PI – KYMRIAH® (TISAGENLECLEUCEL) SUSPENSION

WARNING: CYTOKINE RELEASE SYNDROME

- Cytokine Release Syndrome (CRS), including fatal or life threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life threatening CRS with tocilizumab as per the CRS management algorithm.

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Summary

- Crucial aspects of clinical CAR-T delivery are:
  - Apheresis quality control
  - Clinical protocol development
  - Approach to referral management
  - Education
  - Ability to move patient quickly through acute care pathway
  - Overall hospital engagement


GHOST