CPCI

Consortium for Pediatric Cellular Immunotherapy

5th Annual Meeting
October 17 – 18, 2022

Welcome | October 17, 2022

Julie Park

CPCI

Consortium for Pediatric Cellular Immunotherapy

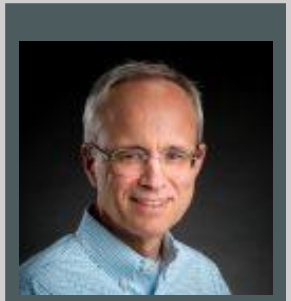

FINISH STRONG

Special Guest | NCATS

PJ Brooks, PhD

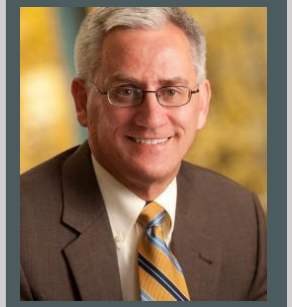
Program Director
National Center for Advancing Translational Sciences
National Institutes of Health

Special Guests | External Advisory Board



Stephen Gottschalk, MD | St. Jude Children's Research Hospital
Member, St. Jude Faculty
Chair, Department of Bone Marrow Transplantation & Cellular Therapy
Endowed Chair in Bone Marrow Transplantation & Cellular Therapy

Leslie Kean, MD, PhD | Dana-Farber/Boston Children's Cancer and Blood Disorder Center
Director, Stem Cell Transplant Center
Robert A. Stranahan Professor of Pediatrics, Harvard Medical School



Michael Konstan, MD | Case Western Reserve University
Gertrude Lee Chandler Tucker Professor of Pediatrics, Department of Pediatrics, School of Medicine
Vice Chair for Clinical Research, Department of Pediatrics Division of Pulmonology Allergy and Immunology, School of Medicine
Vice Dean for Translational Research, School of Medicine
Principal Investigator, Clinical and Translational Science Collaborative, School of Medicine

CPCI

Consortium for Pediatric Cellular Immunotherapy

Accelerate cellular immunotherapy for pediatric disease

Develop and disseminate resources for the implementation of novel cellular immunotherapy

Expand patient access to novel cellular immunotherapy


Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION
UCSF Benioff Children's Hospital
Oakland
Children's Hospital Colorado
Children's National
Health System
Children's
Hospital
LOS ANGELES

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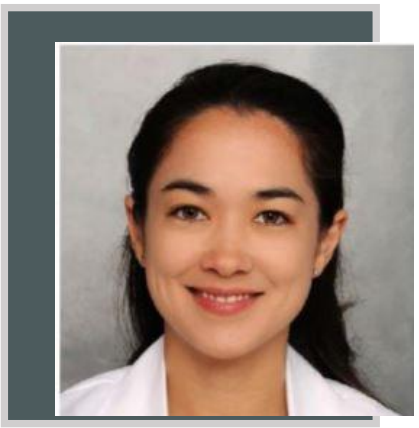
CTSI Alignment

- Collaboration
  - GMP working group
  - Protocol Review Committee
  - Patient Advocacy Committee
  - Biobank working group
  - CNS correlative studies working group
- Education
  - Proficiency Training
- Dissemination
  - CPCI Website resources
  - Clinical Trials (PLAT-02, ACES, **PLAT-05**, -06, **-07**, **PrevCAR**)

Training & Mentoring

Scientific Talks

Katie Albert, MD
Seattle Children's Hospital



Hannah Kinoshita, MD
Children's National Hospital

Michael Leibowitz, MD, PhD
Children's Hospital Colorado

Sarah Richman, MD, PhD
Children's Hospital Los Angeles

Brian Shy, MD, PhD
University of California San Francisco

Jianming Xie, PhD
University of Southern California

Symposia

CNS
March 7, 2022

Employee Retention
March 21, 2022

Personnel Changes

- Bonnie Ramsey
  - Decrease effort to 3% but will remain as co-PI
- Julie R. Park
  - Assuming new role as Chair Department of Oncology St. Jude Children's Research Hospital on 16Jan2023
  - Will remain co-PI and maintain current effort
  - Grant will remain at Seattle Children's Research Institute

AGENDA

Aim 1 | cGMP Working Group
Break

Aim 2 | Protocol Review Committee
Break

Aim 2 | Patient Advocacy Committee
Aim 3 | Correlative Working Group
Day 1 Wrap Up

Aim 1
cGMP Working Group

Stephanie Mgebroff & Chris Brown

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Consortium for Pediatric Cellular Immunotherapy

Develop the infrastructure to expand manufacturing capabilities of cellular immunotherapy products developed for treatment of pediatric disease

Define and align best practices across cGMP facilities

Expand distribution of cellular therapies to sites of patient care

Expand available cGMP facilities across CTSA

Membership

Mohamed Abou-el-Enein, MD, PhD, MSPH	***Executive Director, Joint USC/CHLA Cell Therapy Program - CHLA***
Julie Annis	*Supervisor, BMT Laboratory – CHLA*
Christopher Brown	*Director, GMP Cell Production - SCTx*
Amaia Cadinanos-Garai	***Quality Control Specialist - CHLA***
Jonathan Esensten, MD, PhD	*Medical Director, Regulatory T Cell Manufacturing Group - UCSF*
Roger Giller, MD	*Medical Director, Charles C. Gates Biomanufacturing Facility – CU*
Patrick Hanley, PhD	*Director, GMP for Immunotherapy - CNH*
Catherine Lindgren	*Senior Director, Therapeutic Cell Production & Quality Assurance – SCRI*
Chase McCann, PhD	***Cell Therapy Lab Lead - CNH***
Stephanie Mgebroff	*Director, Research Quality Control - SCTx*
Matt Seefeldt	*Director of Cell Therapy, Charles C. Gates Biomanufacturing Facility – CU*
Abeer Shibli, MT	*Cell Therapy Lab Specialist - CNH*

Membership (continued)

• **Sandeep Srivastava, PhD**	***Cell Therapy Lab Lead - CNH***
• Jay Tanna	*Quality Assurance Lead – CNH*
• Chandresh Undhad	*Associate Director Quality Charles C. Gates Biomanufacturing Facility – CU*
• **Alix Vaissié, PhD**	***cGMP Manufacturing Specialist, Joint USC/CHLA Cell Therapy Program - CHLA***

Accomplishments

1

Conducted one cGMP facility audit in 2022. CNH visited TCPC (Seattle Children's)

2

Construction and commissioning completed at one additional site (CHLA)

3

Presented work associated with retention / engagement at symposium

Focus Discussions

- Continued to focus discussions on supply chain issues and impact
  - Standing agenda item at working group meetings
  - Escalation of shortages with potential impact across sites
  - Collaborative mitigation planning

- Numerous conversations around supporting retention of cGMP staff
  - Collaborating with HR partners
  - Hiring strategies

- Ad-hoc conversations
  - Laboratory information management systems (LIMs)

Goal	Metric
cGMP facility audits between 2 consortium sites	One site visit and audit performed between 2 consortium sites by July 2023
Evaluate strategies for implementation of electronic inventory and lab management systems in early-phase cGMP production facilities	Evaluate current state across working group sites by dedicated discussion at monthly and formulate lessons learned and key considerations in an accessible forum and/or format for dissemination across sites.
Continue to refine best practices and key considerations to facilitate third-party microbiology testing of early-phase GMP production facilities	Finalize and launch a survey across consortium sites and other cGMP production facilities to develop understanding of current thinking of the field with the goal of pursuing a manuscript in this area
Develop platform for the continued collaboration of the cGMP working group following Y5	

Setting up a new cGMP facility

USC/CHLA Cell Therapy experience

Mohamed Abou-el-Enein, MD, PhD, MSPH

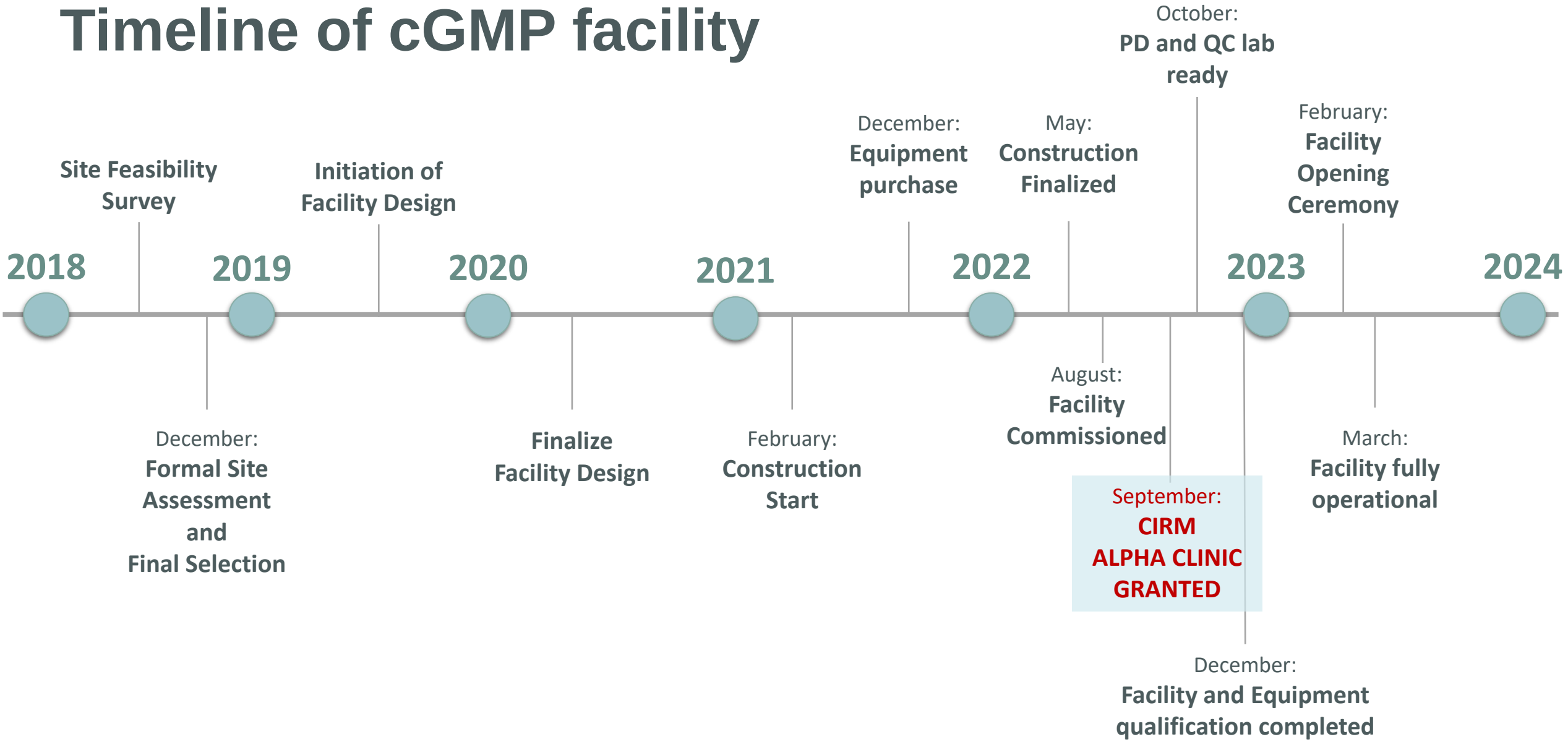
USC/CHLA
Cell Therapy Program

Our mission

- Create an **ecosystem** of clinical translation
- Utilize advanced analytical and proof-of-principle approaches
- Support **internal and external** investigators

The centerpiece is a state-of-the-art cGMP facility

Timeline of cGMP facility



Construction

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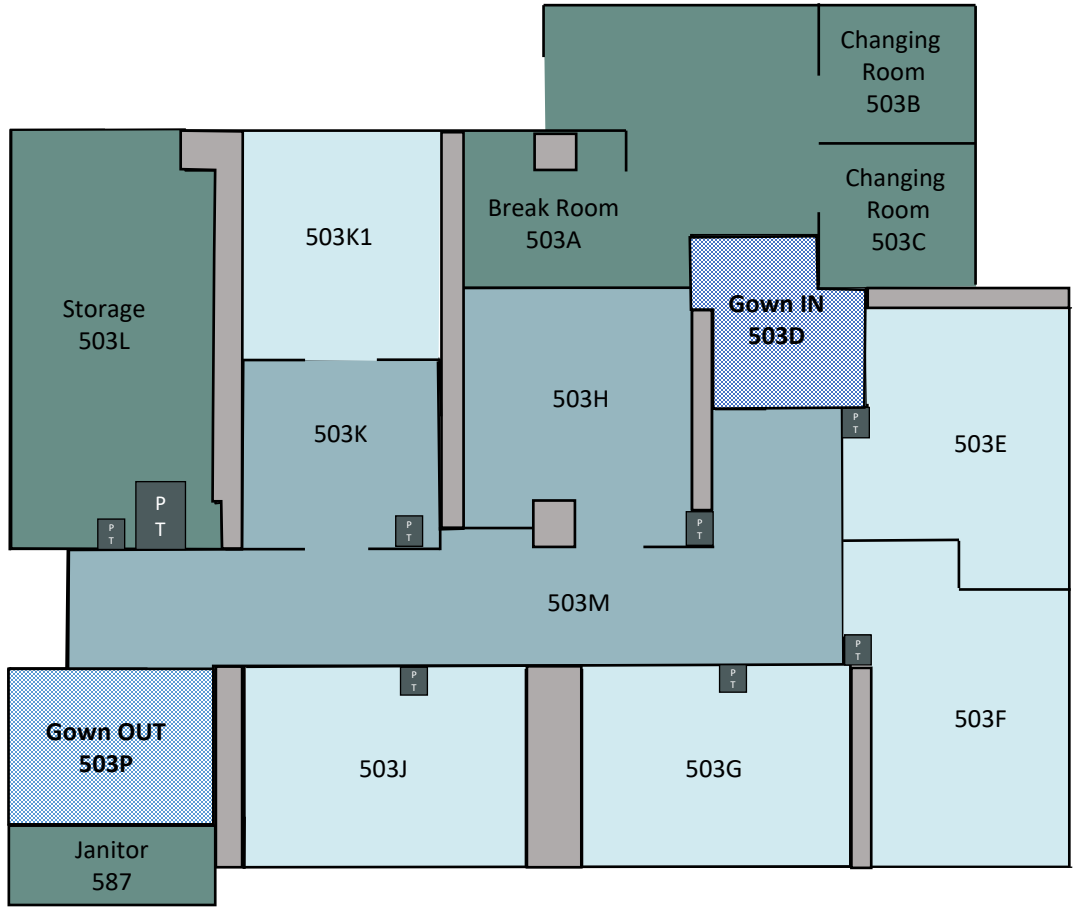
cGMP facility – Description

The cGMP facility spans 3,184 sf and has:

- Four ISO-7 cleanrooms for manufacturing
- One ISO-7 cleanroom for vector
- One ISO-8 cleanroom for **closed** system manufacturing
- One 800 sf Quality Control lab
- One 300 sf Process Development lab
- Storage area



cGMP facility - Equipment

Fully equipped rooms for OPEN and CLOSED manufacturing, vector production and storage capabilities

OPEN

-Dedicated ISO5 **Biosafety Cabinets**

-Incubators **-Centrifuges**

-Automatic cell counters & Microscopes with **high resolution cameras**

CLOSED

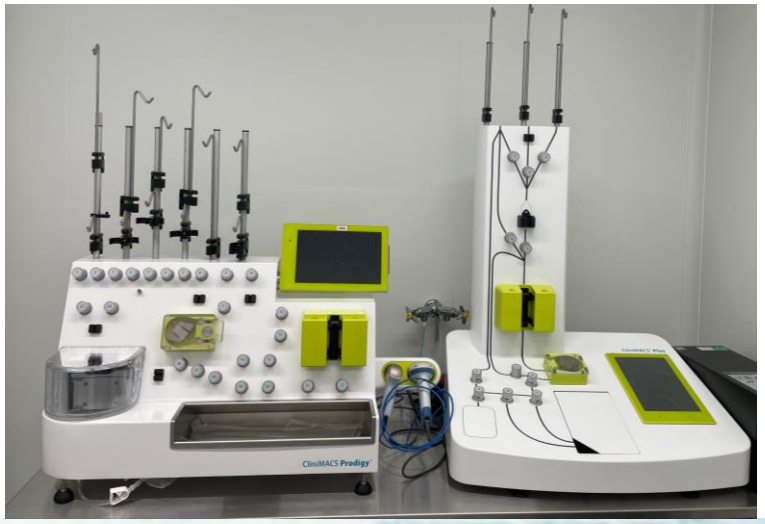
-Miltenyi **CliniMACS** -Miltenyi CliniMACS **Prodigy**

VECTOR PRODUCTION

-Optima XE **ultracentrifuge**

CRYOPRESERVATION AND STORAGE

-Multiple **controlled rate freezer** (CRF) & **LN_2 tanks**



QC laboratory - Equipment

BD FACSLyric 12 color **flow cytometer**

BD **Bactec** FX40

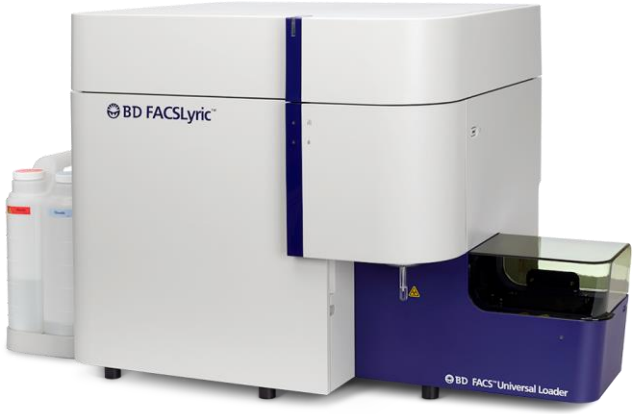
Endosafe® nexgen-PTS™

ProFlex™ 3 x 32-well **PCR system**

CFX96 Touch Deep Well **Real-Time PCR system**

C1000 Touch **Thermal Cycler** with Dual 48/48 Fast Reaction Module

Microbiological incubators



USC/CHLA Cell Therapy – Capabilities

PROCESS DEVELOPMENT	MANUFACTURE	QUALITY CONTROL	REGULATORY

- **Tech transfer**
- **Scaling up** protocols
- Transfer of process **from open to close system**
- Validation of reagents for GMP compliance
- QC assay **development** and **validation**
- Development of Standard Operating Procedures **(SOPs)** and Target Product Profile **(TPP)**
	- Autologous and allogenic product **manufacture** in closed and open systems
	- Implementing **modular** systems for manufacturing
	- **Vector** manufacture
	- **Product formulation**
	- Vendor management
	- Cryostorage
	- Shipping/coordination with clinical site
	- Full **Quality Assurance** services
		- **Raw materials**
		- **In-process** and **release** testing
		  - Sterility
		  - Identity
		  - Viability
		  - Purity
		  - Potency
		  - Safety
			- Assistance in writing Chemistry, Manufacturing, and Controls **(CMC)** section for Investigational New Drug **(IND)** submission
			- Support in clinical study **design**
			- Support grant applications
			- Preparation for Audits
			- Coordinate **CRO** Services

USC/CHLA Cell Therapy – Supporting activities

1

TRANSLATIONAL SUPPORT
For early-stage research

2

NEW COURSE
Cell and Gene Therapy Development – Translating Basic Research into Clinical Applications

3

MONTHLY SEMINARS
with experts in the CGT sector

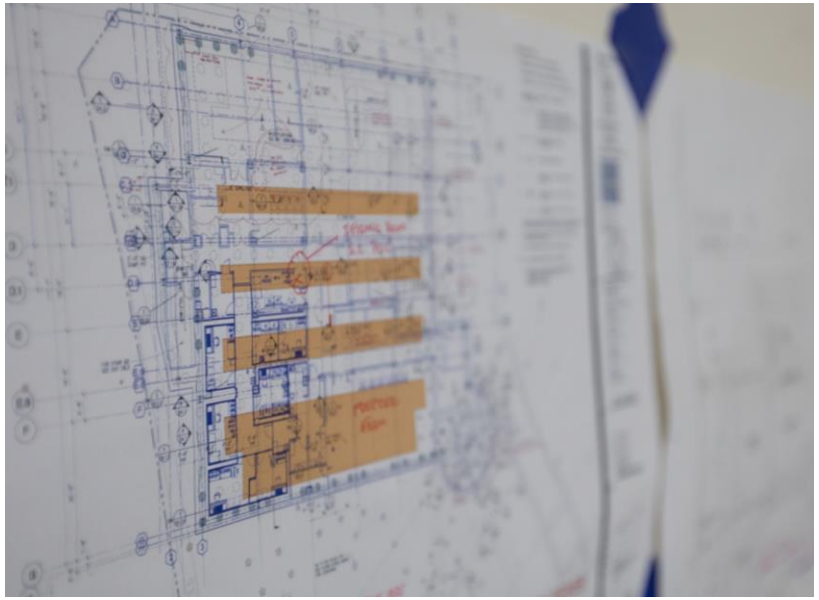
cGMP facility - troubleshooting

Personnel:

- Ensuring understanding between all collaborating parties: PM, architect, contractor
- University and facilities team involvement
- Implementation of regular meetings

Documentation:

- Reviewing drawings / submittals from architects & contractor
- Understanding of record keeping and documentation requirements for GMP compliance



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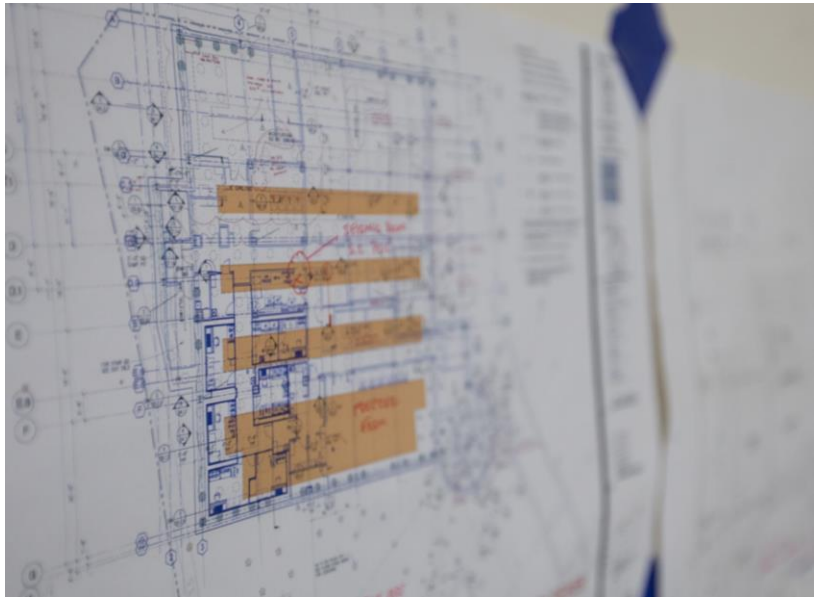
cGMP facility - troubleshooting

Facility:

- **HVAC system** requirements
- LN_2 Supply and environmental requirements
- Gas line connection (CO_2, CA) and manifold
- Independent **power supply**
- Emergency power / special connections requirements
- Building and Environmental Monitoring System
- Digital operating system
- Spacious storage (RT, +4ºC, -20ºC, -80ºC, LN_2) and quarantine areas



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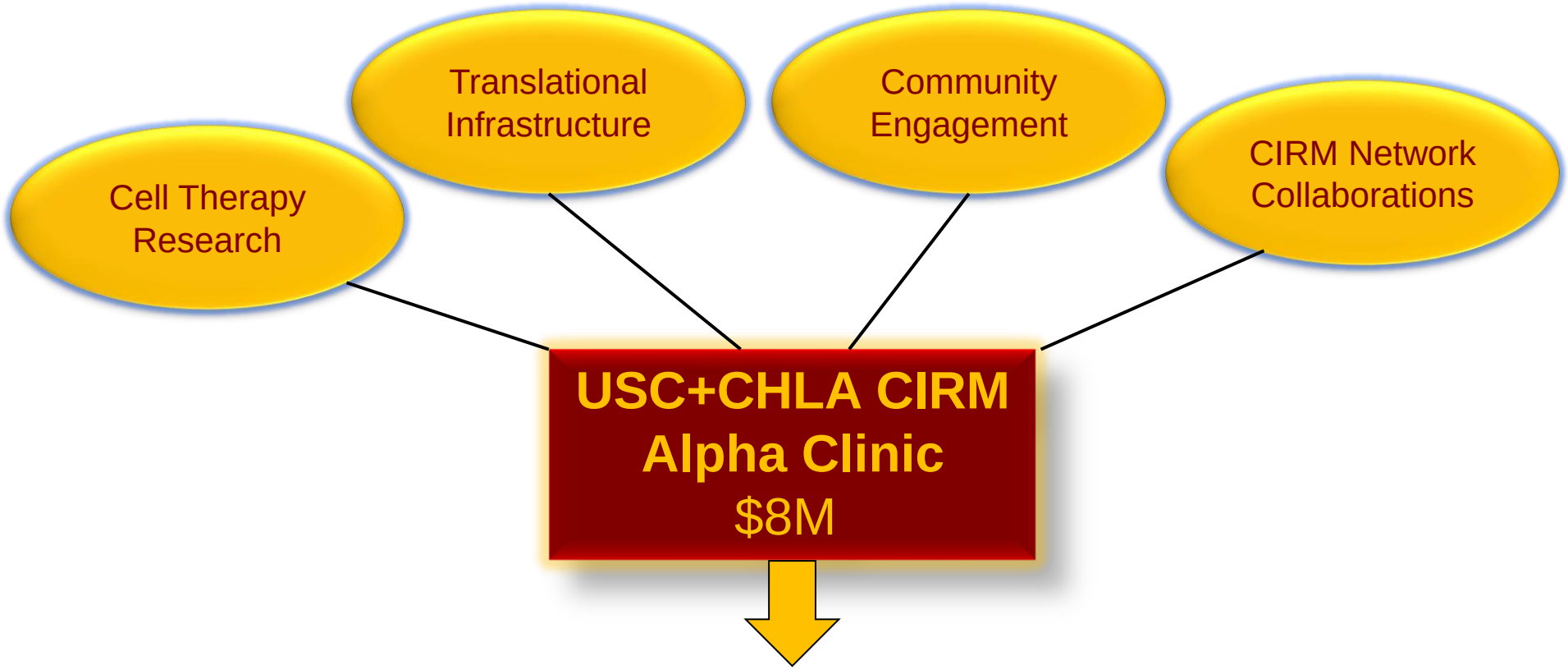
USC+CHLA CIRM Alpha Clinic



Accelerate Translation of Research to Novel Cell and Gene Therapies in the California region and beyond

USC+CHLA CIRM Alpha Clinic

Alpha Clinic Network Expansion for Cell and Gene Therapies

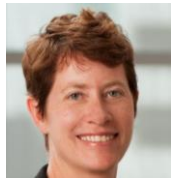
- Thomas Buchanan, MD,
- Director

- Mohamed Abou-el-Enein, MD PhD,
- Associate Director

- Alan Wayne, MD,
- CHLA Site PI

- Juliane Glaeser, PhD,
- Network Liaison

- Michele Kipke, PhD,
- Community Engagement



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THE FUTURE of Cell Therapy at USC & CHLA

THANK YOU

USC/CHLA
Thomas Buchanan
Alan Wayne
Caryn Lerman
…& countless support structures

CTP Team
Alix Vaissié
Amaia Cadiñanos-Garai
Nadia Sellami
Victoria Olvera
Alejandro Bustamante

Questions?

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Forum Discussion

Discussion

The working group acknowledges the common goal across consortium sites of implementing electronic inventory management and/or laboratory information management systems (LIMS) to support cGMP manufacturing.

Discussion

Continuation of cGMP Working Group pre-meeting discussion

Discussion

Benefits of site visits/audits

Aim 2
Clinical Trial Implementation

CPCI

Consortium for Pediatric Cellular Immunotherapy

Expand the clinical development of cell-based immunotherapy for pediatric disease

Establish the training and infrastructure to promote development and implementation of clinical immunotherapy trials in pediatric patients

Utilize clinical trial designs that account for the unique constraints of rare disease-focused clinical trials in pediatric populations

Ensure equitable access for all participants who may directly or indirectly benefit from cellular immunotherapies clinical trials

Aim 2
Protocol Review Committee

Michael Verneris & Rebecca Gardner

CPCI

Consortium for Pediatric Cellular Immunotherapy

Membership

• **Cheri Adams, MSHS, RN, RAC**	***Pharmacovigilance Specialist, Cell Therapy Operations Program - CHC***
• Paibel Aguayo-Hiraldo, MD	*Pediatric Hematologist-Oncologist – CHLA*
• Karin Chen, MD	*Pediatric Immunologist – SCH*
• Dana Dornsife	*Founder and Chair - Lazarex Cancer Foundation*
• Leslie Elliott	*Clinical Scientist, Senior - SCTx*
• Rebecca Gardner, MD	*Pediatric Hematologist-Oncologist – SCH*
• Emily Hsieh, MD	*Pediatric Hematologist-Oncologist – CHLA*
• Michael Keller, MD	*Pediatric Immunologist – CNH*
• Jennifer Michlitsch, MD	*Pediatric Hematologist-Oncologist - BCHO*
• Julie Park, MD	*Pediatric Hematologist-Oncologist – SCH*
• **Keri Toner, MD**	***Pediatric Hematologist-Oncologist - CNH***
• Michael Verneris, MD	*Pediatric Hematologist-Oncologist – CHC*
• Vicky Wu, PhD	*Bio-Statistician - FHCRC*

Goal	Metric
Develop tools to enhance PV at academic sponsors of cellular therapy products/trials	• Publish Manuscript regarding academic PV programs • Develop Safety Database in Redcap • Distribute IB template
Activate PrevCAR at all CPCI sites	• Subjects enrolled on PrevCAR from all CPCI sites
Enhance data collection to align with industry standards	• Develop Global CRFs and variables that can be transferrable between CPCI sites

PrevCAR Update

5.2.1 **Inclusion criteria**

1. Age ≤ 30 years
2. Planning to undergo treatment with B cell directed CAR T cell therapy (inclusive of CD19 or CD22 CAR T)
3. Willing to receive vaccination with Prevnar 13
4. Willing to donate blood at the specified times

5.2.2 **Exclusion criteria**

1. History of hypersensitivity or intolerance to Prevnar 13
2. Prevnar 13 vaccination within the past 6 months
3. Receiving IV or SQ immunoglobulin replacement within the 3 months prior to expected first dose of Prevnar 13

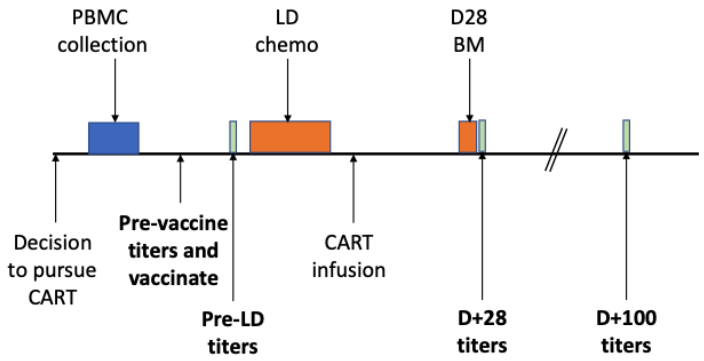

Figure 6-1 Study schema Research events, which are blood samplings, are shown in bold and performed pre-vaccination, prior to LD chemotherapy, at D+28 and D+100.

9.3 Power Analysis

The primary endpoint is antibody response, defined as having measurable titers at D100. If there are signs of response, we will consider for further development and a larger cohort study. Assuming p0 is approaching 0, at a 1-sided alpha level 0.025, 20 patients will provide approximately 91% power if true response rate p1 = 0.15, over 95% power if p1 = 0.2, and over 99% power if pA = 0.25. The power analysis is using online tools from SWOG https://stattools.crab.org/Calculators/oneArmBinomial.html. See Table 9-1.

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Site Status

Site	IRB subm/approval	DUA w/SCH	MTA w/CNH	comment
SCH	approved	NA	complete	
B-CHO	approved	complete	complete	
CNH	subm wk of 10/24	complete	NA	
CHCO	unknown	requires IRB approval	unknown	SRC complete, pending ONA, CR2C prior to IRB subm, possible subm Nov/early Dec
CHLA	subm wk of 10/24	complete	not started	CHLA contracts to contact CNH

Pneumococcal Conjugate Vaccine Does Not Induce Humoral Response When Administrated Within the Six Months After CD19 CAR T-Cell Therapy

Dasom Lee[1], Aryanna I Jordan[1], Meghan A. Menges[2], Alexandr Lazaryan[2], Taiga Nishihori[2], Sameh R. Gaballa[3], Bijal D Shah[3], Javier Pinilla-Ibarz[3], Aliyah Baluch[4], Olga V. Klinkova[4], Julio C. Chavez[3], Michael D. Jain[2], Frederick L. Locke[2,*]

Table 2
Humoral Protective Immunity Against Pneumococcus Diminishes After CD19-Targeted CAR-T Until Day 540

Number of Vaccine-Specific Serotypes at Protective Level	Baseline	Day 90	Day 180	Day 270	Day 360	Day 540
0	11 (14%)	19 (27%)	18 (32%)	8 (28%)	10 (33%)	8 (22%)
1-3	39 (51%)	26 (37%)	23 (40%)	14 (48%)	9 (30%)	15 (41%)
4-5	7 (9%)	13 (19%)	7 (12%)	4 (14%)	8 (27%)	6 (16%)
6	19 (25%)	12 (17%)	9 (16%)	3 (10%)	3 (10%)	8 (22%)

All vaccine-specific pneumococcal serotypes are pooled together regardless of vaccination status at baseline (n = 76) and days 90 (n = 70), 180 (n = 57), 270 (n = 29), 360 (n = 30), and 540 (n = 37) after CAR-T.

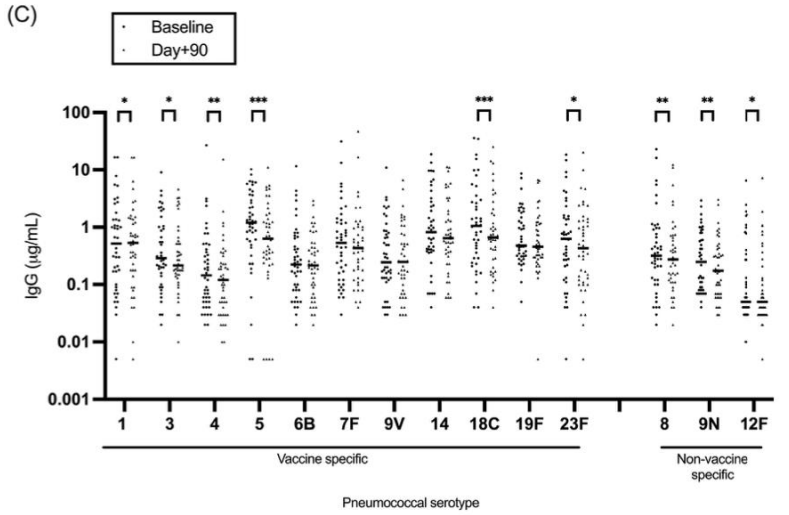

Table 3
Characteristics of Patients Meeting the Criteria of Humoral Protection Against Pneumococcus at Day 540

Patient	Underlying Disease	Absolute Count (at Day 540)			PCV13 Vaccination*	IVIG†	Number of Vaccine-Specific Serotypes at Protective Level		
		CAR-T Response	CD4 T Cells (cells/μL)	CD19 B Cells (cells/μL)			Baseline	Day 360	Day 540
1	TFL	CR	324	512	Yes	No	Unknown	0	11
2	PML	CR	41	0	Yes	No	Unknown	1	8
3	DLBCL	CR	348	96	No	No	6	6	6
4	DLBCL	CR	454	51	No	No	7	6	6
5	DLBCL	CR	183	88	No	No	Unknown	Unknown	7
6	DLBCL	CR	146	154	Yes	Yes	4	0	9
7	DLBCL	CR	189	0	Yes	Yes	Unknown	6	8
8	DLBCL	CR	665	0	No	Yes	Unknown	9	8

TFL indicates transformed follicular lymphoma; PML, primary mediastinal lymphoma; DLBCL, diffuse large B-cell lymphoma; CR, complete response.
* PCV13 vaccination that occurred from day 360 to day 540 was indicated.
† IVIG was given within 16 weeks before pneumococcal antibody collection at day 540 for recurrent or severe infections.

Brief Summary:

The purpose of the study is to evaluate whether receiving the pneumococcal 13-valent conjugate vaccine (PCV13) before and after CD19-targeted CAR T cell therapy will optimize cellular and humoral immunity to pneumococcus.

Detailed Description:

This is a phase II, single-institution study to investigate if pneumococcal vaccination before and after CD19-targeted CAR T cell therapy elicits cellular and humoral immunity to pneumococcus in patients with relapsed or refractory B cell lymphomas. All the participants will receive the same treatment. Immunoglobulins (IgG) against pneumococcal serotypes not included in the vaccine will be served as an internal control. Treatment includes the same dose (0.5ml) of PCV13 one time prior to apheresis followed by two times after CAR T cell therapy

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Development of a Fit For Purpose Pharmacovigilance Program within an Academic Research Organization:

A Case for Cell and Gene Therapy INDs

Cheri Adams, MSHS RN RAC
Pharmacovigilance & Regulatory Strategy Lead

Michael R. Verneris, MD
Cell Therapy Operations Program
Scientific & Medical Director

AGENDA

I. What is Pharmacovigilance (PV)?
   a. Scope of PV
   b. Four Domains of Safety Oversight
   c. Governance: Oversight Committees

I. Unique Considerations of Cell and Gene Therapy (CGT) Products

II. Benefit: Risk Framework

III. CPCI Protocol Committee Project: PV Toolbox for CGT INDs
   a. Sponsor/Investigator Framework
   b. PV SOPs
   c. Assessment Tools
   d. Risk Management Tools
   e. Guidance Documents

IV. Conclusion

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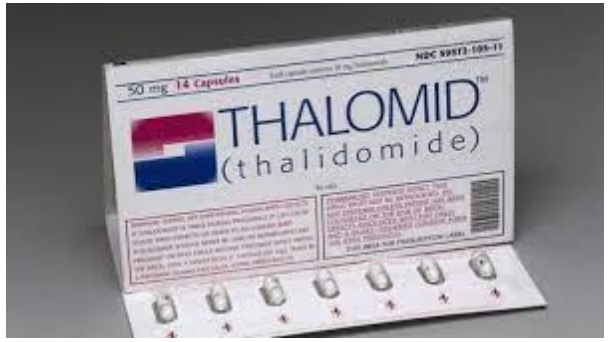
What is Pharmacovigilance (PV)?

The science of detecting, assessing, analyzing, and mitigating adverse effects of a drug product throughout the lifecycle

FDA U.S. FOOD & DRUG ADMINISTRATION

1962 – Kefauver-Harris Amendments to the Food Drug & Cosmetic Act



Scope of Pharmacovigilance

- **Patient Safety**
- Investigational Product (IP) **Efficacy**
- **SAEs** (Track SAEs)
- **Population** (Improve public health)
- **Risk: Benefit** (Review risk, benefit, efficacy, or rationalized use of IP)
- **Educate** (Educate on IP safety)

ICH harmonisation for better health **Safety Guidelines**

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Safety Oversight & Pharmacovigilance (PV) Goals & Operating Model

PROGRAM GOAL

- Reduce risk to patients
  - Begins in the preclinical setting
- Improve patient safety
- Increase compliance

CTOP PV MODEL

Core Capabilities

- Adverse Event Management
- Aggregate Reporting
- Signal Detection
- Risk Management

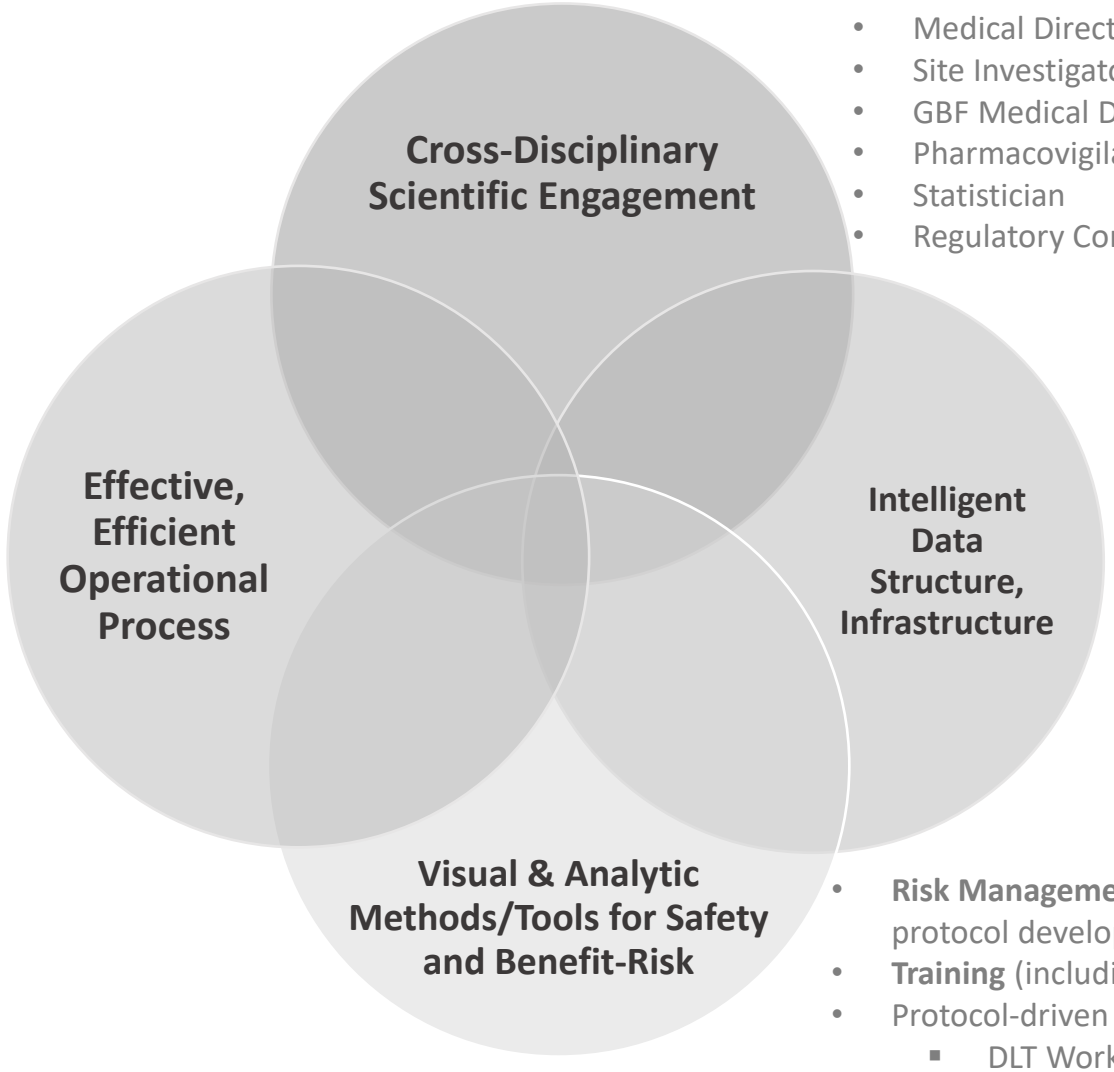
Strategy

- Start early!

Governance

- Effective issue escalation and resolution requires clear governance. Closed-loop process, linked to organization-wide management processes can mitigate safety risks while maintaining compliance

The Four Domains of Safety Oversight



- Medical Director (IND Sponsor)
- Site Investigator
- GBF Medical Director (if manufacturing-related)
- Pharmacovigilance Specialist
- Statistician
- Regulatory Compliance

- External Safety Monitoring Committee (SMC)
  - ❖ UCCC DSMC (Internal)
- Treatment Review Committee (TRC)
- Safety Management Team (SMT)
- Quality Review Committee (QRC)
- SAE Reporting & Reconciliation Process
- SOPs and other controlled quality documents

- Electronic CRFs(Advarra EDC)
- External CRA/Monitoring oversight
- Manage transition from treatment protocol to FDA-mandated LTFU study

- **Risk Management Plan** – Identification of QTLs and KPIs during protocol development.
- **Training** (including inspection readiness training)
- Protocol-driven requirements for AE collection and reporting.
  - ▪ DLT Worksheet
- EDC data constraints (e.g., pop-up messages)
- Weekly safety calls with sites

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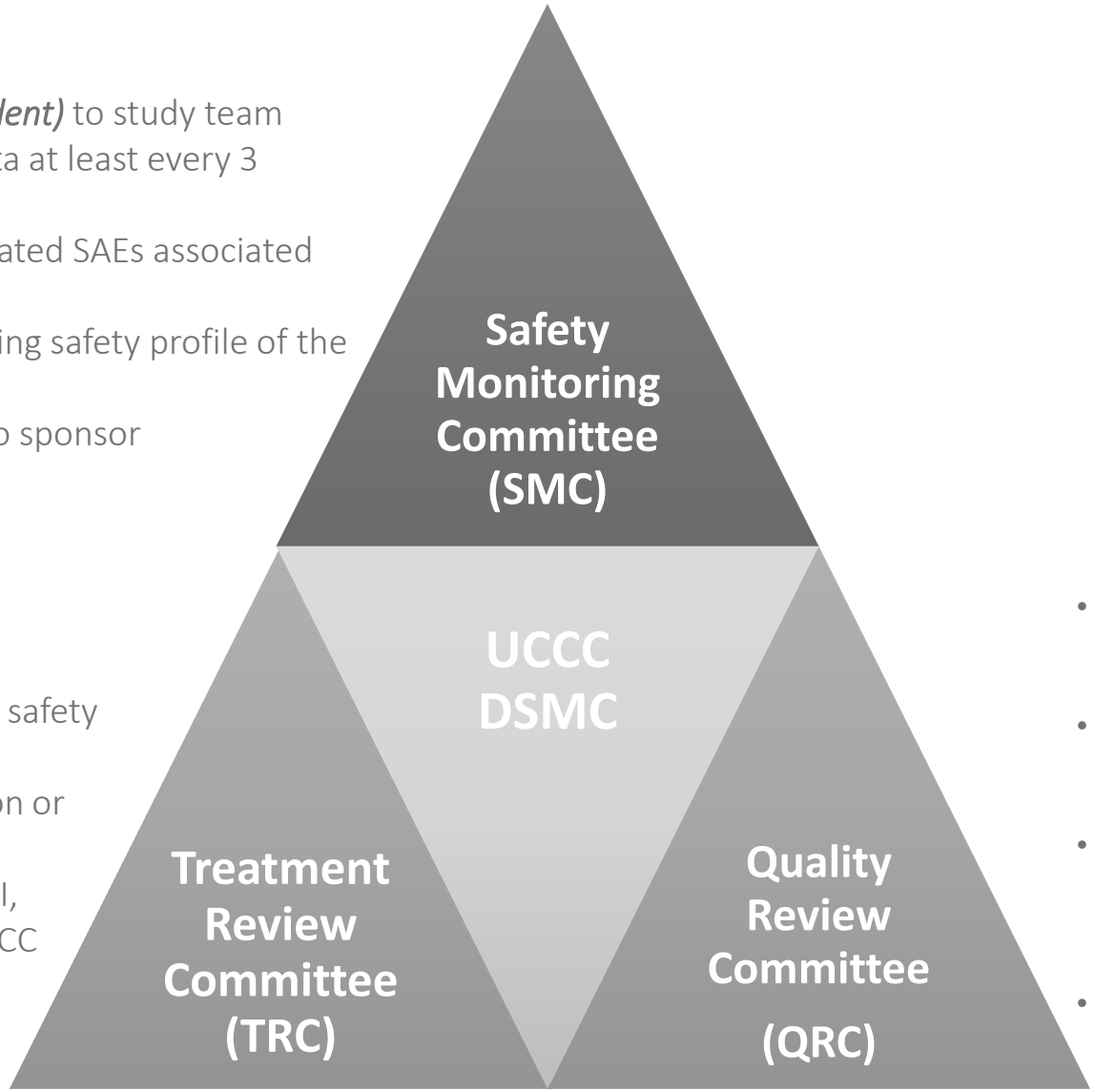
Governance: Oversight Committees

- *External (independent)* to study team
- Reviews safety data at least every 3 months
- Reviews unanticipated SAEs associated with IP
- Oversee the evolving safety profile of the IP
- Report provided to sponsor



- *Internal* to study team
- Reviews DLTs
- Reviews each cohort's safety and feasibility data to determine continuation or dose de-escalation
- Findings reported to PI, sponsor, SMC, and UCCC DSMC

- Reports to the Vice Chancellor of Research with focus on cell therapy IITs on campus.
- Provides oversight of quality-related processes, KPIs, and documents for program
- Reviews "near misses", manufacturing-related deviations/failures, events requiring reporting to FDA, and toxicity review.
- Provides recommendations

Unique Safety Considerations of CGT Products

SCIENCEINSIDER | BIOLOGY

Cancer immunotherapy company tries to explain deaths in recent trial

Juno Therapeutics says it is developing a safer T-cell therapy

16 NOV 2017 • BY RONI DENGLER

BIOTECH

Death in Cellectis off-the-shelf CAR-T trial triggers FDA hold

By **Nick Paul Taylor** • Jul 7, 2020 07:55am

Development of CAR T-cell lymphoma in 2 of 10 patients effectively treated with *piggyBac*-modified CD19 CAR T cells

David C. Bishop,[1-4] Leighton E. Clancy,[1,5] Renee Simms,[1,2,5] Jane Burgess,[1,2,5] Geetha Mathew,[1,5] Leili Moezzi,[1,5] Janine A. Street,[1,5] Gaurav Sutrave,[1-4] Elissa Atkins,[3] Helen M. McGuire,[6-8] Brian S. Gloss,[1] Koon Lee,[1,2] Wei Jiang,[1,2] Karen Maddock,[3] Georgia McCaughan,[2,3] Selmir Avdic,[1,5] Vicki Antonenas,[5] Tracey A. O'Brien,[9-11] Peter J. Shaw,[12,13] David O. Irving,[14,15] David J. Gottlieb,[1-5] Emily Blyth,[1-5] and Kenneth P. Micklethwaite[1-5]

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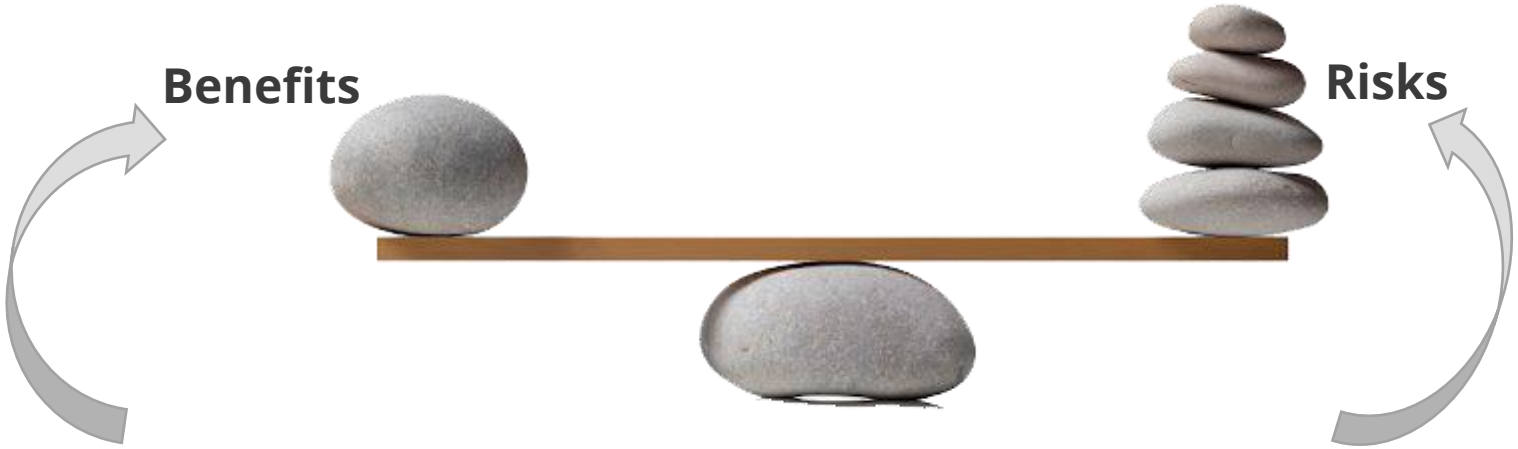
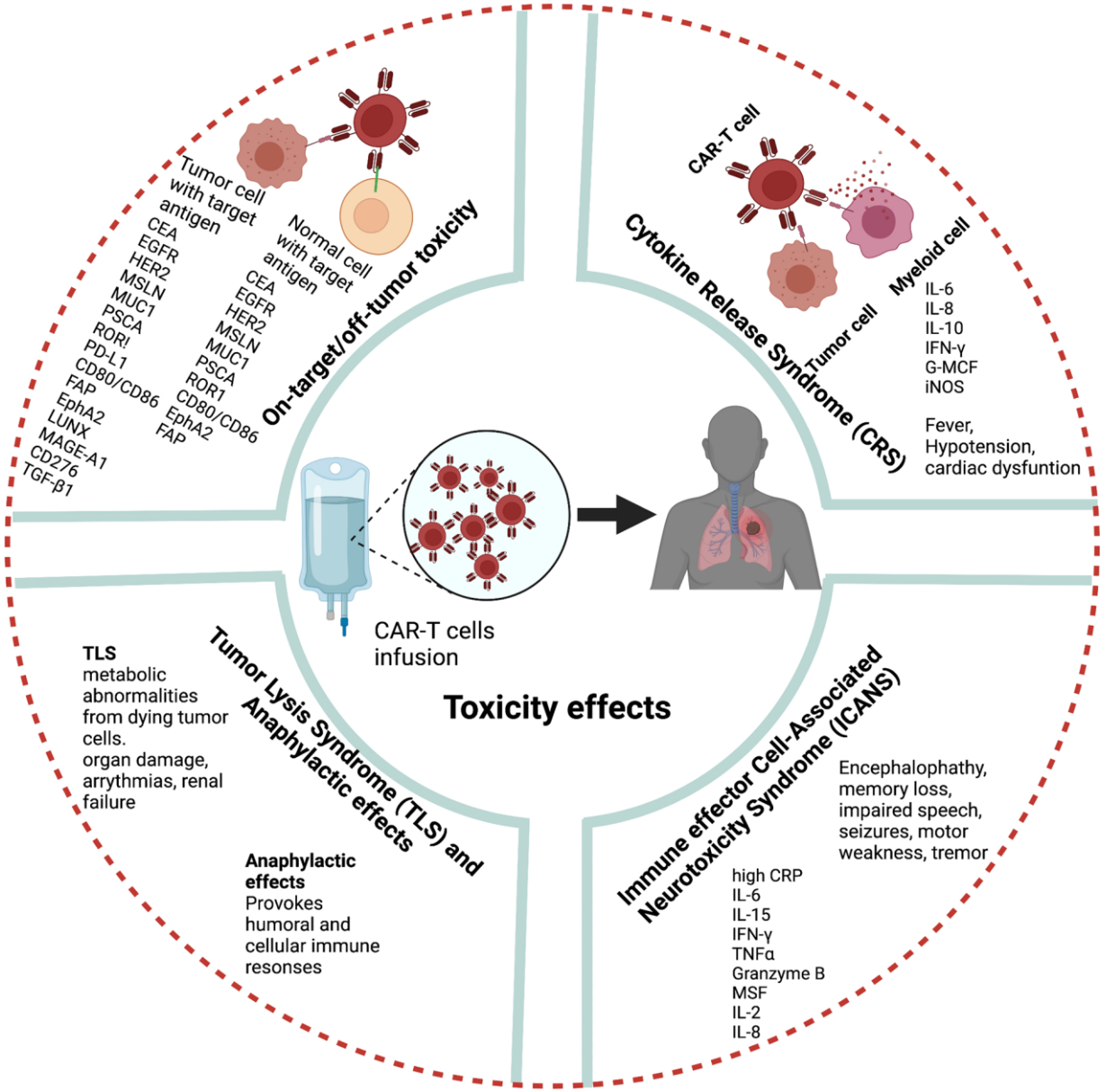
Assessing Benefit: Risk



Efficacy	Safety	Quality
Dynamics of efficacy (PD)	**Oncogenic potential**	Starting materials
Duration of efficacy	**Immunogenicity**	Stability and compatibility
Need/Option for re-administration	**Migration or distribution**	Comparability after process changes
Impact of safety parameters on efficacy (e.g., immunogenicity)	**Off-target effects**	Impurities and sterility

Need to balance regulatory compliance against resources

Unique Safety Considerations of CGT Products



Gene Therapy
Long-Term Follow-up
Clinical Trial Participants

Risk/Benefit

- Higher risk
- Safety and efficacy not proven

Unique Needs

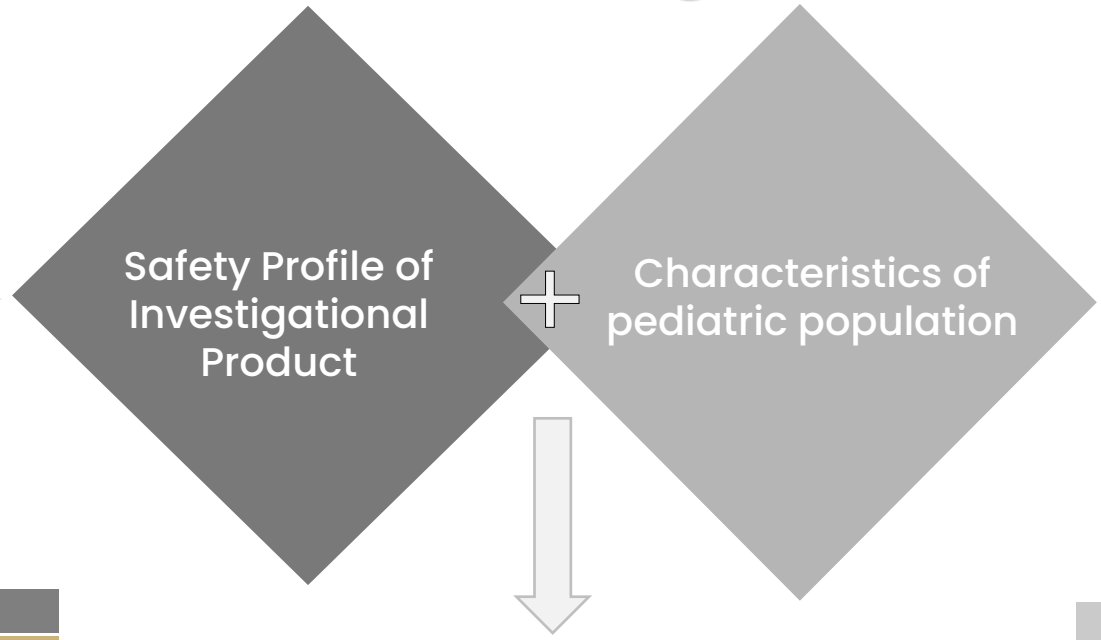
- Monitor and manage patients over an extended period
- Fewer interactions but still needs medical oversight
- Real-time information may influence ongoing trials

Challenge

- Monitoring patients over extended periods without increasing patient/site burden and still ensuring quality

The Relationship between Product Safety Profile, Pharmacovigilance, and Risk Mitigation

- Non-clinical safety data
- PK/PD (on & off-target)
- Pharmacogenetics
- Formulation (adverse reactions to excipients)
- Clinical Safety Reports
- Class effects (adverse drug reactions)
- Literature review on adverse drug reactions



- Age-corrected reference values (e.g., lab tests, vital signs, developmental assessment)
- Comorbidities
- Outcomes
- Limited availability of biosamples
- Limitations on invasive study procedures

Clinical Development

Pharmacovigilance

Safety Data
- Collection
- Analysis
- Reporting

Risk Mitigation
- Inclusion/Exclusion criteria
- Staggered enrollment
- Dose reduction/study design
- Stopping criteria
- Prohibited con-meds or treatments
- Safety monitoring
- DSMB

Pediatric Safety Profile

Pediatric Pharmacovigilance

Pediatric Risk Mitigation Strategies

Post-Market Approval

Pharmacovigilance
- Spontaneous reports

Risk Mitigation
- Prescribing information in the product label
- Educational tools
- REMS

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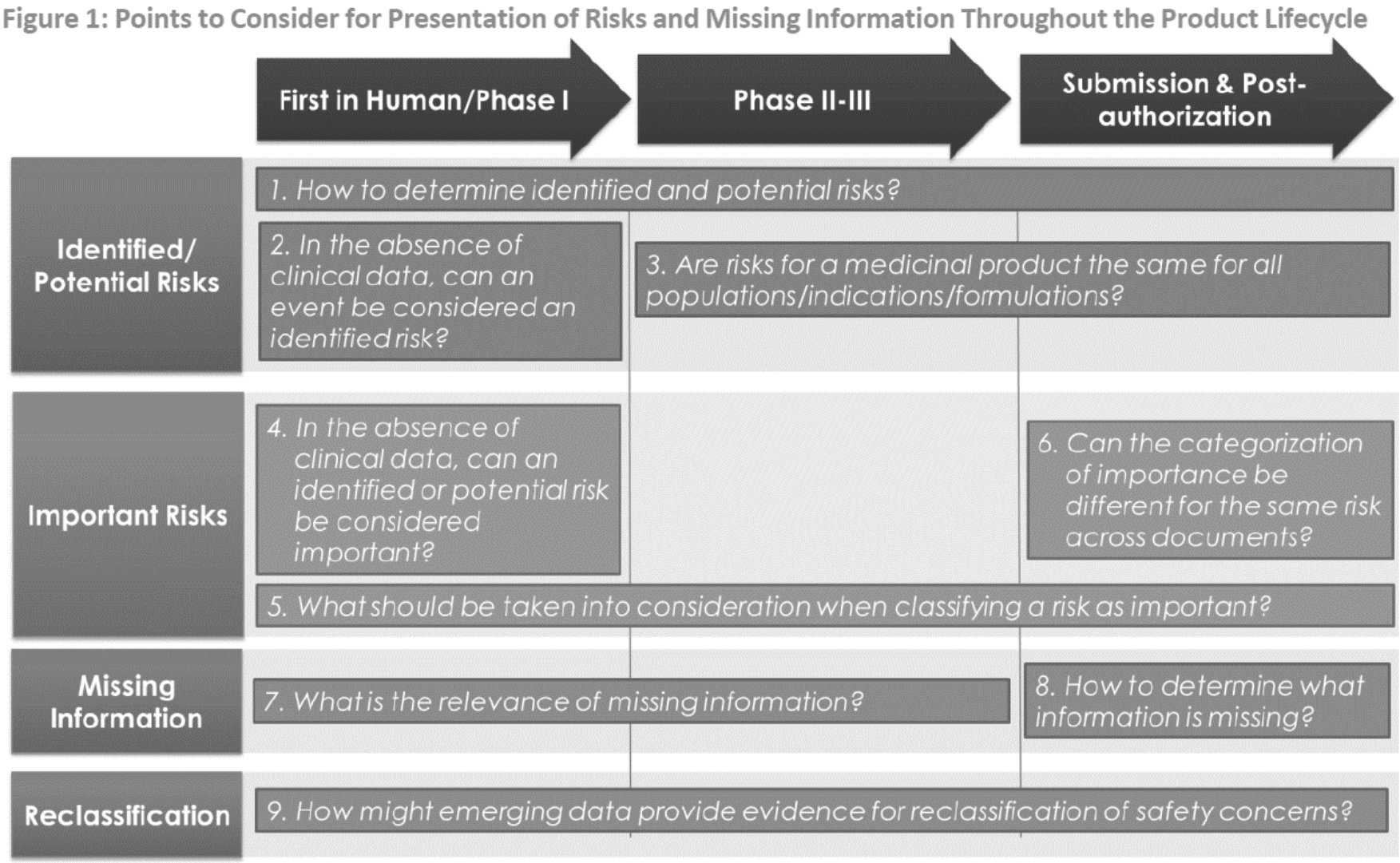
(Adapted from Aurich et al., *Br J Clin Pharmacol*. 2021

Definitions: What's in a name?

AEs of Special Interest (AESI)

Safety Concern

Comprehensive AEs and Potential Risks List (CAEPR)



Adapted from *Safety Assessment for IND Safety Reporting: Guidance for Industry* (FDA, 2015).

CPCI Protocol Committee

Establish PV best practice processes across CPCI sites

SPONSOR RESPONSIBILITIES

Person or entity responsible for the initiation and oversight of an investigational study

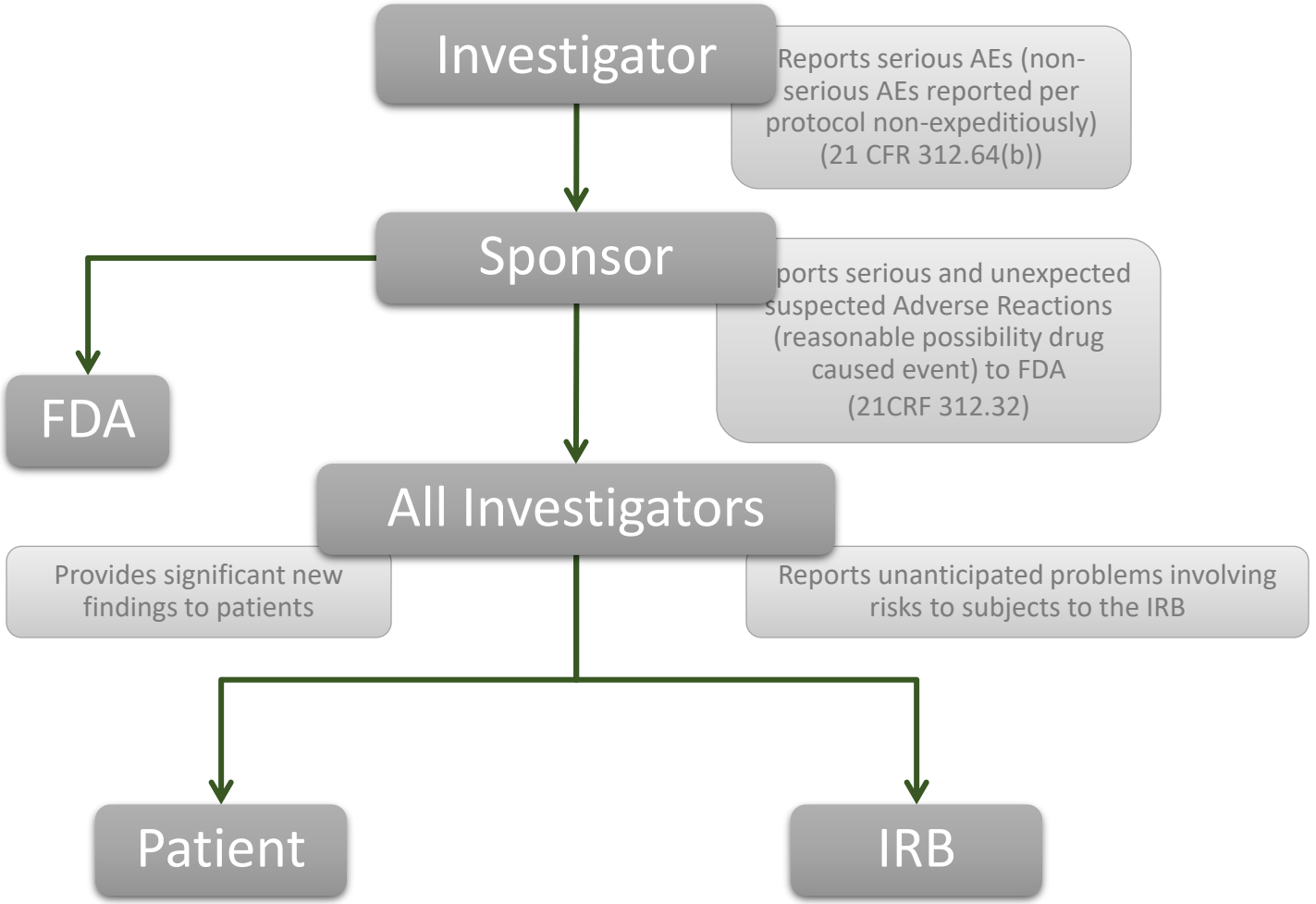
- Notification/Submissions to the regulatory authority(ies)
- Delegation of duties and functions, including site and investigator selection and training
- Medical expertise
- Trial design
- Maintaining all information on investigational products, including safety information
- ADR/unanticipated AE reporting
- Monitoring and auditing
- Trial and data management
- Quality assurance & quality control
- Management of investigator non-compliance

INVESTIGATOR RESPONSIBILITIES

Person responsible for the conduct of an investigational study

- Assurance of local IRB approval and communication
- Compliance with the protocol
- Ensuring investigator qualifications and adequate resources to conduct the study
- Protects the rights, safety, and welfare of participants
- Safety reporting to the sponsor and local IRB
- Progress and final reports to the sponsor

Different IND Framework among Sites


Investigator
Reports serious AEs (non-serious AEs reported per protocol non-expeditiously) (21 CFR 312.64(b))
Sponsor
ports serious and unexpected suspected Adverse Reactions (reasonable possibility drug caused event) to FDA (21CRF 312.32)
FDA
All Investigators
Provides significant new findings to patients
Reports unanticipated problems involving risks to subjects to the IRB
Patient
IRB

CPCI PV Toolbox

- ❑ Serious adverse event reporting
- ❑ Safety case handling (intake, process flow, assessment, documentation, archiving)
- ❑ Safety Database
- ❑ Review of patient (clinical/laboratory) data
- ❑ Aggregate data review
- ❑ Signal detection
- ❑ Regulatory reporting of safety information and 24-hour coverage

Assessment Tools:

- ❑ AE/SAE Reporting Template
- ❑ PI/Medical Monitor Form
- ❑ How to build a safety database

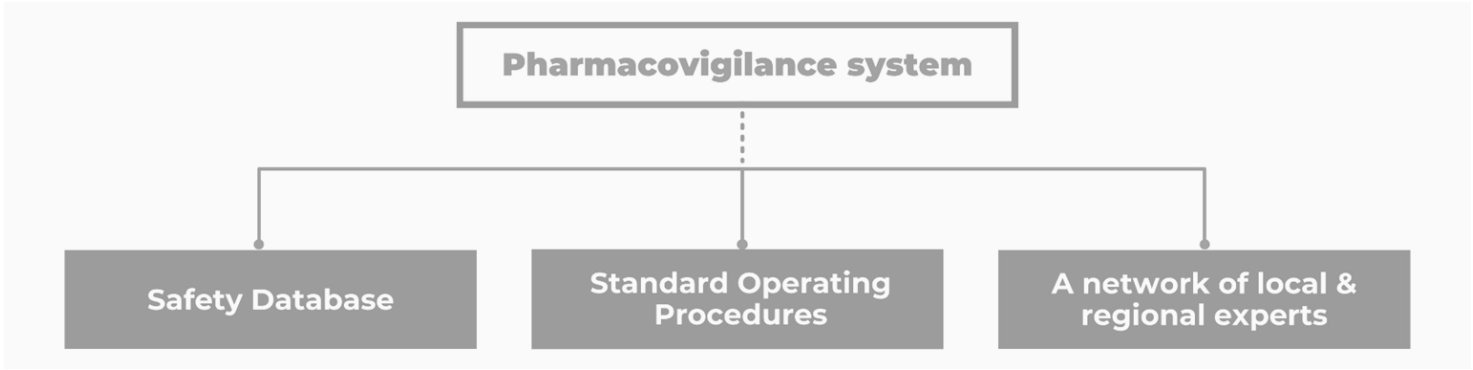
Risk Management Tools:

- ❑ Risk Management Plan (RMP) Template for CGT INDs
- ❑ DSMC Charter Template
- ❑ Investigator's Brochure Template
- ❑ Communication Templates (Dear Investigator Letter)
- ❑ Protocol-specific document

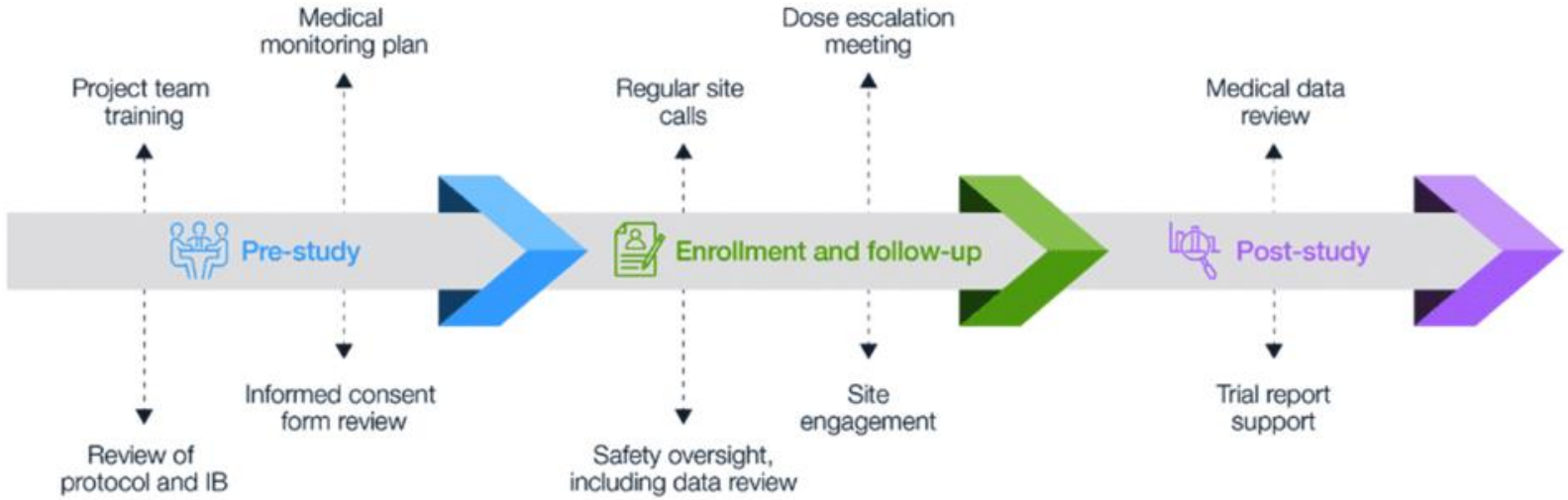
IND Safety & Pharmacovigilance Guidance Documents

- *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients – Guidance for Industry and IRBs 2020:* https://www.fda.gov/media/161740/download
- *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products:* https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm564952.pdf
- *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products – Draft Guidance for Industry, 2022:* https://www.fda.gov/media/156896/download
- *E2F Development Safety Update Report – Guidance for Industry, 2011:* https://www.fda.gov/media/71255/download
- *Ethical Considerations for Clinical Investigations of Medical Products Involving Children – Guidance for Industry, Sponsors, and IRBs (Draft Guidance):* https://www.fda.gov/media/161740/download
- *Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events:* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products
- *Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices (Draft Guidance) 2021:* https://www.fda.gov/media/152530/download
- *Long Term Follow-up After Administration of Human Gene Therapy Products – Guidance for Industry, 2020:* https://www.fda.gov/media/113768/download
- *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, 2013:* https://www.fda.gov/media/116754/download
- *Premarket Risk Assessment – Guidance for Industry:* https://www.fda.gov/media/71650/download
- *Safety Reporting Requirements for INDs and BA/BE Studies – Guidance for Industry and Investigators (2012):* *https://www.fda.gov/media/79394/download*
- *Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies (Draft Guidance) 2021:* https://www.fda.gov/media/150356/download

Conclusion



Continuum of Safety Monitoring throughout the product lifecycle



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THANK YOU

REDCap Safety Database

Summary of Database Development Work to Date

CPCI Annual Meeting

October 17, 2022

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Overview

SCTx Safety Data Overview

REDCap Safety Database - Core Version

REDCap Safety Database - Deluxe Version

Sneak peak

Development Status Update

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SCTx Safety Data Overview

Clinical Data

Data as recorded on the Adverse Events CRF, used by statistical team in all reports, abstracts, and manuscripts (Medidata Rave EDC -> .sas7bdat files)

Serious Adverse Event Report Forms (SAERFs)

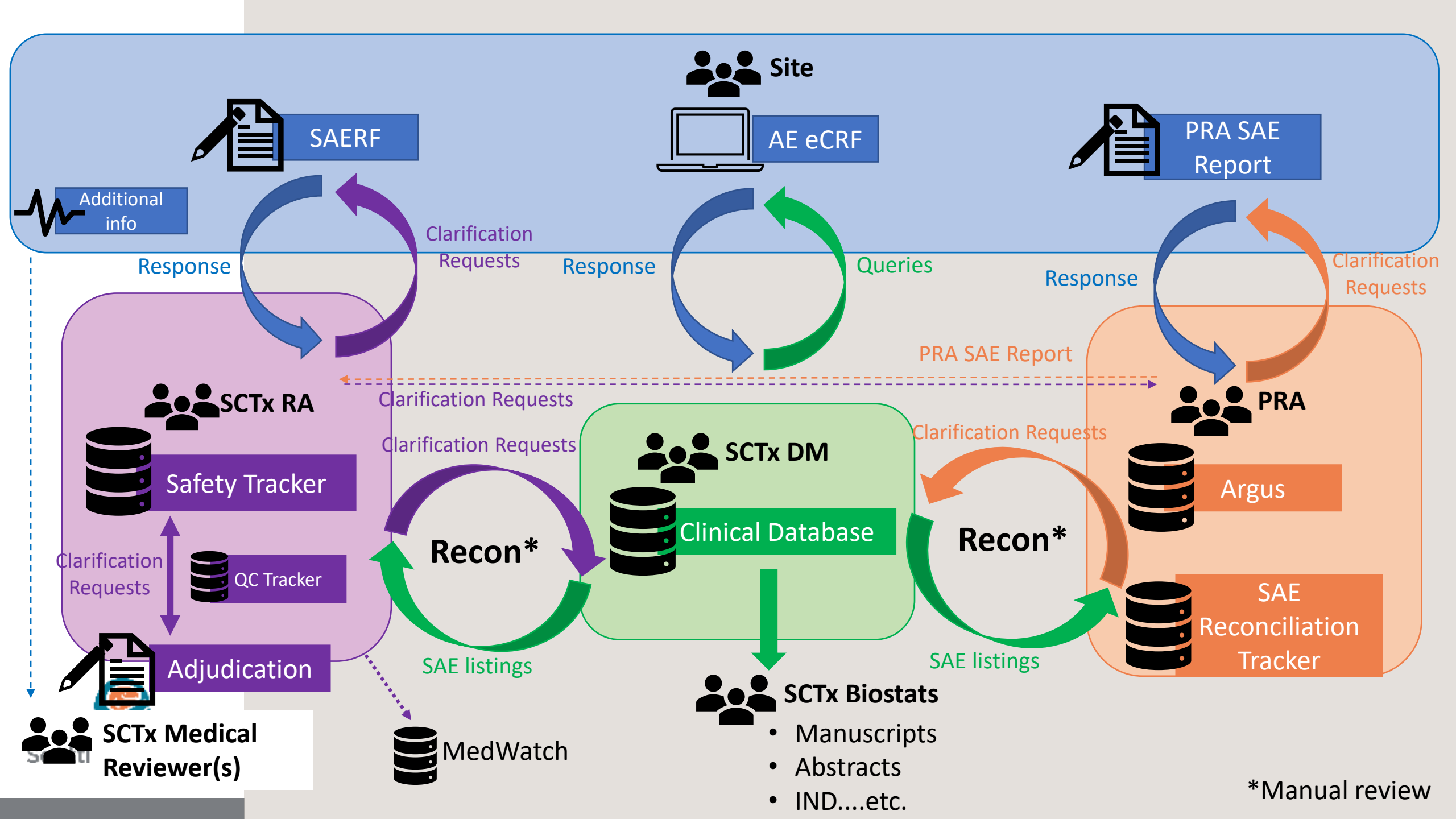
Data on serious adverse events as reported by site staff directly to QA/RA (.docx)

Adjudication Forms

Adjudication of serious adverse events as requested by QA/RA and recorded by medical monitors (currently Rebecca Gardner and Julie Park) (.docx)

Safety Tracker Data

Select data from SAERF and Adjudication. Used by Quality Assurance and Regulatory Affairs (QA/RA) to add case report number and to track PRA notification (if applicable), submission to MedWatch (if applicable), and adjudication status (.xlsx).


Site
SAERF
AE eCRF
PRA SAE Report
Additional info
Response
Clarification Requests
Response
Queries
Response
Clarification Requests
PRA SAE Report
Clarification Requests
SCTx RA
Clarification Requests
SCTx DM
Clarification Requests
PRA
Safety Tracker
Argus
Clarification Requests
QC Tracker
Recon*
Clinical Database
Recon*
SAE Reconciliation Tracker
Adjudication
SAE listings
SAE listings
SCTx Biostats
SCTx Medical Reviewer(s)
MedWatch
• Manuscripts
• Abstracts
• IND....etc.
*Manual review

Safety Data Overview

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REDCap®

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Core Version

- “Economy” Option
- Safety tracking database only
- Allows RA to input the data they normally would input into Excel into REDCap instead
- REDCap database export will look similar to Excel file previously used by RA

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Core Version

Advantages		Challenges
Simple, flat data structure		Manual data entry for new events
“Logging” capability (audit trail)		SAERF remains paper form
Customizable REDCap reports and exports		Adjudication remains paper form
REDCap data can be programmatically compared to clinical database (manual step removed)		Queries to site remain in email
Minimal data management required		

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Safety Data Overview

Clinical Data

Data as recorded on the Adverse Events CRF, used by statistical team in all reports, abstracts, and manuscripts (Medidata Rave EDC -> .sas7bdat files)

Serious Adverse Event Report Forms (SAERFs)

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Safety Tracker Data

Select data from SAERF and Adjudication. Used by Quality Assurance and Regulatory Affairs (QA/RA) to add case report number and to track PRA notification (if applicable), submission to MedWatch (if applicable), and adjudication status (.xlsx).

REDCap®

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Deluxe Version

- “Luxury”, bells and whistles version
- SAERF eForm
- Safety tracking database
- Adjudication form converted to eSurvey
- Data from SAERF directly populates fields in the Safety Tracker and the Adjudication Form (Investigator Section)

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Deluxe Version

Advantages	Challenges
“Logging” capability (audit trail)	Multiple reports with multiple events (complicated data structure)
Customizable REDCap reports and exports	Initial vs. Follow-up reports
REDCap data can be programmatically compared to clinical database (manual step removed)	REDCap training for sites and adjudicators
Greatest reduction in potential for data entry errors	High maintenance – requires data management
Clarification requests to site can be completed within REDCap Data Resolution Workflow	Scalability/size considerations
Tools for tracking adjudication survey responses	

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Sneak Peak – Core Version

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Record Status Dashboard (all records)

Displayed below is a table listing all existing records/responses and their status for every data collection instrument (and if longitudinal, for every event). You may click any of the colored buttons in the table to open a new tab/window in your browser to view that record on that particular data collection instrument. Please note that if your form-level user privileges are restricted for certain data collection instruments, you will only be able to view those instruments, and if you belong to a Data Access Group, you will only be able to view records that belong to your group.

Legend for status icons:

- Incomplete
- Incomplete (no data saved) ?
- Unverified
- Partial Survey Response
- Complete
- Completed Survey Response
- Many statuses (mixed)
- Many statuses (all same)

Dashboard displayed: [Default dashboard] Create custom dashboard

Displaying Data Access Group -- ALL --

Displaying record Page 1 of 1: "99991-S001" through "99994-SC of **20** records ALL (20) records per page

+ Add new record

Displaying: Instrument status only | Lock status only | All status types

TEST DATA

Subject Study ID:	Admin		Event
	Subject and Demography	T-cell Infusion(s)	Safety Tracker
99991-S001			
99991-S002			
99991-S003			
99991-S004			
99991-S005			
99992-S001			

Record Home Page

The grid below displays the form-by-form progress of data entered for the currently selected record. You may click on the colored status icons to access that form/event. If you wish, you may modify the events below by navigating to the Define My Events page.

Choose action for record

Legend for status icons:

- Incomplete
- Incomplete (no data saved)
- Unverified
- Partial Survey Response
- Complete
- Completed Survey Response
- Many statuses (mixed)
- Many statuses (all same)

Subject Study ID: **99991-S002**

001 - Seattle Children's Hospital

TEST DATA

Data Collection Instrument	Admin	Event 12-10-2018,Anemia (#1)	12-11-2018,White blood cell decreased (#2)	12-16-2018,White blood cell decreased (#3)	+ Add new 12-23-2018,White blood cell decreased (#4)
Subject and Demography	●				
T-cell Infusion(s)	●				
Safety Tracker		●	●	●	●
Delete all data on event:	×	×	×	×	×

Subject and Demography

TEST DATA

Data Access Group: **001 - Seattle Children's Hospital** ?

Editing existing Subject Study ID: **99991-S002**

Event Name: **Admin**

Subject Study ID:	99991-S002 To rename the record, see the record action drop-down at top of the Record Home Page.
Study Number	BRAINCHILD-01
Site Name	001 Seattle Children's Hospital
Date of Birth	08-01-2010 Today M-D-Y
Age	8 View equation
Sex	○ Male ● Female reset
Form Status	
Complete?	Complete
Lock this instrument? If locked, no user will be able to modify this instrument for this record until someone with Instrument Level Lock/Unlock privileges unlocks it.	☐ Lock

Save & Exit Form | Save & ...

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T-cell Infusion(s)

TEST DATA

Data Access Group: **001 - Seattle Children's Hospital** ?

Editing existing Subject Study ID: **99991-S002**

Event Name: **Admin**

Subject Study ID:	99991-S002
T-cell Infusion Date 1	12-01-2018 Today M-D-Y
Add another infusion date?	Yes / No reset
T-cell Infusion Date 2	12-01-2021 Today M-D-Y
Add another infusion date?	Yes / No reset
Form Status	
Complete?	Complete
Lock this instrument? If locked, no user will be able to modify this instrument for this record until someone with Instrument Level Lock/Unlock privileges unlocks it.	Lock

Save & Exit Form | Save & ... | -- Cancel --

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Safety Tracker

TEST DATA

Data Access Group: **001 - Seattle Children's Hospital**

Editing existing Subject Study ID: **99991-S002**

Event Name: **Event** (Instance #2)

Subject Study ID:	99991-S002
Case Number	PL992018_00002
Infusion dates per Case Report Forms:	2018-12-01,2021-12-01,,,
Date of last dose prior to SAE:	12-01-2018 Today M-D-Y
Last Dose Prior to SAE:	36.8
Age at Infusion	8 View equation
Action taken i.e. infusions d/c	(●) Dose not changed ( ) Dose reduced ( ) Drug withdrawn ( ) Not applicable ( ) Unknown reset
Adverse Event Term	White blood cell decreased

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Sneak Peak – REDCap Export

TEST DATA

	A	E	F	G	H	I	J	K	L	M	N	O	P
1	Subject Study ID:	Case Number	Infusion dates per Case Report Forms:	Date of last dose prior to SAE:	Last Dose Prior to SAE:	Age at Infusion	Action taken i.e. infusions d/c	Adverse Event Term	Preferred Term (PT)	Adverse Event a baseline toxicity	Event Onset Date	Event End/ Resolution Date	Initial/ Follow-up
2	99991-S002	PL992018_00001	2018-12-01,2021-12-01,,,	12/1/2018	36.8	8	Dose not changed	Anemia	Anemia	No	12/10/2018	12/22/2018	Initial
3	99991-S002	PL992018_00002	2018-12-01,2021-12-01,,,	12/1/2018	36.8	8	Dose not changed	White blood cell decreased	White blood cell decreased	Yes	12/11/2018	12/15/2018	Initial
4	99991-S002	PL992018_00003	2018-12-01,2021-12-01,,,	12/1/2018	36.8	8	Dose not changed	White blood cell decreased	White blood cell decreased	No	12/16/2018	12/22/2018	Follow-up
5	99991-S002	PL992018_00002	2018-12-01,2021-12-01,,,	12/1/2018	36.8	8	Dose not changed	White blood cell decreased	White blood cell decreased	No	12/23/2018	12/30/2018	Follow-up
6													
7													

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Development Status Update

Core Version

- Core validation of SCTx REDCap instance (v12.4.16) underway
- Database development concurrent with validation work
- REDCap project validation testing, user acceptance testing pending
- SOP development pending
- Goal go-live date: Q1 2023

Deluxe Version

- To be developed from the core version

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SCTx Global CRF Library

CPCI Annual Meeting

October 17, 2022

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Overview

Background

GLIB Development Process

GLIB Development Status Update

What's Next

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Background

Global Library

A digital repository of data collection instruments such as electronic case report forms (eCRFs) within a clinical data management system, along with their associated programming elements.

- Forms (eCRFs)
- Folders (visits)
- Data dictionaries
- Unit Dictionaries
- Matrices
- Edit checks
- Derivations
- Custom functions

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Background

Benefits

- Time-saving
- Cost-saving
- Standardized data
- Ease of programming
- Reduced site burden
- Reduced CRA and staff burden
- Enhanced data quality

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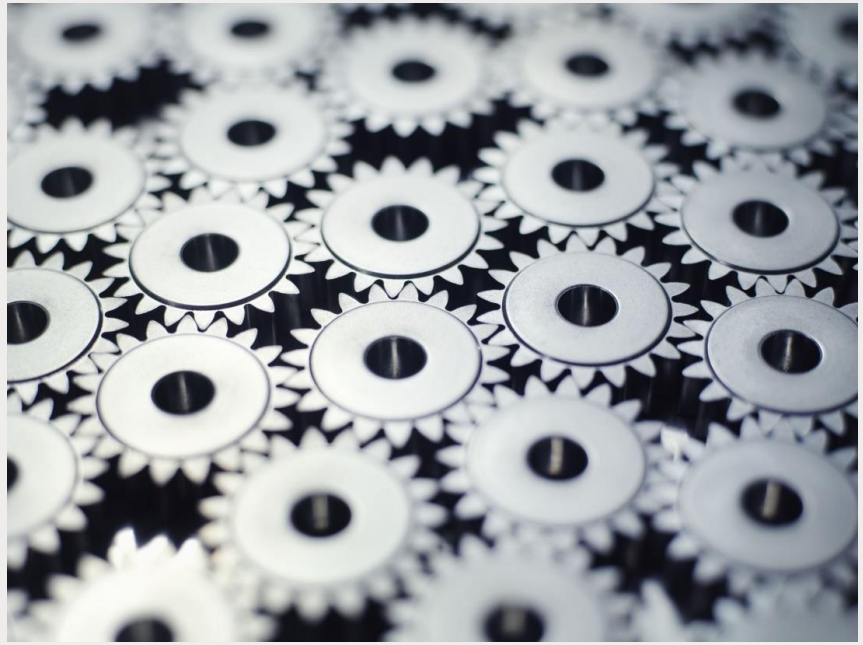
Background

Challenges

- Requires consensus on standards
- Alignment across programs, functional areas
- Protocol language
- Specialized data collection



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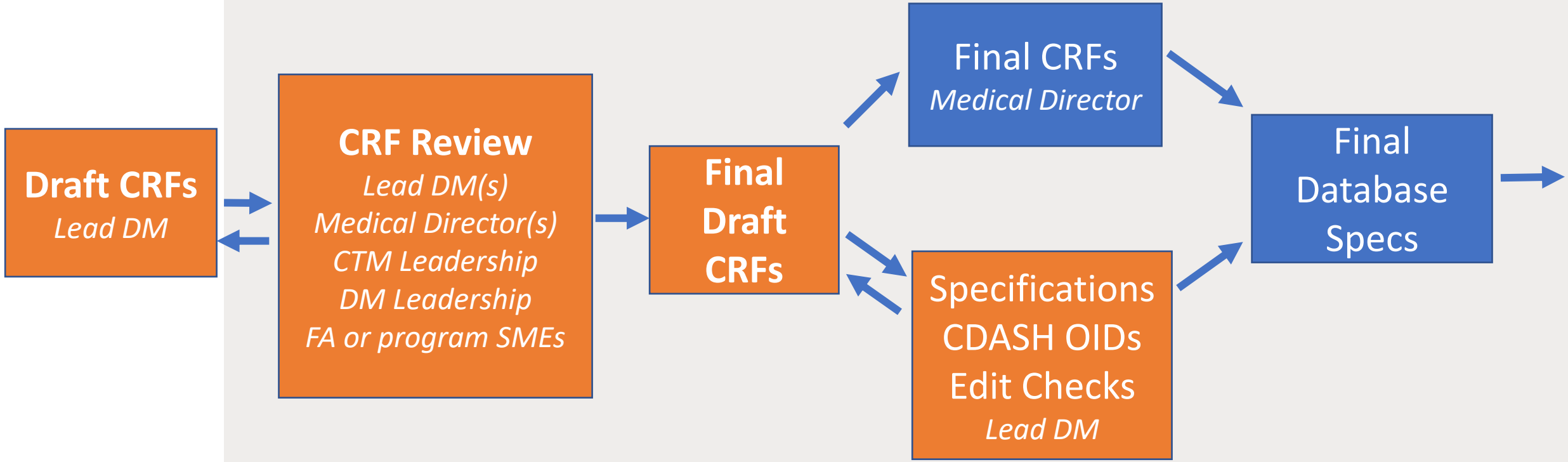
GLIB Development Process



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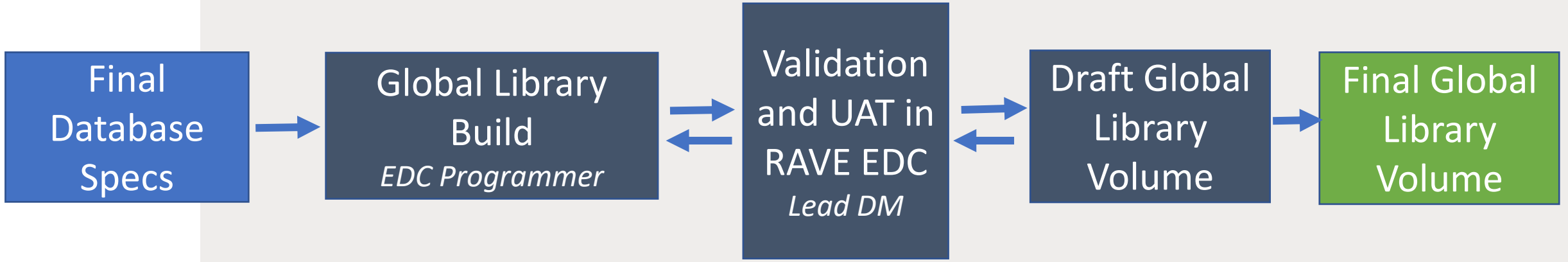
GLIB=Global library, CTM=Clinical Trial Management, DM=Data Management, FA=Functional Area, SME=Subject Matter Expert, CDASH=Clinical Data Acquisition Standards Harmonization, OID=Object ID

GLIB Development Process (cont.)



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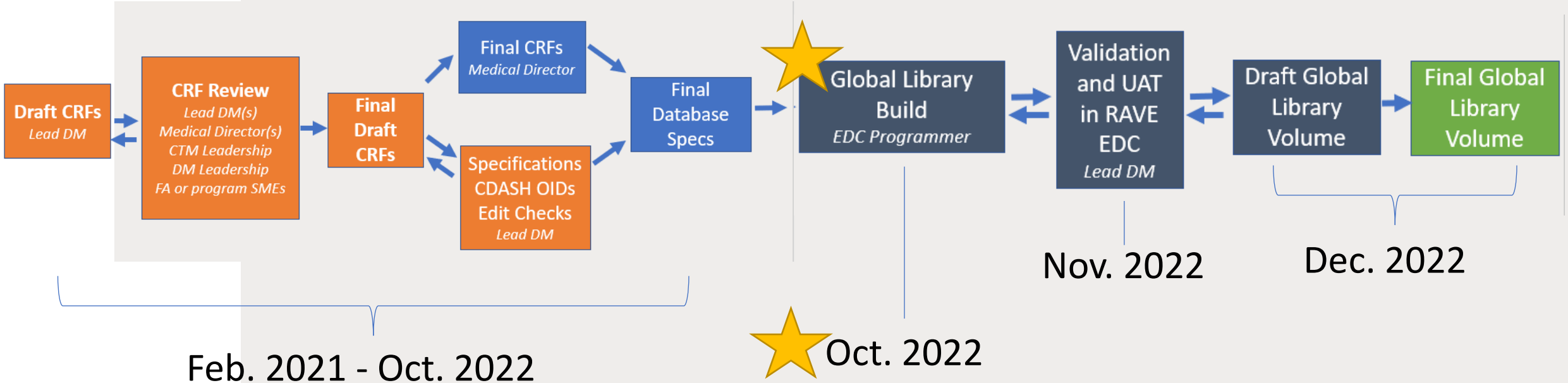
GLIB=Global library, EDC=Electronic Data Capture, DM=Data Management

GLIB Development Status Update



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What's Next

- **Program-specific global libraries**
  - Brain – December 2022
  - Solids – January 2022
  - Leukemia and Lymphoma – February 2022
- **First revision to the Core library**
- **Documentation**

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Extra content 1 – CRF Layout

	A	B	C	D	E
1	**Physical Exam and Vital Signs**				
2					
3	**Physical Exam**				
4	Was a physical exam done?	oYes oNo oN/A			
5	Date of physical exam	MM/DD/YYYY			
6	Was height assessed?	oYes oNo oN/A			
7	If Yes, height	___ [unit drop-down]			
8	Was weight assessed?	oYes oNo oN/A			
9	If Yes, weight	___ [unit drop-down]			
10	**Vital Signs**				
11	Was temperature assessed?	oYes oNo oN/A			
12	Was heart rate assessed?	oYes oNo oN/A			
13	Was respiratory rate assessed?	oYes oNo oN/A			
14	Was blood pressure assessed?	oYes oNo oN/A			
15	Was pregnancy test done?	oYes oNo oN/A			
16	Was pulse oximetry assessed?	oYes oNo oN/A			
17	Comments	[free-text]			
18					
19					
20					
21					
22					
23					
24					

CRF Layout | CRF Specifications | Data Dictionaries | Edit Checks

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Extra content 2 – GLIB Dev Status tracker

	A	B	C	D	E	F	G	H
1	**GLIB Dev Status**							
2								
3		Applicable Programs				Pre-programming Specifications		
4	CRF Name	All	Solid	Brain	Leukemia Lymphoma	CRF Specifications/ Layout	CDISC OIDs	Edit Checks Specifications
5	Active Medical Conditions	X				Final	Final	Ready for review
6	Additional Assessments	X				Not Started	Not Started	Not started
7	Adverse Events	X				Final	Final	Ready for review
8	Anatomic Imaging	X				Final	Final	N/A
9	Apheresis	X				Final	Final	Ready for review
11	Bridging Therapy: Chemotherapy/Targeted Agents	X				Final	Final	Ready for review
12	Bridging Therapy: Radiation	X				Final	Final	Ready for review
13	Bridging Therapy: Surgery or Therapeutic Procedures		X	X		Final	Final	Ready for review
16	Cell Product Generation	X				Final	Final	Not started
17	Cell Product Generation Details	X				Final	Final	Not started
18	Chemistry Lab	X				Final	Final	Not started
19	Concomitant Medications	X				Final	Final	Ready for review
20	Correlative Studies	X				Under review	Not Started	Not started
21	CSF Lab	X				Final	Final	Not started
22	Cytokine Release Syndrome	X				Final	Final	Ready for review
23	Cytokine Release Syndrome Labs	X				Final	Final	In progress
24	Demographics	X				Final	Final	Ready for review

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Aim 2
Patient Advocacy Committee

Anurag Agrawal

CPCI

Consortium for Pediatric Cellular Immunotherapy

Ensure cellular therapy trial development includes discussion and strategies to ensure equitable access, with input by families about what is important to them

Membership

- Anurag Agrawal, MD — *Pediatric Hematologist-Oncologist - BCHO*
- Paibel Aguayo-Hiraldo, MD — *Pediatric Hematologist-Oncologist - CHLA*
- Lourdes Baezconde-Garbanati, PhD — *Director, Community Outreach and Engagement; Associate Dean, Community Initiatives, Keck SOM – USC*
- Tumaini Coker, MD, MBA — *Research Director, Center for Diversity and Health Equity – SCRI*
- Dana Dornsife — *Founder and Chair - Lazarex Cancer Foundation*
- Devan Duenas, MA — *Clinical Research Coordinator, Treuman Katz Center – SCRI*
- Anurekha Hall, MD — *Pediatric Hematologist-Oncologist – SCRI*
- Amy Keating, MD — *Pediatric Hematologist-Oncologist – CHC*
- Adam Lamble, MD — *Pediatric Hematologist-Oncologist – SCRI*

Membership

• Jonathan Marron, MD, MPH	*Pediatric Hematologist-Oncologist, Director of Clinical Ethics, Harvard Medical School Center for Bioethics*
• Diana Merino Vega, PhD	*VP Advocacy – Childhood Cancer Survivor Canada*
• Julie Park, MD	*Bushnell, Towne and Wilkerson Endowed Chair in Pediatric Neuroblastoma; Medical Director, ICC - SCRI*
• Bonnie Ramsey, MD	*Director, Center for Clinical and Translational Research; Associate Director, Pediatric Clinical Research Center - SCRI*
• Anant Vatsayan, MBBS	*Blood and Marrow Transplantation – CNH*
• Mark Walters, MD	*Director, Blood and Marrow Transplantation Program – BCHO*
• Ben Wilfond, MD	*Investigator, Treuman Katz Center for Pediatric Bioethics – SCRI*
• Lena Winestone, MD, MSHP	*Pediatric Hematologist-Oncologist - UCSF*

Accomplishments

1

Completion of retrospective dataset manuscript

2

Completion of referring provider surveys and interviews

3

Completion of caregiver surveys and interviews

Accomplishments

4

Completion of manuscript for retrospective data project

Overview of Works In Progress

- Retrospective review of ALL patients treated at consortium institutions
- Survey/interviews of patients/families that have undergone CAR-T trials at consortium sites (Anu H)
- Survey/interviews of providers that have referred to consortium sites for CAR-T trials (Anu H)
- State-level survey of CAR-T coverage (Anu A)

Goal	Metric
Completion of caregiver and referring provider interviews	Completed October 2022
Analysis of caregiver and referring provider surveys	Completed December 2022
Analysis of caregiver and referring provider interviews	Completed December 2022
Completion of caregiver manuscript	Completed March 2023

Goal	Metric
Completion of referring provider manuscript	Completed March 2023 (Note: Discuss joint submission with caregiver manuscript)
Analysis of insurance landscape	
Development of policy statement based on insurance landscape data	Completed December 2022
Submission of additional grant applications	Completed March 2023

Goal	Metric
Collaboration with additional consortia	

Forum Discussion

Discussion

Thoughts regarding survey and interview data to date (LW and JM)

- Potential impact on future trial design
- Additional resources at the referring institution level
- Additional resources for potential families interested in clinical trials

Discussion

- Additional stakeholders
- Possible additional projects or grant opportunities
- Development of educational materials
- Opportunities to collaborate with other consortia

Discussion

Beyond the 5-year grant period

- Using the Real World consortium as a model for patient advocacy
- Other grant opportunities or consortia with whom to collaborate
- CIRM for other similar disease processes

Aim 3
Correlative Working Group

Ashley Wilson

CPCI

Consortium for Pediatric Cellular Immunotherapy

Enhance rigorous assessment of key biologic correlates uniquely associated with cellular immunotherapy mechanism(s) of action in conjunction with safety and outcome metrics

Develop reproducible sample collection and process standards for use across Consortium trials

Apply a web-based data platform for the integration, analysis visualization and sharing of data across sites

Establish outcome measures to assess safety, efficacy and promote rapid translation of findings

Membership
Correlative & Biobank Working Groups

- Hisham Abdel-Azim, MD, MS — *Pediatric Hematologist-Oncologist – CHLA*
- Jennifer Cotter, MD — *Director, Pediatric Biorepository, Neuropathologist – CHLA*
- Anushree Datar, MS — *Cell Therapy Lab Lead – CNH*
- Amy Hont, MD — *Pediatric Hematologist-Oncologist – CNH*
- Wenjun Huang, PhD — *Supervisor, Data Scientists – SCTx*
- Kimberly Jordan, PhD — *Assistant Director, Human Immunology & Immunotherapy Initiative – CU*
- Monica Mendez — *Manager, Pediatric Biorepository – CHLA*
- Angela Minic, MS — *Project Manager, Human Immunology & Immunotherapy Initiative – CU*
- Julie Saba, MD, PhD — *Professor of Pediatrics – UCSF*
- Keri Toner, MD — *Pediatric Hematologist-Oncologist – CNH*
- Ashley Wilson, PhD — *Director, Therapeutics Correlative Science – SCTx*
- Silvia Yu — *Front End Developer – SCTx*

Accomplishments

1

Manuscript published in *Cytotherapy* that summarizes best practices for **peripheral blood** collection and processing across multicenter pediatric cell therapy trials

2

Biobank Working Group shared SOPs and hosted discussions related to **specimen management**, storage, and labeling practices

3

SCTx BBWG designed a cloud-based biobank request workflow in **LabKey**, integrating clinical and correlative data

4

CNS Working Group created to focus on best practices for collection, processing, and analysis of **CSF** within the context of cell therapy for pediatric **CNS tumors**

CPCI

Biobanking SOPs shared between CPCI sites

Storage/Equipment/Operations:

- Temperature and equipment monitoring
- Refrigerator and freezer maintenance
- Storage of cell therapy products and samples
- Emergency response and contingency plans related to storage or equipment failure
- Deviation Reporting

Research Sample/Data Movement:

- Request and release of specimens and data
- Retrieval and internal distribution of specimens and associated data
- Clinical annotation practices
- Sample transfers to external parties
- Sample labelling and tracking

Gap analysis: Correlative specimen storage

	SCH	CNMC	CHLA
Freezer Monitoring System	AeroScout	Isensix	Isensix
Storage Location	Lab space	Hospital space	Lab space
Specimen Management Software	FreezerPro	FreezerPro in progress, currently using centralized databases	BSI (biospecimen inventory)
Setup Responsibility	Facilities	Facilities	Facilities
Monitoring Responsibility	Lab	Lab	Lab
Cadence	-	-	2x/day
Weekly check ups	-	-	Manually check freezers 3x/week
Escalation path established	Yes	Yes	Yes
Capacity	Yes	Yes	Yes
Back-up plan	Yes	Yes	Yes
Biospecimens being stored	PBMC, Serum, CSF	PBMC, Plasma	Tissue in OTC, urine, BMA
Tissue temp	FFPE at RT	FFPE at RT	RT or Frozen
RNA analysis temp	4C	-	-
Samples in/out of freezers	Recorded in FreezerPro	Annotate centralized lab database for correlative samples (more formal GMP process for products)	Request thru BSI, reserve samples or note sample usage
Sample transfer process	Yes	No	Yes
Training	Grow@SC coursework, 1-on-1, R/U for SOPs, technical training 3 sessions	No formal coursework, mostly 1-on-1, GMP has formalized technical training on SOPs, competency check	Media lab courses to begin bench work and 1-on-1 training, R/U for related SOPs, competency checklist

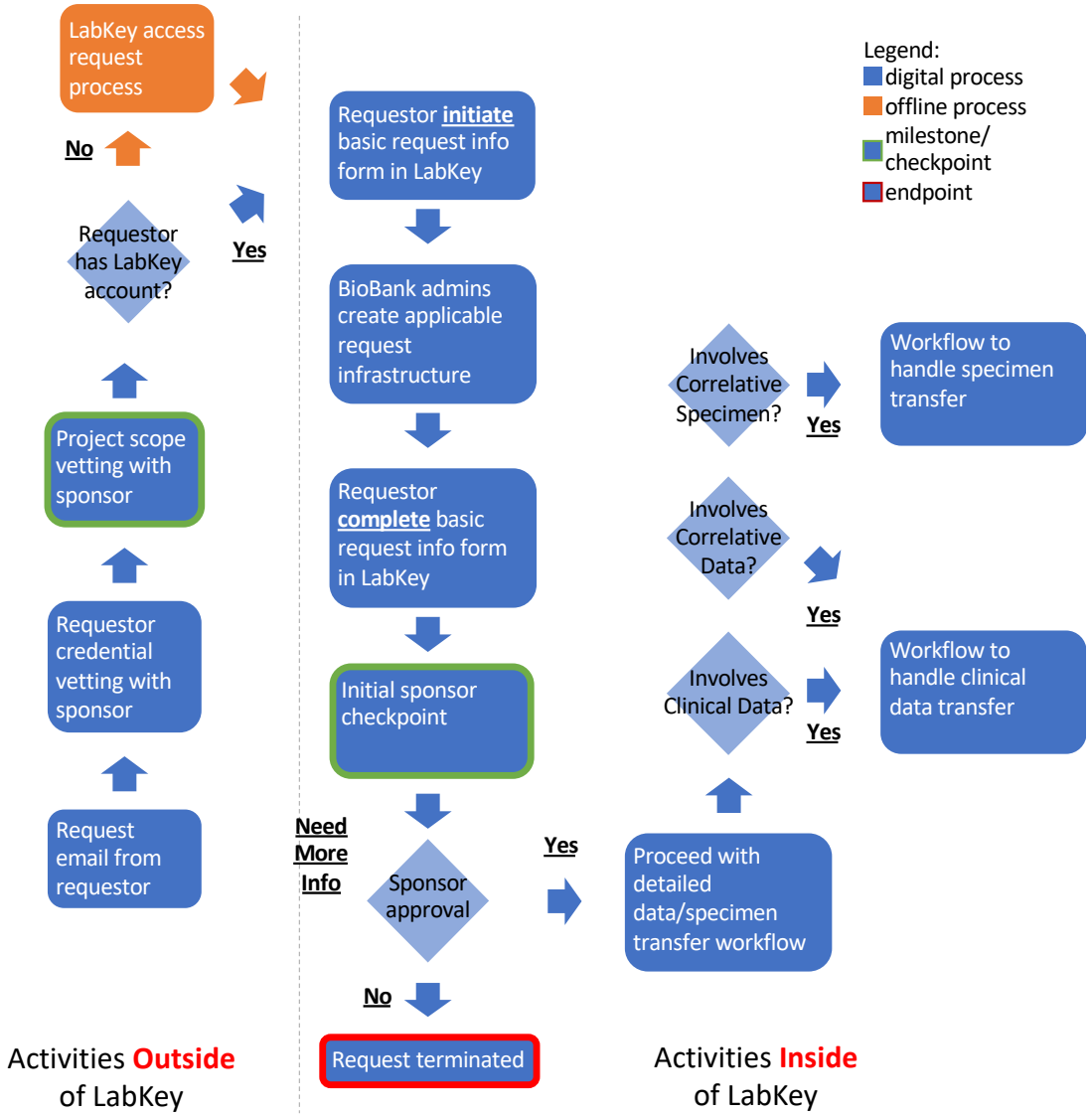
Troubleshooting Discussions

1. Correlative sample labeling practices

2. Barcoding and sample tracking

3. Correlative studies in line with protocol objectives vs biobanking

Digital Biobank Request Workflow



Lessons Learned

1. Alignment on sample and data sharing practices in advance by all parties.

2. Criteria for what constitutes protocol objectives vs exploratory biobanking.

3. Consent issues for genomic testing related to future research.

4. Consistency in sample labelling (or barcoding) and tracking throughout collaboration.

5. Defined clinical annotation practices and integration with correlative data.

Biobanking and LabKey

Goal	Metric
Develop LabKey biobank request workflow SOPs and a biobank administrator guide to aid admins/users	Share SOPs with CPCI sites
Continue to leverage LabKey to link specimen inventory to correlative and clinical data	SOP created linking FreezerPro and LabKey related workflows
Increase biobanking and specimen management at one CPCI site through dissemination of SOPs	One CPCI site has enhanced ability to share biobanked specimen with an external site

Membership: Pediatric CNS Working Group

• Shahab Asgharzadeh, MD	*Director, Neuroblastoma Basic and Translational Program – CHLA*
• Erin Crotty, MD	*Pediatric Neuro-Oncologist – SCH*
• Tom Belle Davidson, MD	*Pediatric Neuro-Oncologist – CHLA*
• Eugene Hwang, MD	*Associate Division Chief, Oncology; Pediatric Neuro-Oncologist – CNH*
• Sabine Mueller, MD, PhD	*Professor of Neurology, Neurosurgery and Pediatrics – UCSF*
• Julie Park, MD	*Chief Medical Officer – SCTx*
• Brain Rood, MD	*Director, Clinical Neuro-Oncology; Pediatric Neuro-Oncologist – CNH*
• Sophia Tahiri	*Graduate Student – SCRI*
• Nick Vitanza, MD	*Pediatric Neuro-Oncologist; CNS CAR T Cell Lead, SCTx*
• Leo Wang, MD, PhD	*Pediatric Hematologist-Oncologist – COH*
• Ashley Wilson, PhD	*Director, Therapeutics Correlative Science – SCTx*

CNS CSF Analytics

Goal	Metric
Develop best practices for collection, processing and analysis of CSF within the context of pediatric cell therapy trials	Share a consensus SOP with CPCI sites
Write a review article summarizing current literature and recommendations for CSF correlative studies for pediatric cell therapy CNS trials	Publish a review article in *Current Oncology Reports*
Continue to generate datasets with CSF samples to identify biomarkers of CAR bioactivity, safety and toxicity	Identify at least 1 biomarker

Current Oncology Reports – proposed outline

INTRO

1. General background of cell therapy for pediatric CNS tumors
2. Brief review of preclinical and clinical experience with cell therapy
3. Brief review of current Phase 1 clinical practice (supportive care metrics, survival endpoints, and QOL)

BODY

1. CSF Cytokine/chemokine correlatives and molecular endpoints (flow and PCR)
2. Neuro-imaging and radiographic endpoints
3. CSF proteomics

CONCLUSION

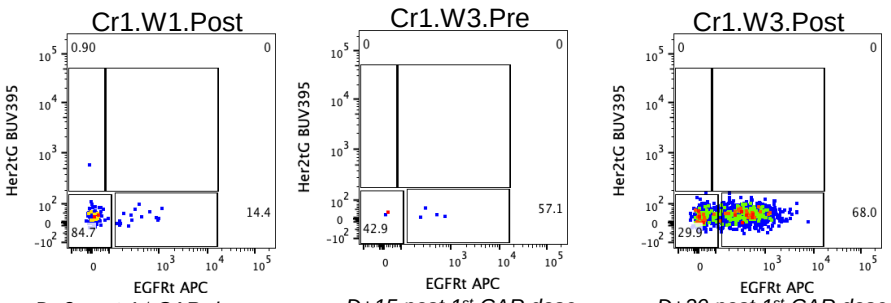
Future clinical trial directions and alignment of data collection across sites

Figures/Tables:

1. Graphical abstract/CSF analytics schema
    - Collection of CSF, processing for downstream assays (flow, cytokine, proteomics)
2. Table 1: Current CAR T cell trials for pediatric brain tumors

CSF analytics - pediatric cell therapy trials for CNS tumors

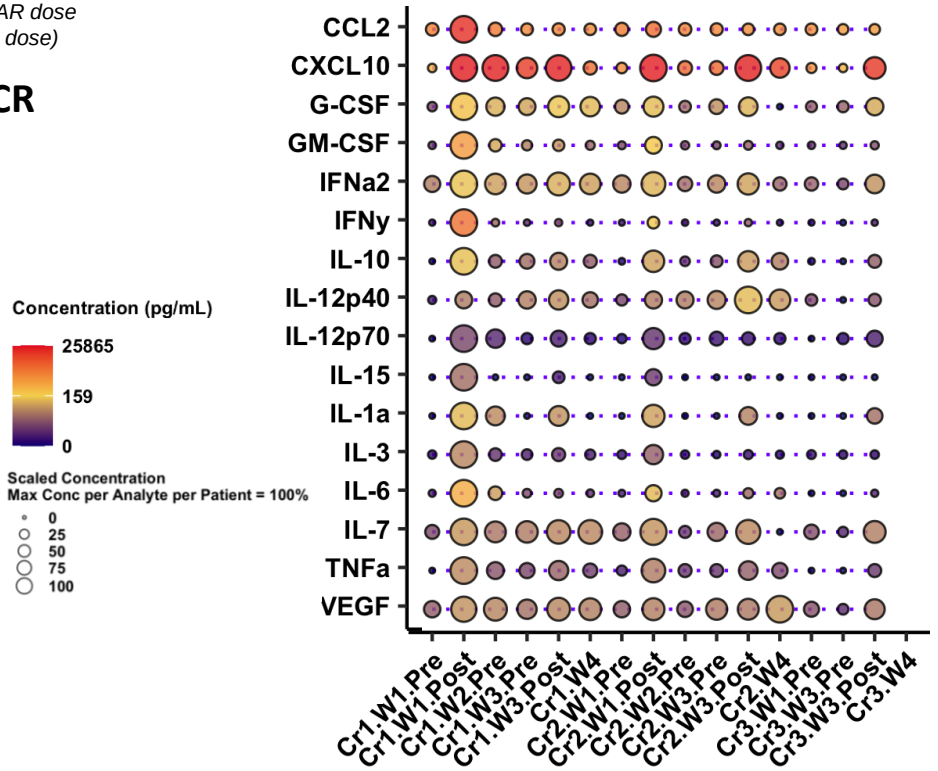
1. CAR T cell detection



D+2 post 1st CAR dose | *D+15 post 1st CAR dose (prior to 2nd CAR dose)* | *D+20 post 1st CAR dose (after 2nd CAR dose)*

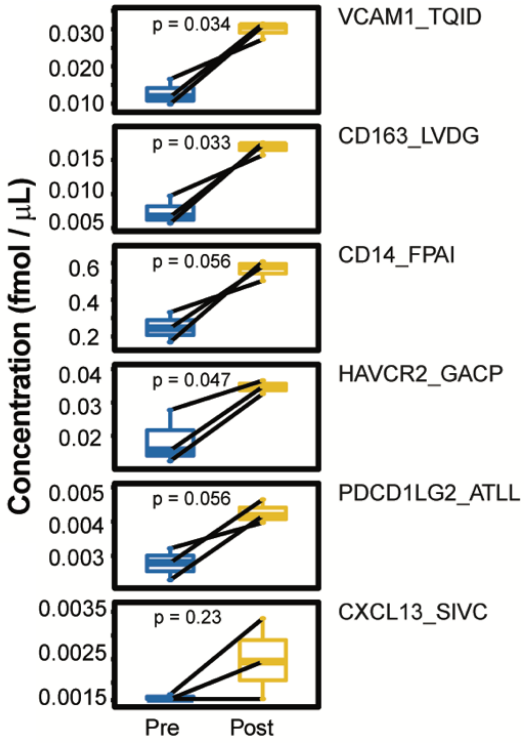
CARs via flow vs CAR DNA via FLAP ddPCR/qPCR

2. Cytokines/chemokines



CSF (local) vs serum (peripheral) responses

3. Proteomics

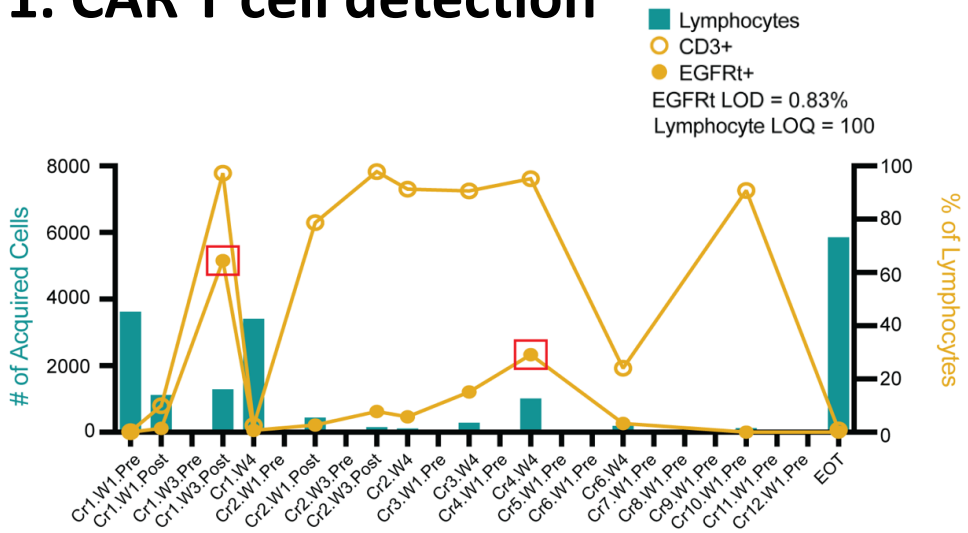


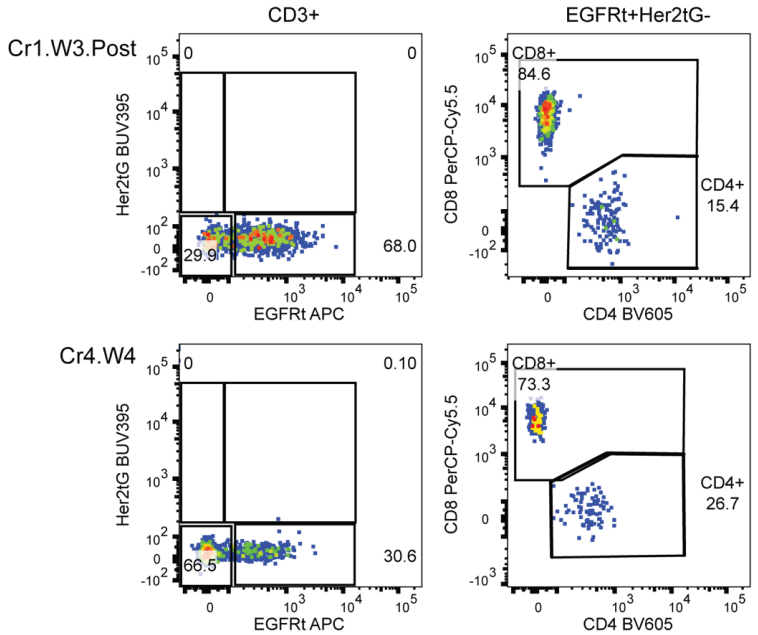
CSF matched pre/post infusion timepoints

Images adapted from Vitanza, Wilson, Huang, et al. ***Cancer Discovery***, 2022 (accepted)

BrainChild CSF correlatives: what are we learning so far?

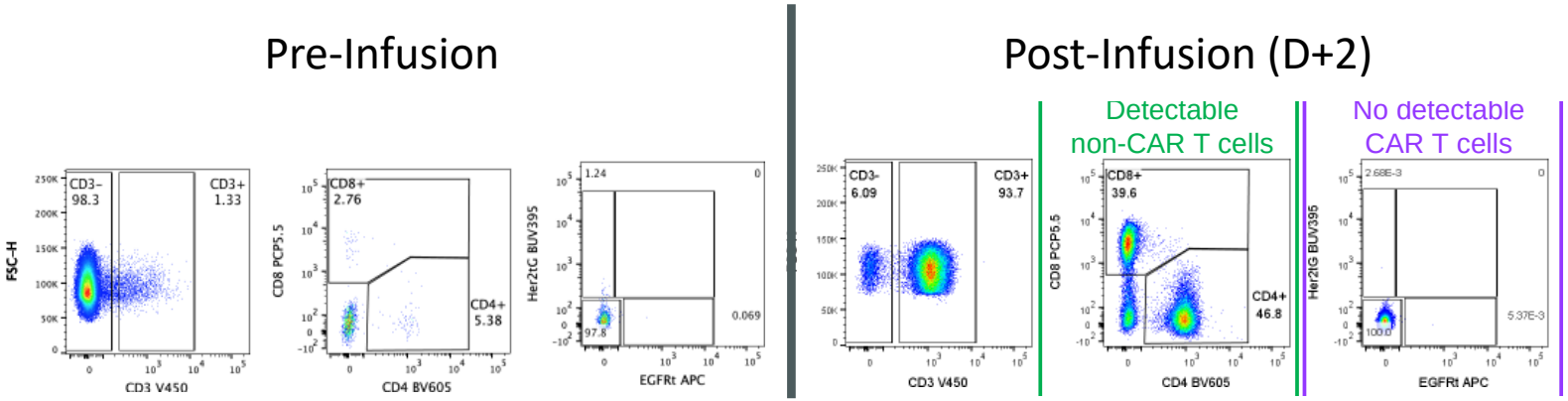
1. CAR T cell detection





Highlights:

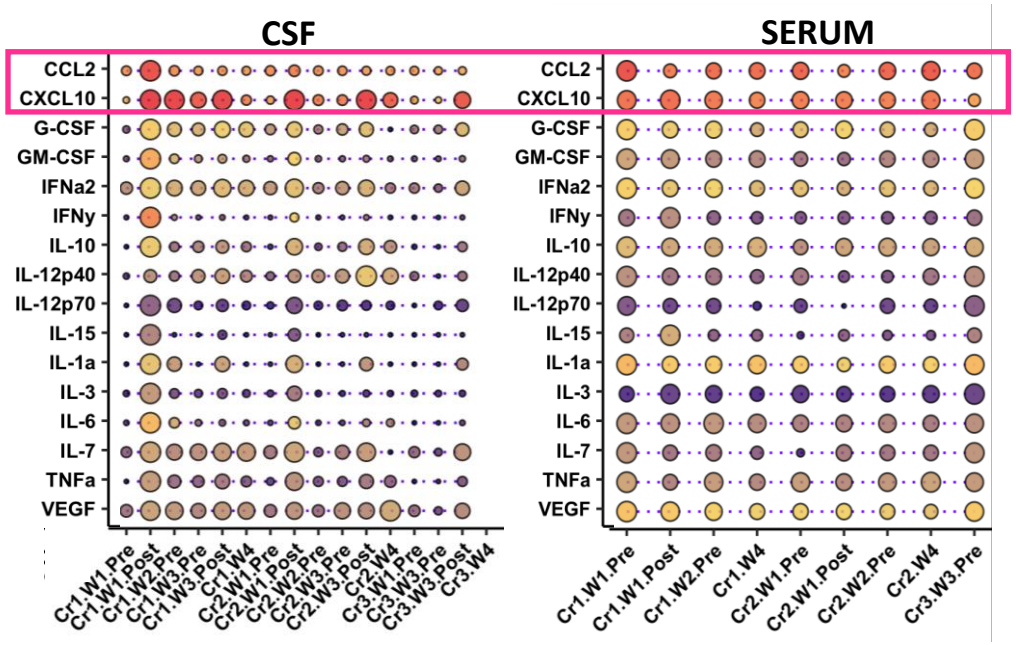
- CAR detection has varied between BC trials
- Engraftment not robust like leukemia/solid (some exceptional cases)
- FLAP predominantly negative
- **Pattern: CSF detection predominantly on BC-03 for DIPG**
- **Pattern: Substantial non-CAR T cell infiltrates in CSF post infusion**



Left: Vitanza, Wilson, Huang, et al. ***Cancer Discovery***, 2022 (accepted)
Right: Vitanza, Johnson, Wilson et al. ***Nature Medicine***, 2021

BrainChild CSF correlatives: what are we learning so far?

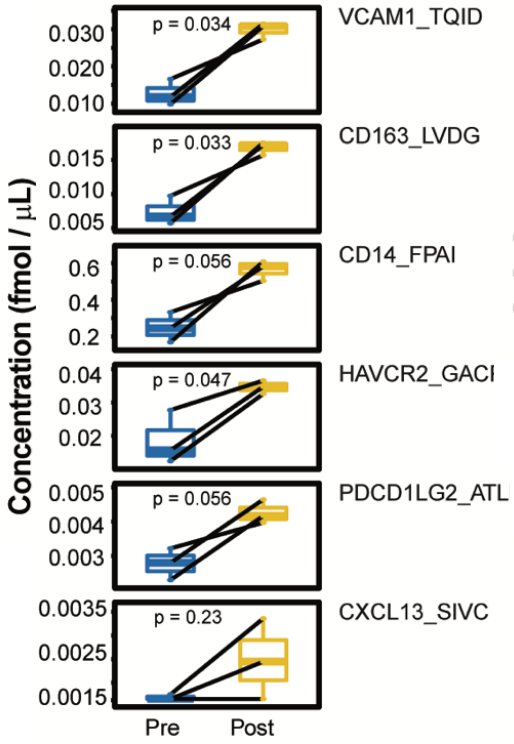
2. Cytokines/chemokines

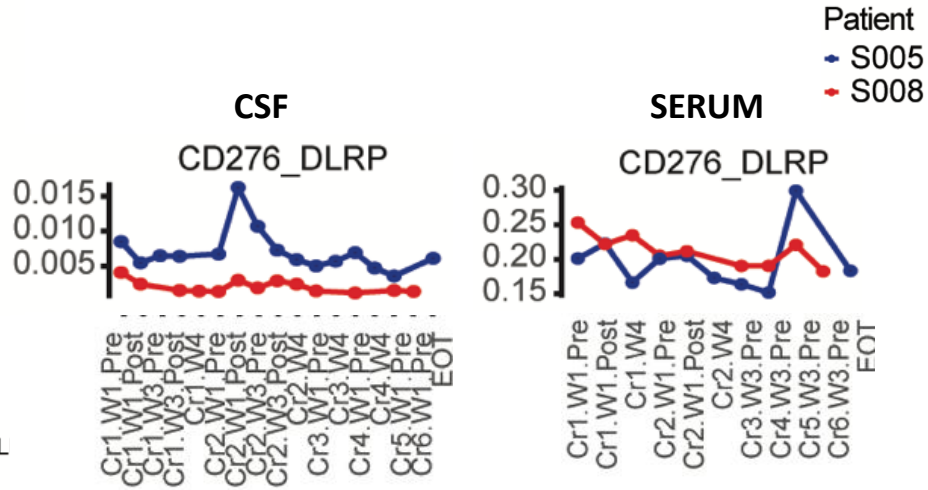


Highlights:

- CXCL10 and CCL2 are consistently highly detected analytes
- Immune response appears localized to CSF
- Markers of macrophage maturation and recruitment are evident
- Detection (or lack thereof) of target Ag may indicate CAR bioactivity

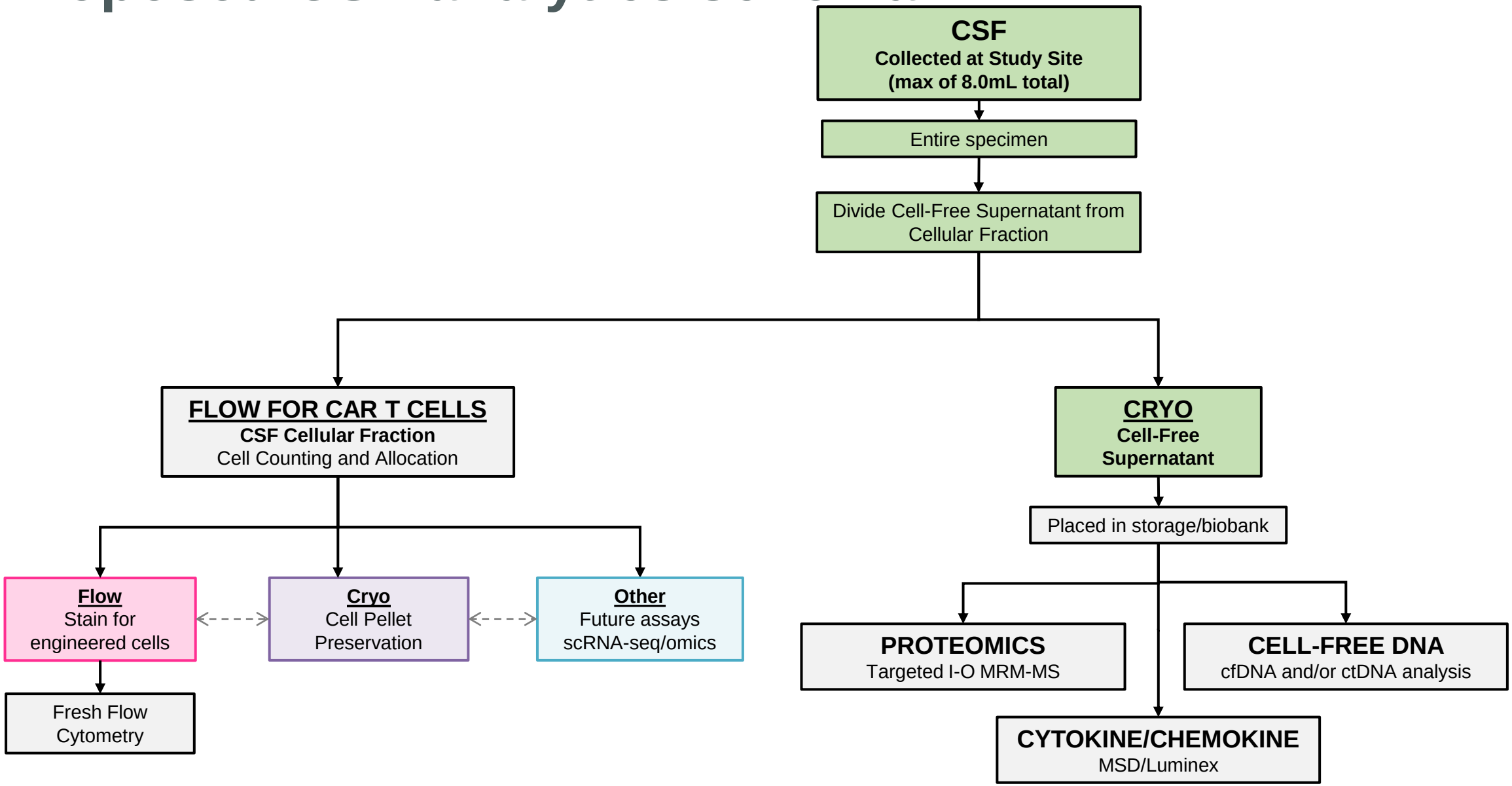
3. Targeted proteomics





Vitanza, Wilson, Huang, et al. ***Cancer Discovery***, 2022 (accepted)

Proposed CSF analytics schema:



CPCI

THANK YOU!

Welcome | October 18, 2022

Julie Park

CPCI

Consortium for Pediatric Cellular Immunotherapy


FINISH STRONG

AGENDA

Aim 4 | Sustainability
Science Talk
Break

EAB and SC Break-Out Groups
EAB Preliminary Report Out to SC

CPCI

Aim 4
Sustainability

Julie Park & Bonnie Ramsey

CPCI

Consortium for Pediatric Cellular Immunotherapy

Develop infrastructure and collaborations to facilitate sustainable access to the most promising novel cellular immunotherapies for children

Sustain through extramural grant funding and pharmaceutical collaborations

Establish an organizational model to develop a sustainable infrastructure

Accomplishments

1

Ongoing philanthropic support to sustain PLAT series of clinical trials for pediatric ALL and NHL

2

California Institute of Regenerative Medicine (CIRM)-funded Alpha Stem Cell Clinics (ASCC) leveraged to sustain support for California sites

3

CTSI engagement: UW ITHS supported website build; UCSF CTSI assisted with development of the ASCC staff and resources (CEHP, PRP)

4

Pharmaceutical collaboration/Grants awarded at CPCI sites to implement novel trials (AML, OS, Brain, COVID)

Ongoing

1

NCI U01 grant submissions by 3 CPCI sites
NCI U24; UG3/UH3 funding minimal and timing inopportune

2

CureWorks – 501c3 spinoff proposal, formation and negotiations ongoing

3

No Cost Extension?

What will be the Legacy of CPCI?

What has CPCI Accomplished?

- Established both a Clinical and Data Coordinating Center with expertise in pediatric cellular immunotherapy (PCI) trials
- Successfully completed several Phase 2 multi-center PCI trials (more than any other group in the world?)
- Expanded GMP capability for CAR-T cell therapies across multiple sites and developed processes and procedures for safe distribution
- Addressed critical priorities for long-term success and sustainability of cellular immunotherapy in children
    - Equitable access to cell therapies (Patient advocacy committee)
    - Biobanking and optimal processing of data and specimens for correlative studies (e.g.,CSF)
    - Pharmacovigilance studies
    - Workforce development and retention

Sustainability of CPCI is a Challenge

- U-01 mechanism is not renewable
- Grant mechanisms for sustaining network infrastructure across institutions are rare
- Cureworks business model works for only a subset of CPCI sites, and it may change to a stand alone, non-profit (501c3)
- Most promising funding mechanism (UH3/UG3) came at a suboptimal time (B Ramsey retiring and J Park transitioning to St. Jude's)

What Can We Accomplish in the Next 2 Years*

- Ensure that key standard processes/procedures and templates are disseminated on the CPCI website- (ITHS will maintain CPCI website for 2 years)
    - GMP product handling and distribution
    - Study protocol design and global CRF library
    - Specimen processing and biobanking for correlative studies

- Establish curriculum for specialized PCI workforce development and retention
    - Example – UW Bothell is creating experiential training in cell/gene therapy as BS major

- Develop a symposium/conference to feature research at the CPCI sites and publish the proceedings

- Publish a review article(s) summarizing the State of the Art of pediatric cellular immunotherapy

**Including NCE*

Other Potential Sources of Funding

- Apply for supplemental funds through member CTSA's for CPCI support at the time of CTSA grant renewal
    - Element E – supports a particular disease/intervention that could be applied in other areas increasing efficiency and effectiveness of translational research
    - RC-2 –ground-breaking, innovative program to further clinical/ translational research such as promote collaboration, address DEI, or transformative technologies

- Other funding sources
    - Become U-01 funded sites based upon recent RFA (LA Children's, Colorado, Seattle Children's)

Scientific Talk
Health disparities in cellular therapy and stem cell transplant

Lena Winestone

CPCI

Consortium for Pediatric Cellular Immunotherapy

UCSF Benioff Children's Hospitals

Health Disparities in Cellular Therapy and Stem Cell Transplant

Lena Winestone, MD, MSHP

Division of Allergy, Immunology, and Blood & Marrow Transplant

18 October 2022

Disclosures

- I have nothing to disclose.

Overarching Goal: Understand the mechanisms that underlie racial, ethnic, and socioeconomic status (SES) disparities in pediatric leukemia survival

Terminology

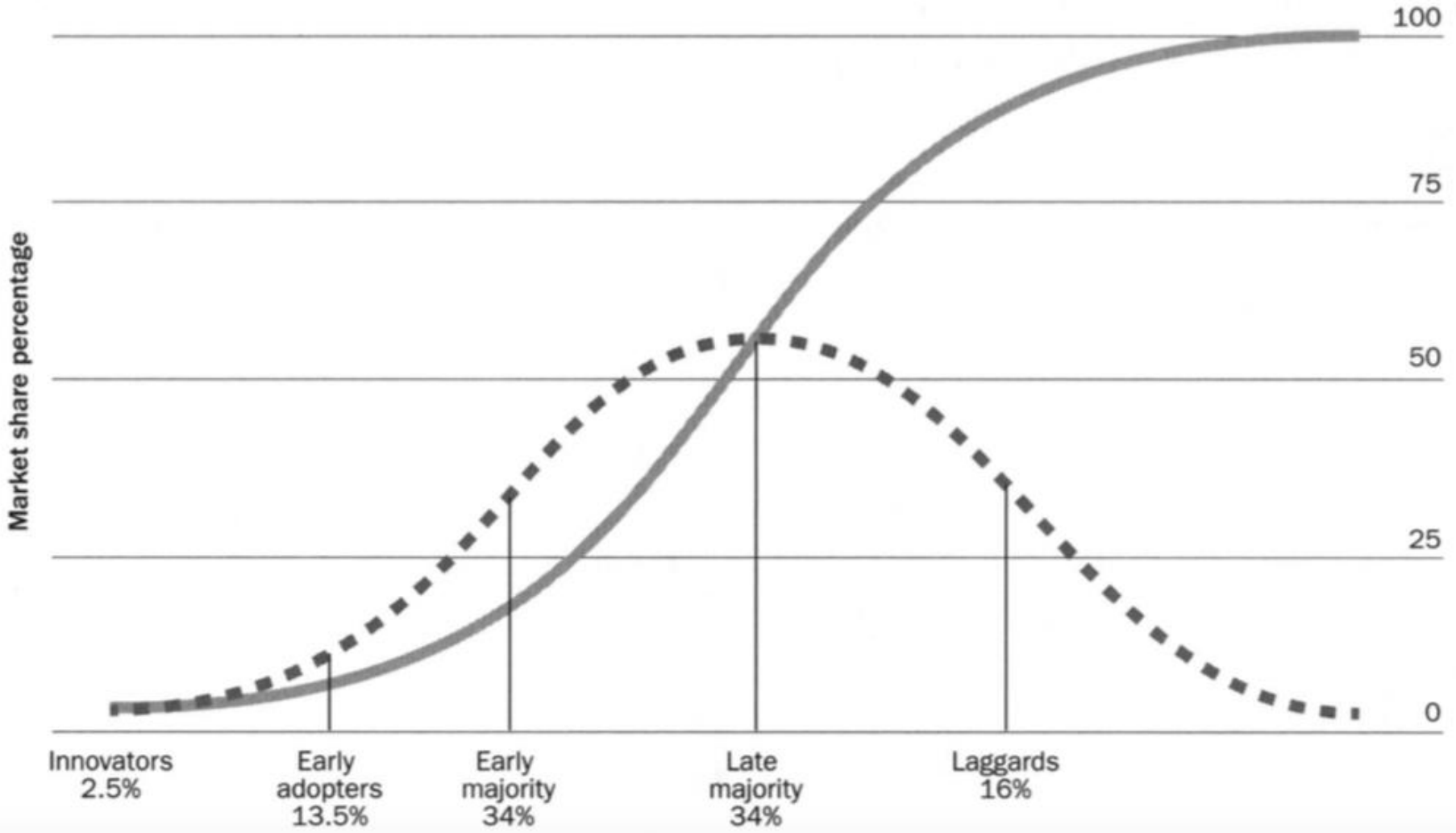
- **Health Disparities** - systematic and plausibly avoidable health differences that adversely affect socially disadvantaged groups; a specific subset of health differences that arise from intentional or unintentional discrimination or marginalization and are likely to reinforce social disadvantage and vulnerability
- **Health Equity** - the principle underlying a commitment to reducing disparities in health and its determinants; social justice in health
- **Race** - a social category constructed by socioeconomic and political forces that determine its content and importance; distinct from genetic ancestry
- **Structural Racism** - way in which our society fosters interrelated and mutually reinforcing discriminatory systems, institutions, and laws that confer preferential access to societal goods, services, opportunities, rights, and power by race
- **Socioeconomic status (SES)** – reflected by income, education, material hardship; often at the neighborhood level, health insurance as a proxy for income

Braveman AJPH 2011; Jones, AJPH 2000

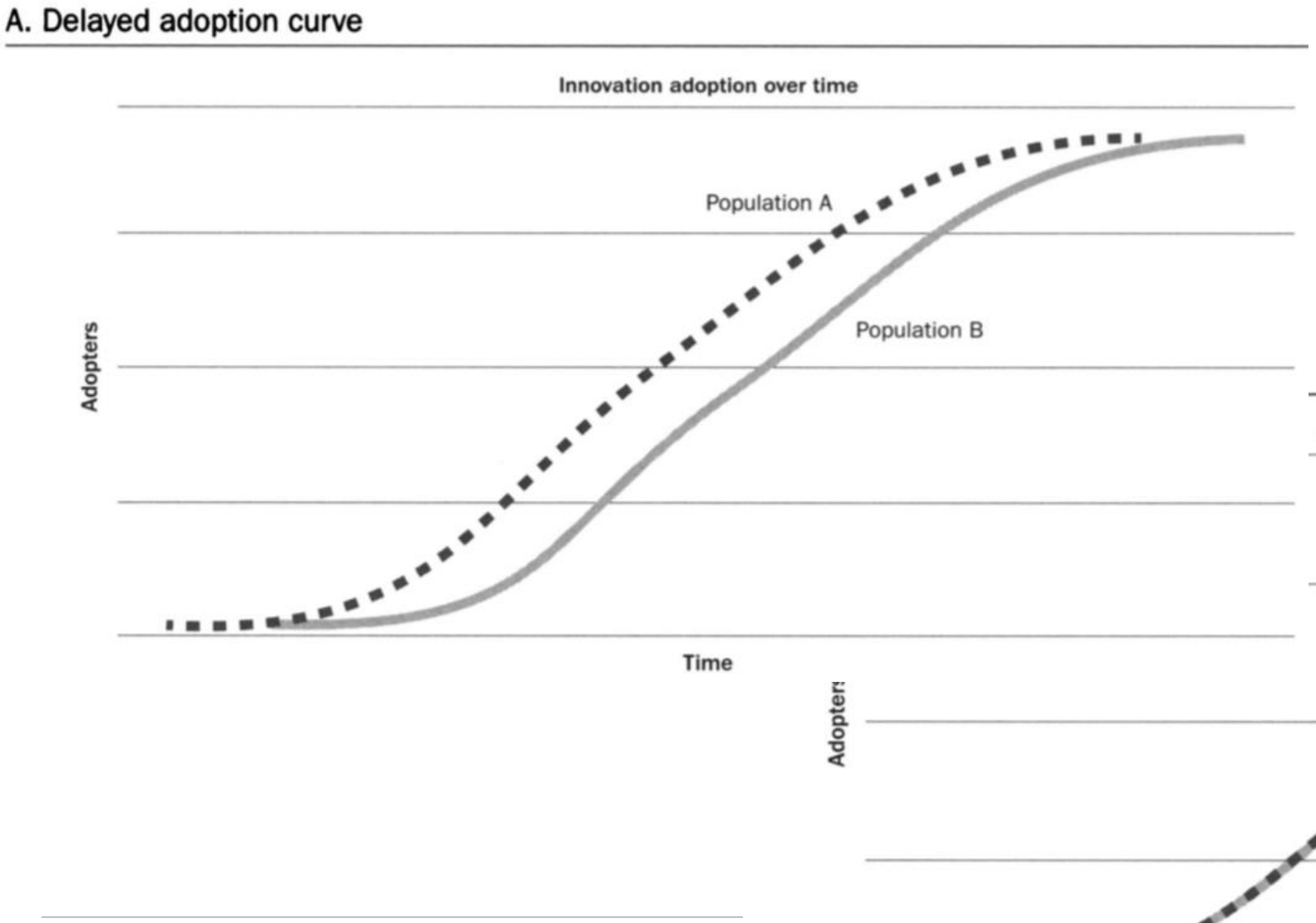
Outline

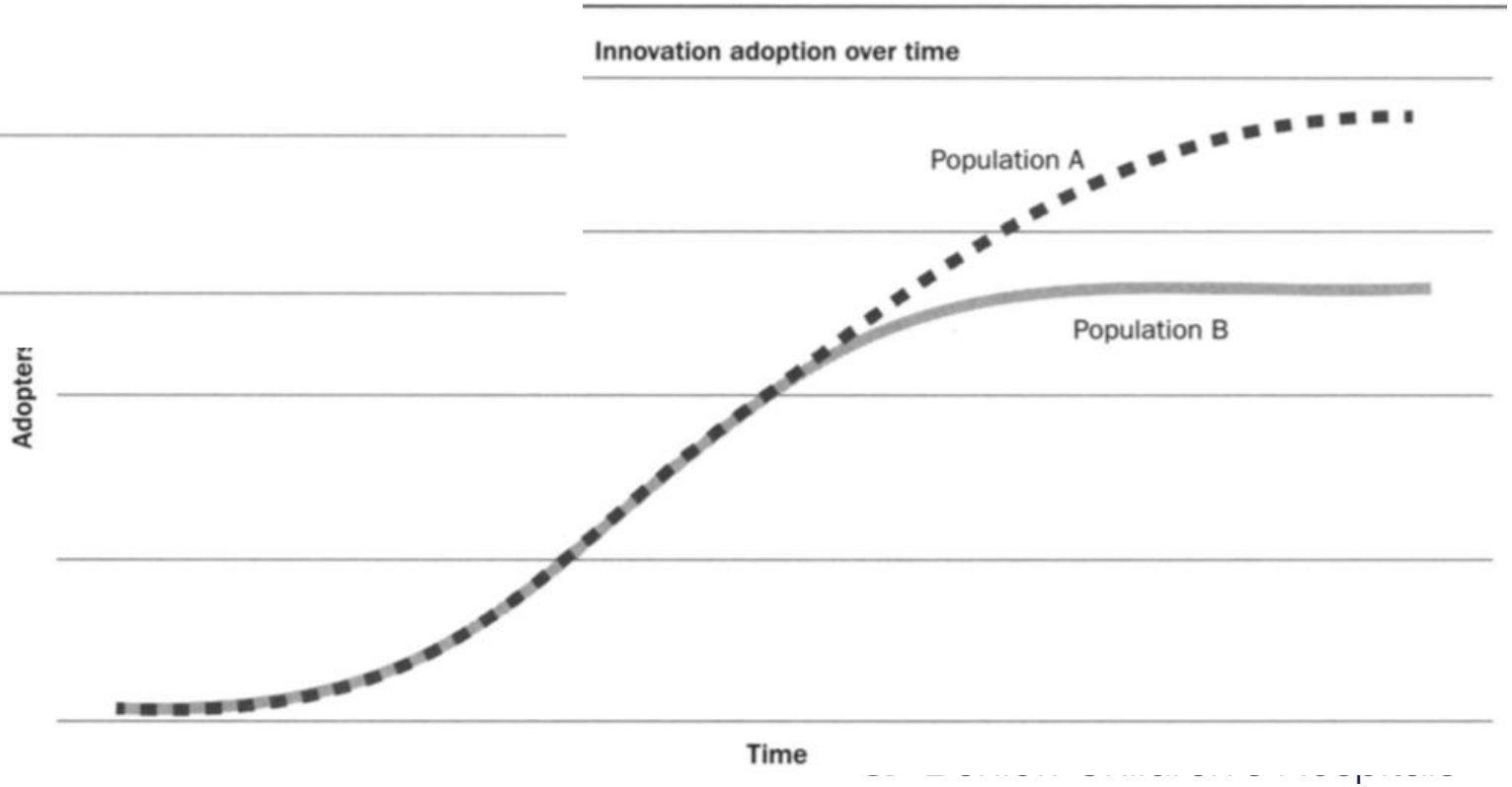
- Widening and narrowing disparities
- Adult CAR T disparities
- Access to CAR T cell therapy
- Outcomes following CAR T cell therapy
- Access to Stem Cell Transplant
- Outcomes following Stem Cell Transplant

Innovation Adoption Pattern



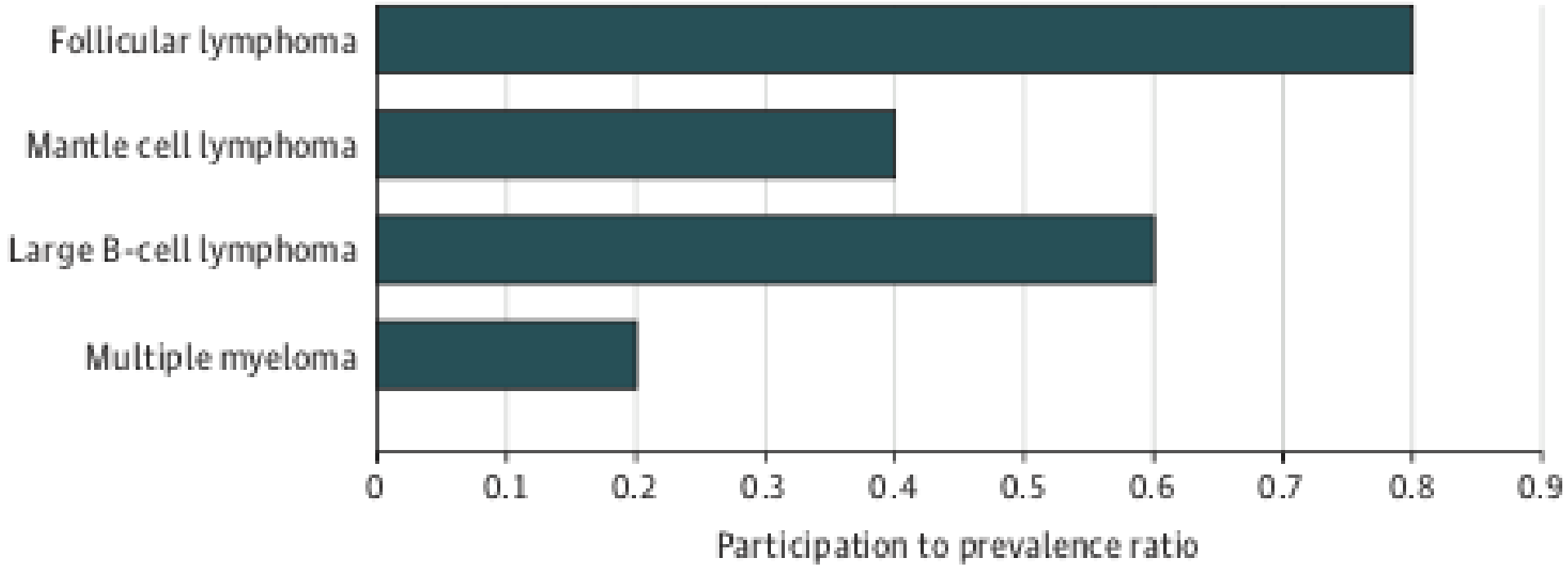
Variations in Innovation Adoption





Adult CAR-T Cell Therapy Trials

Figure. Participation to Prevalence Ratio of Black Participants Enrolled in Clinical Trials That Supported Approvals for Chimeric Antigen Receptor–T Cell Therapy in Various Hematological Malignant Neoplasms



Al Hadidi JAMA Network Open 2022

UCSF Benioff Children's Hospitals

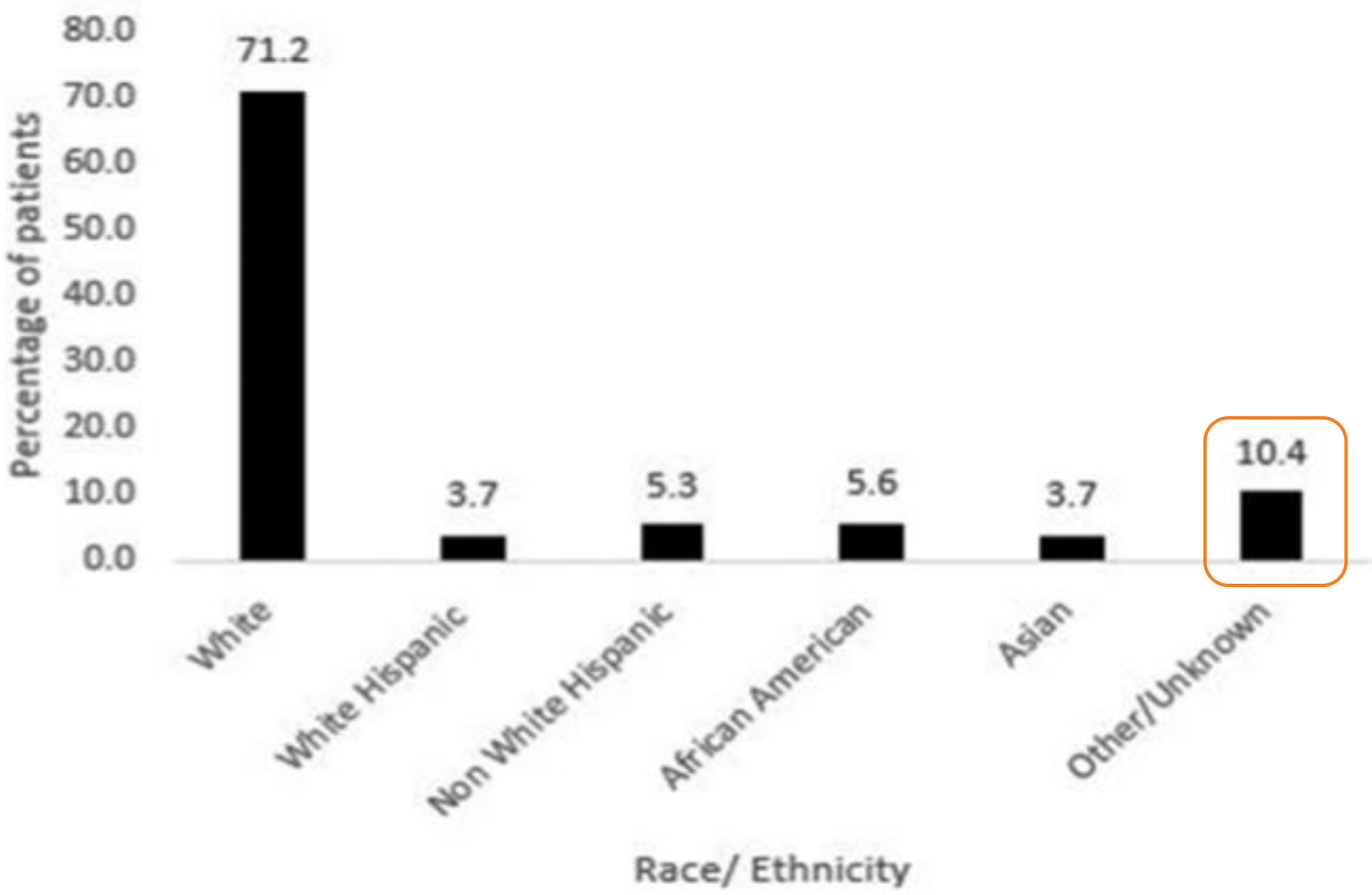
Clinical Trials for Tisagenlecleucel

Table. Characteristics of Clinical Trials That Supported Approvals for Chimeric Antigen Receptor–T Cell Therapy in Various Hematological Malignant Neoplasms

Therapy and study	Approval date	Indication	Participants, No. (%)			Black participants to whom the product was given, No. (%)
			Enrolled set	Safety analysis set	Efficacy analysis set	
Tisagenlecleucel, Maude et al[4]	August 30, 2017	Patients up to age 25 y with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse	88 (100)	68 (100)	63 (100)	NR
			Asian: 10 (11)	Asian: 6 (9)	Asian: 6 (10)	
			White: 65 (74)	White: 51 (75)	White: 46 (73)	
			Other: 13 (15)	Other: 11 (16)	Other: 11 (17)	
Tisagenlecleucel, Schuster et al[7]	May 1, 2018	Adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	160 (100)	106 (100)	68 (100)	2 (3)
			Asian: NR	Asian: NR	Asian: 3 (4)	
			Black or African American: NR	Black or African American: NR	Black or African American: 2 (3)	
			White: NR	White: NR	White: 61 (90)	
			Other: NR	Other: NR	Other: 2 (3)	

CAR T Cell Clinical Trial Population

All adult minority populations are under-represented on CAR T cell trials



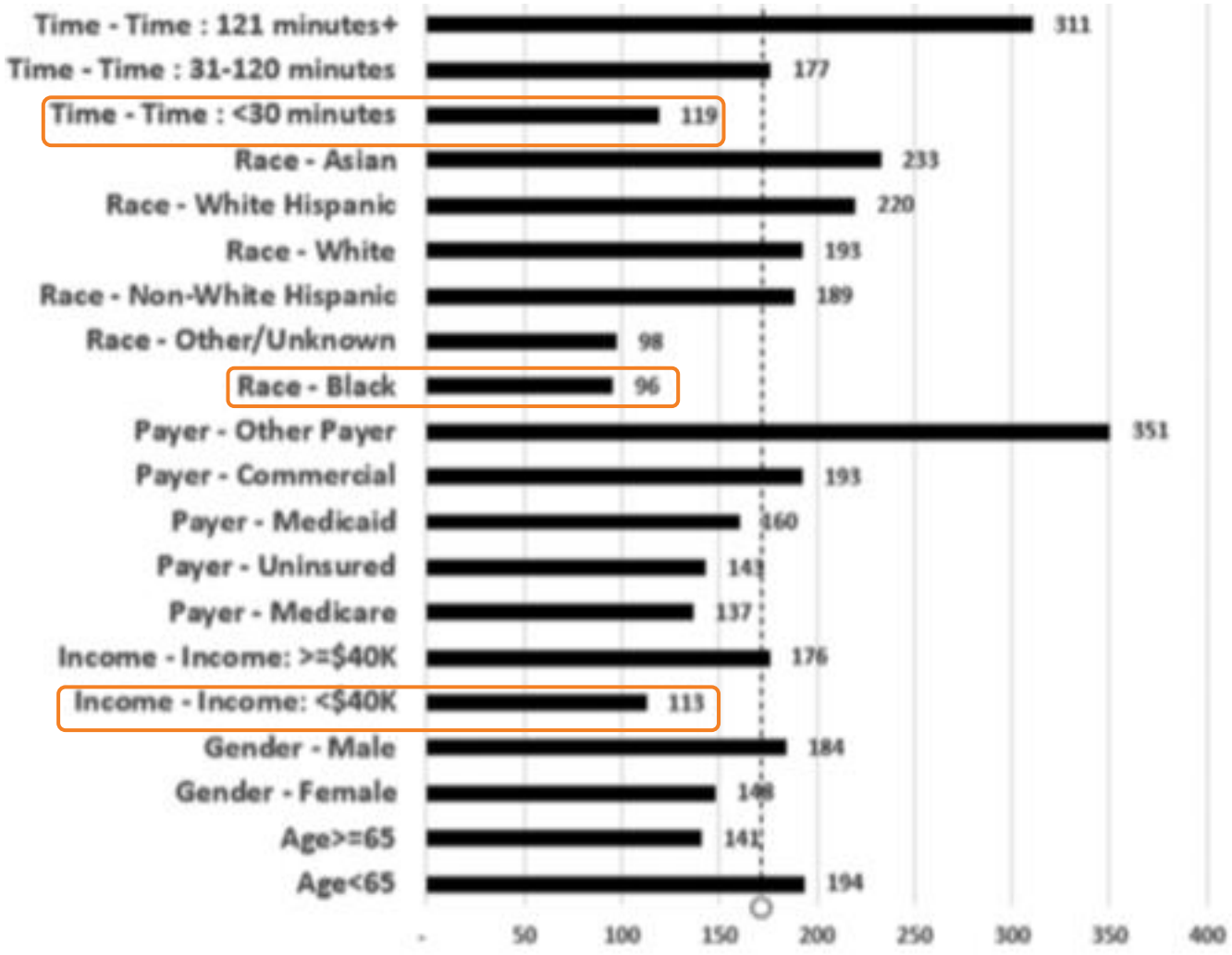
Ahmed TCT 2022

Health Disparities in Cellular Therapy and Stem Cell Transplant

UCSF Benioff Children's Hospitals

CAR T cell case rate (per 100,000 cases)

Black patients and low income patients had lower case rates



Ahmed TCT 2022

Health Disparities in Cellular Therapy and Stem Cell Transplant

UCSF Benioff Children's Hospitals

Interactions between Distance and Income (in CAR T case rate)

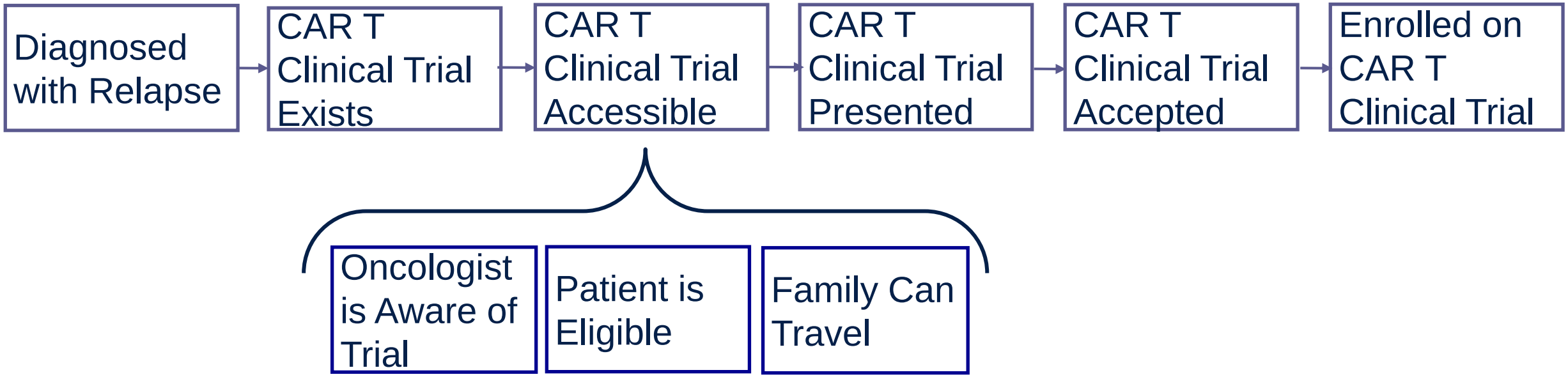
The case rate of patients living >2 hours away and belonging to the privileged SES was higher

Disparities in CAR T Trial Access

Steps to Accessing a Clinical Trial

Conceptual Framework

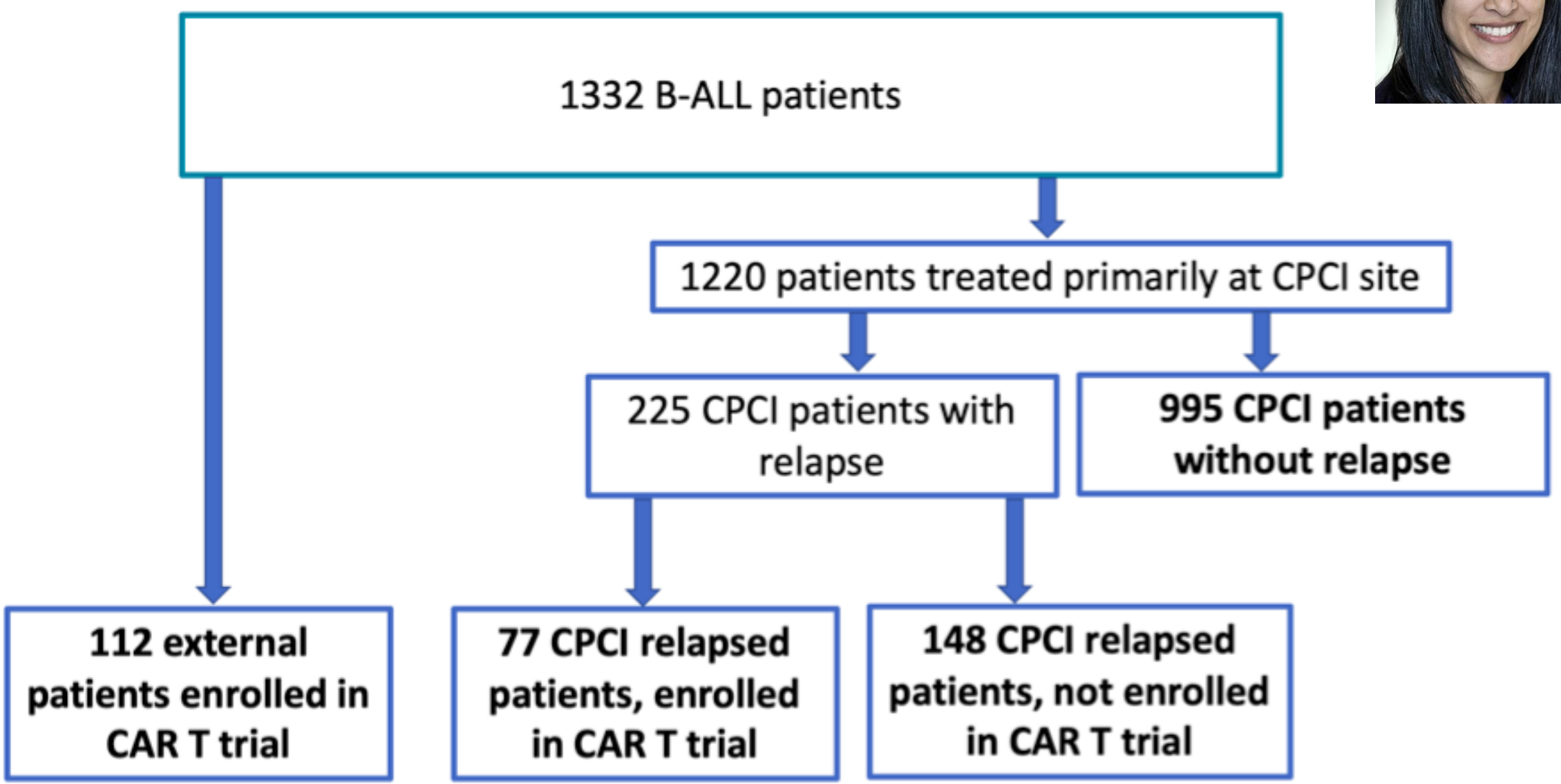
- Complex, multi-step process to enroll on a clinical trial



Freyer Curr Peds Rep 2015

UCSF Benioff Children's Hospitals

CPCI Cohort


1332 B-ALL patients
1220 patients treated primarily at CPCI site
225 CPCI patients with relapse
995 CPCI patients without relapse
112 external patients enrolled in CAR T trial
77 CPCI relapsed patients, enrolled in CAR T trial
148 CPCI relapsed patients, not enrolled in CAR T trial

Characteristics

	All Patients	All CPCI Patients	
	N=1332	**Relapsed or refractory disease** *N=225*	**Without relapse or refractory disease** *N=995*
Race/Ethnicity			
Hispanic	530 (39.8%)	106 (47.1%)	383 (38.5%)
NH White	498 (37.4%)	71 (31.6%)	378 (38.0%)
NH Black	63 (4.7%)	6 (2.7%)	55 (5.5%)
NH Asian	66 (5.0%)	10 (4.4%)	51 (5.1%)
NH Other or Multiracial	143 (10.7%)	26 (11.6%)	108 (10.9%)
Unknown	32 (2.4%)	6 (2.7%)	20 (2.0%)
Language			
English	1072 (80.5%)	166 (73.8%)	803 (80.7%)
Spanish	231 (17.3%)	57 (25.3%)	165 (16.6%)
Other	29 (2.2%)	2 (0.9%)	27 (2.7%)
Insurance			
Private	582 (43.7%)	80 (35.6%)	444 (44.6%)
Medicaid	678 (50.9%)	133 (59.1%)	502 (50.5%)
Other/Unknown	72 (5.4%)	12 (5.3%)	49 (4.9%)

CART Access Disparities

Table 1: Demographic Characteristics by CAR-T Participation and Relapse Status

	Referred CAR-T	Local CAR-T	p-value*	Other relapse	Without relapse
	N=142	*N=80*		*N=150*	*N=1002*
Sex (% Female)	46 (32.4%)	38 (47.5%)	**0.03**	69 (46.0%)	455 (45.4%)
Age at Initial Diagnosis, years	7.8 (6.3)	8.9 (6.2)	0.19	8.4 (6.0)	6.4 (5.0)
Race/Ethnicity			**<0.01**		
Latinx	41 (28.9%)	45 (56.3%)		63 (42.0%)	384 (38.3%)
Non-Latinx White	67 (47.2%)	22 (27.5%)		49 (32.7%)	378 (37.7%)
Non-Latinx Black	2 (1.4%)	2 (2.5%)		4 (2.7%)	55 (5.5%)
Non-Latinx Asian	8 (5.6%)	3 (3.8%)		7 (4.7%)	52 (5.2%)
Non-Latinx Other or Multiracial	16 (11.3%)	6 (7.5%)		22 (14.7%)	112 (11.2%)
Unknown	8 (5.6%)	2 (2.5%)		5 (3.3%)	21 (2.1%)
Language			**<0.001**		
English	120 (84.5%)	60 (75.0%)		107 (71.3%)	806 (80.4%)
Spanish	9 (6.3%)	19 (23.8%)		40 (26.7%)	166 (16.6%)
Other	13 (9.2%)	1 (1.3%)		3 (2.0%)	30 (3.0%)
Insurance					
Medicaid	44 (31.0%)	52 (65.0%)	**<0.001**	83 (55.3%)	504 (50.3%)
Participation in Upfront Therapeutic Trial	68 (47.9%)	33 (41.3%)	0.36	88 (58.7%)	660 (65.9%)

Outcome Disparities following Enrollment

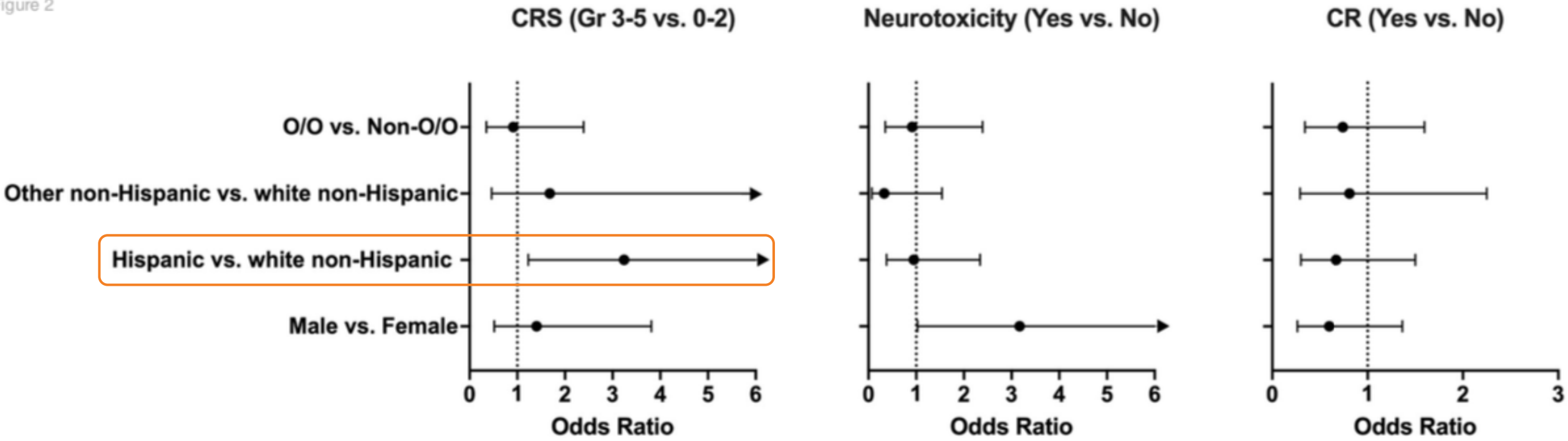
NIH B-ALL CAR T Cohort

- Among 139 patients who receive CAR T between 2012-2021, 29% Hispanic patients and 3.6% Black patients.
- 30 of patients were overweight or obese
- Of note, a lower proportion of Hispanic (35%) and overweight/obese patients (34%) received allo-HSCT compared to non-Hispanic (64%) normal patients

Race and Ethnicity and Outcomes

Hispanic patients were 3 times more likely to experience severe cytokine release syndrome

Figure 2



Faruqi Blood Adv (Aug) 2022

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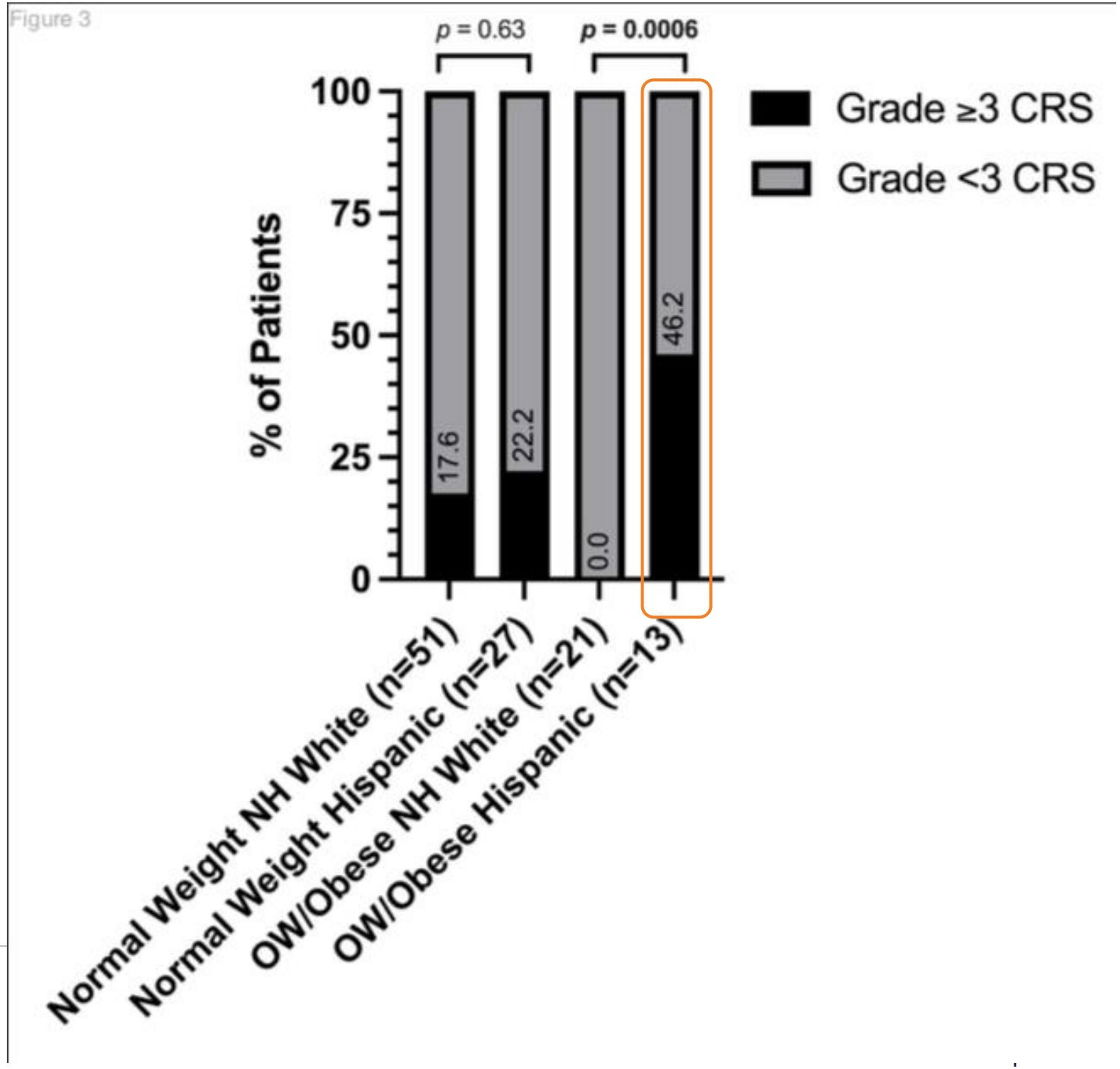
Interaction between Ethnicity and Obesity

Hispanic patients who were overweight or obese had the greatest odds of severe CRS



Faruqi Blood Adv (Aug) 2022

CHOP CAR T Cohort

Among 206 patients who receive CAR T between 2012-2020,

- 21% Hispanic and 8% Black patients
- 36% had public insurance and 25% lived in low-neighborhood opportunity

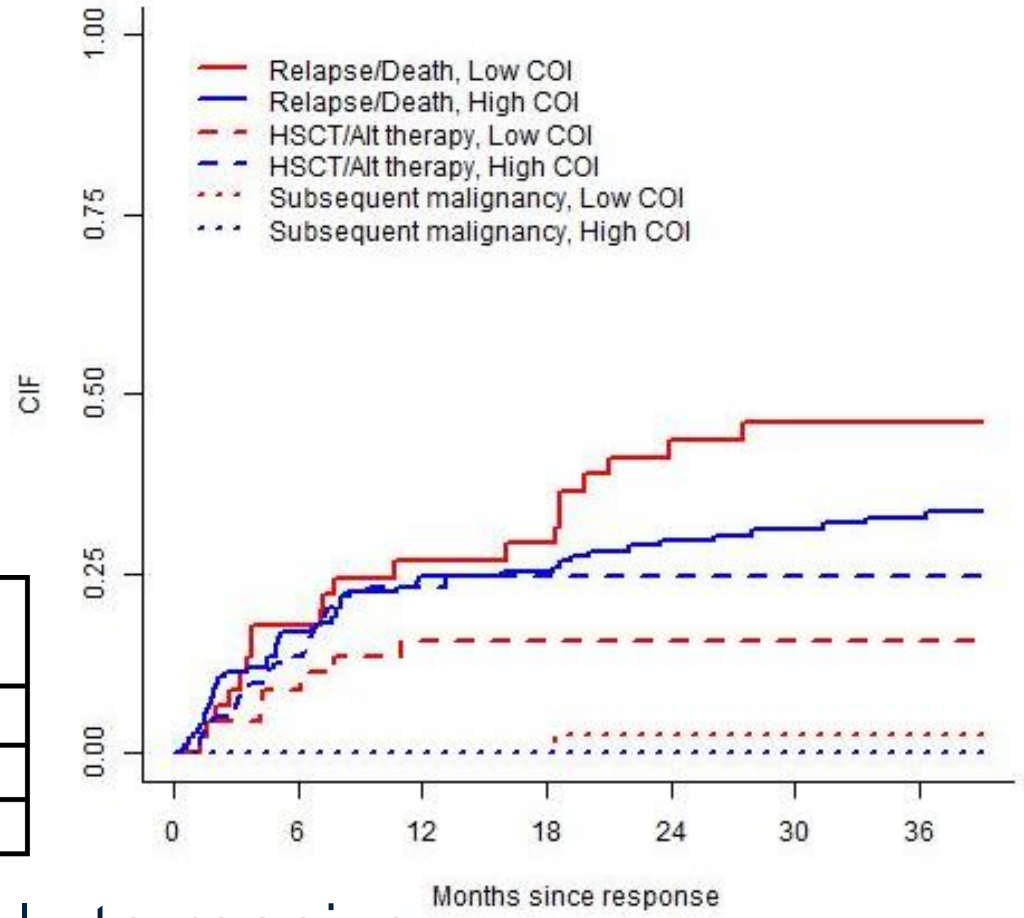
	Local	Referral	p-value
Insurance			0.707
Medicaid	12(32)	62(37)	
Commercial	25(68)	107(63)	
COI			0.679
Low COI	8 (22)	42(26)	
High COI	29(78)	122(75)	
Race and ethnicity			0.391
White non-Hispanic	26(70)	105(62)	
Black or African American	4(11)	11(6.5)	
Hispanic	6(16)	38(22)	
Other	1(2.7)	15(8.9)	
Marrow status pre-infusion			0.533
<0.01	10(27)	66(39)	
0.01-4.99	8(22)	34(20)	
5-24.99	3(8.1)	13(7.7)	
>=25	16(43)	56(33)	

Newman Blood 2022 (in press)

Risk of Relapse

- Low-neighborhood opportunity experienced two-fold increased hazard of relapse (adjusted HR 2.3, 95% CI 1.3-4.1)

	High COI (n=143), n(%)	Low COI (n=45), n(%)
Relapse CD 19+	18(12.59)	11(24.44)
Relapse CD 19-	29(20.28)	8 (17.77)
Death without relapse	0(0)	2(1.40)



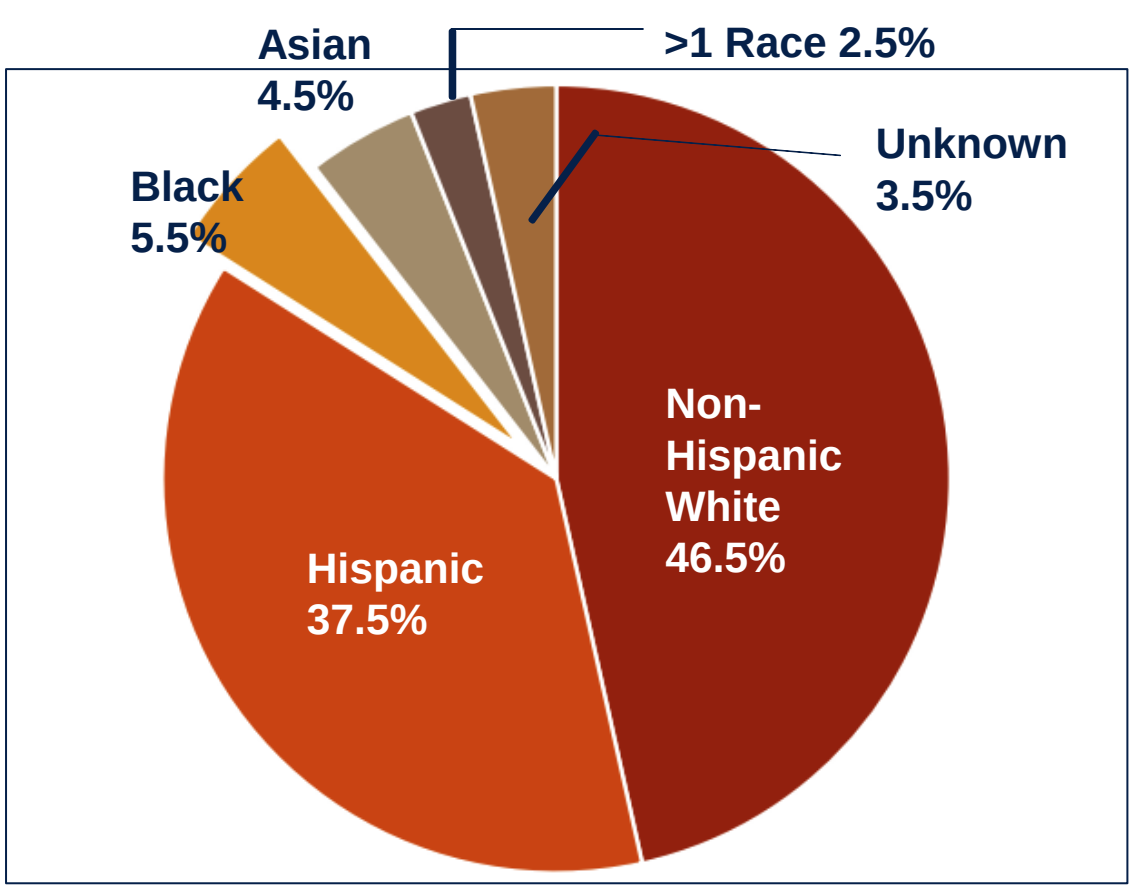
- Children of higher SES are more likely to receive CART with high disease burden (>25%)

Pediatric Real World CAR-T Consortium (PRWCC)

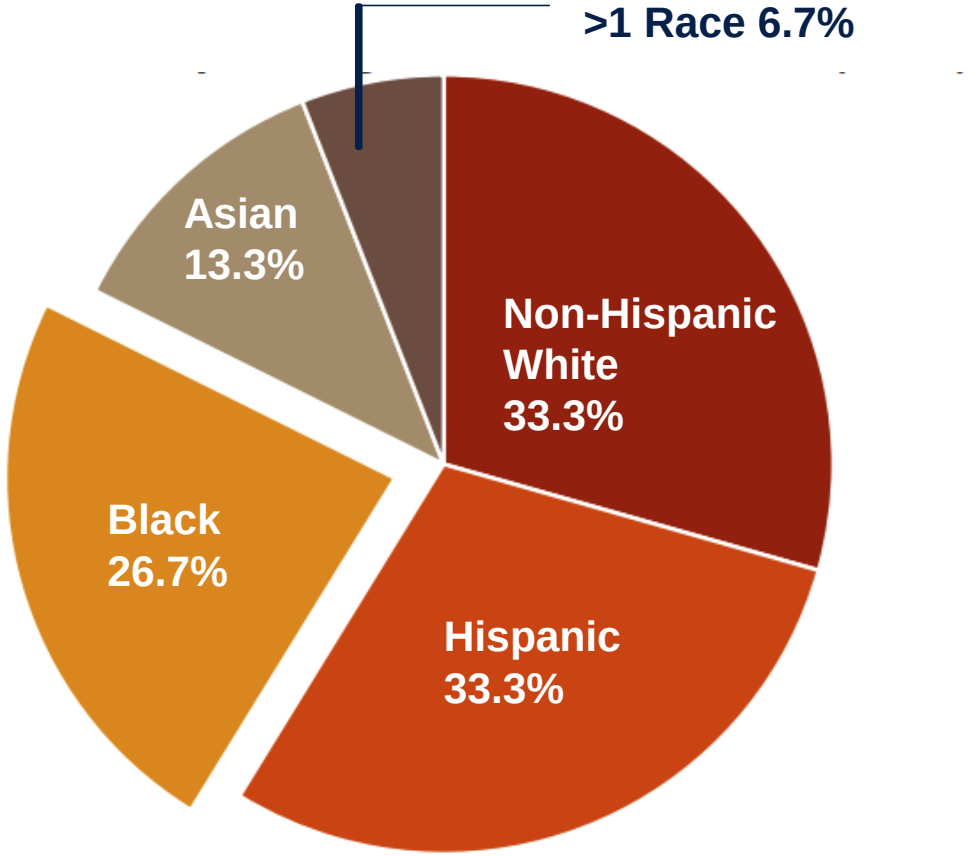
- N = 200 patients with refractory/relapsed B-ALL who underwent manufacture of a commercial tisagenlecleucel at the respective institutions in the PRWCC
  - N = 185 patients were infused
  - 184 patients were evaluable for response and survival outcomes
  - 15 patients did not receive intended tisagenlecleucel after their apheresis products were shipped for manufacturing
  - Infusion date: August 30, 2017 (date of FDA approval) – March 6, 2020

Characteristics of Retrospective Cohort

Race/Ethnicity Among Full Cohort (N=200)



Race/Ethnicity Among Non-Infused Patients (N=15)



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Characteristics of Black Patients in the PRWCC Cohort

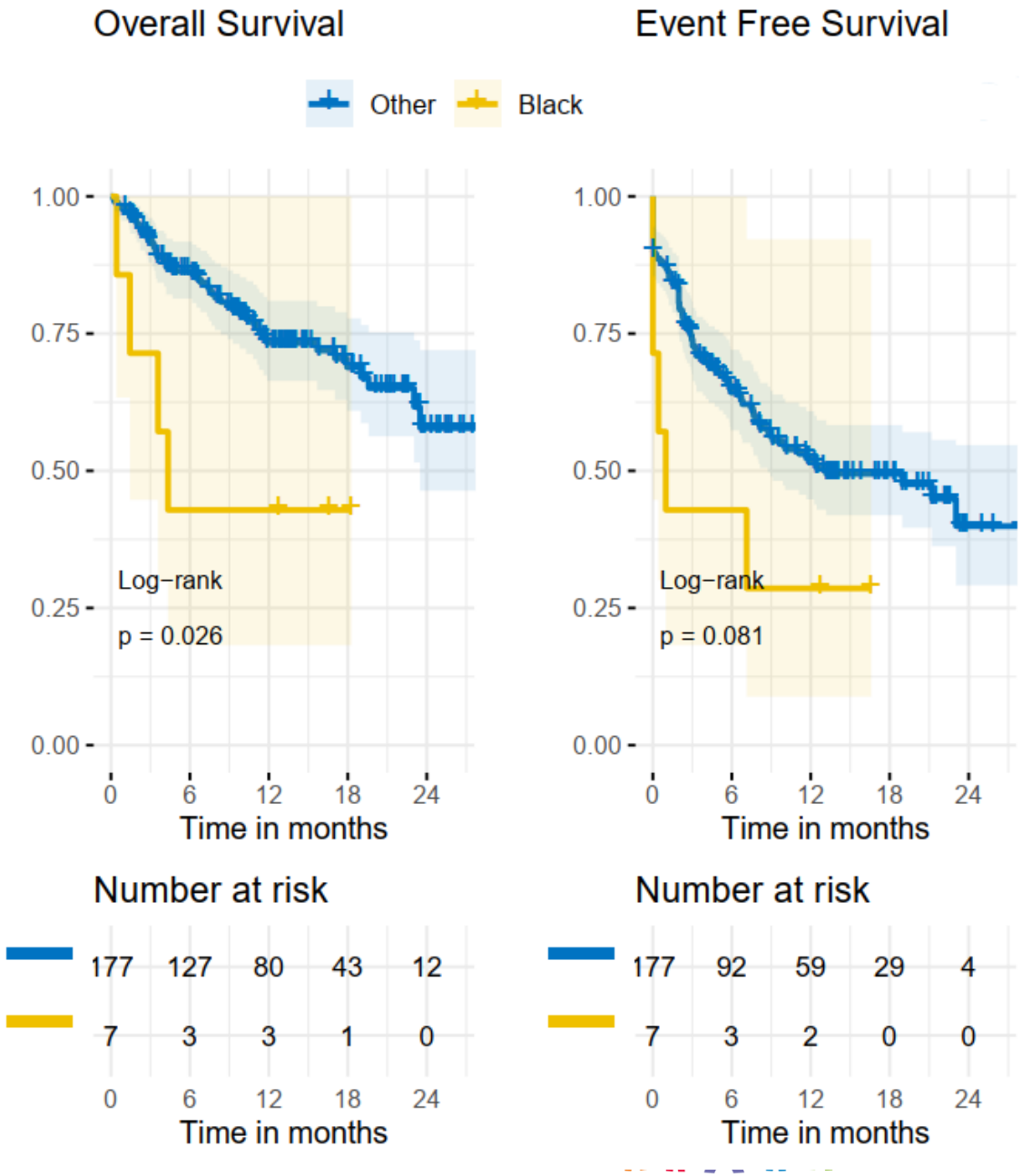
Table 1: Characteristics of Black Patients Intended for CART Treatment

Pt #	Age at Dx (yrs)	Age at Infusion (yrs)	Cyto-genetics at Dx	Prior SCT (Y/N)	Disease Burden @ CART	Reasons Not Infused*	Response to CART	Post SCT (Y/N)	Days to Relapse	Days to Death	Days Follow-up
1	8	12	UNK	N	High		Died D13				
2	<1	1	UNF	Y	High		No CR	N		132	
3	<1	1	UNF	Y	UNK		No CR	Y		44	
4	20	23	INT	Y	ND		Morphologic CR MRD=0.06%	N	30	109	
5	13	20	FAV	N	High		CR by Flow	N	217		556
6	4	10	INT	Y	ND		CR by Flow	N			338
7	4	9	INT	Y	ND		CR by Flow	N			505
8	<1		UNF	N		1,2					
9	1		UNK	N		2, 3					
10	13		UNK	N		1					
11	15		UNK	Y		3					

UNK=Unknown; UNF=Unfavorable/KMT2A-r; INT=Intermediate; FAV=Favorable; ND=Not Detected; SCT=Stem Cell Transplant; *1=ALL Progression, 2=Toxicity; 3=Manufacturing Failure

Survival among Black Patients

	Black Patients	Patients of Other Races	
Background Data			
Median # of Pre-CART Relapses	2	1	*p=0.0105*
Median # Prior Lines of Therapy	5	2	*p<0.0001*
Infants at Diagnosis	27%	7%	*p=0.0468*
Prior SCT	71%	24%	*p=0.0122*
Outcome Data			
CR at Day 28	57%	86%	*p=0.07*
OS at 6 months	43%	86%	*p=0.026*
OS at 12 months	43%	73%	*p=0.026*
EFS at 6 months	43%	64%	*p=0.081*
EFS at 12 months	29%	52%	*p=0.081*



Access to Stem Cell Transplant

Stem Cell Transplant

- Minority patients are less likely to have suitable unrelated donors
  - Only 19% of Black patients find a matched unrelated donor
  - Minority patients are 65% less likely to have a suitable unrelated donors

Leukemia Patients in California

21% of patients underwent transplant

	Total	NH White	Hispanic	Asian/PI	NH Black	Other/ Unknown	p
	N=7183	30	54	11	4.9	1.1	
Neighborhood SES							<.0001
1: Lowest SES	29	10	44	11	26	18	
2	23	18	26	16	32	32	
3	19	22	17	20	20	17	
4	16	25	9.0	29	16	13	
5: Highest SES	13	24	4.2	24	6.2	20	
Insurance Coverage							<.0001
Private	53	71	40	71	48	53	
Public	43	25	56	26	46	43	
No insurance	2.0	1.5	2.5	0.9	2.5	0	
Residence at diagnosis							<.0001
Urban	86	81	86	96	94	75	
Rural/Frontier	14	19	14	4.3	5.6	25	
Leukemia Type							<.0001
ALL	67	59	75	55	53	65	
AML	33	41	25	45	47	35	

Access to Transplant

- Less likely to receive SCT:
  - Black patients
  - Those in poverty
  - Uninsured patients

		OR (95% CI)*
Leukemia Type	ALL	Ref
	AML	1.55 (1.36, 1.77)
Race/Ethnicity	NH White	Ref
	Hispanic	1.02 (0.88, 1.19)
	Asian/PI	1.25 (1.03, 1.52)
	NH Black	0.70 (0.52, 0.96)
Neighborhood SES	1: Lowest SES	0.78 (0.63, 0.97)
	2	0.87 (0.71, 1.08)
	3	0.92 (0.75, 1.14)
	4	0.89 (0.72, 1.10)
	5: Highest SES	Ref
Insurance Coverage	Private	Ref
	No insurance	0.20 (0.11, 0.39)
	Public	1.03 (0.90, 1.18)

* Also adjusted for Sex, Year, Rurality

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Higher Resource Utilization among Black and Hispanic patients

- Hispanic and Black patients had a longer initial transplant admission and more frequent readmissions

	Transplant Admission Length		Days in Hospital at 1 year		Percent with > 2 readmissions	
Overall	Median	p	Median	p	%	p
NH White	35	Ref	7	Ref	25%	Ref
Hispanic	39	<0.0001	11	0.005	32%	0.005
Asian/PI	37	0.28	8	0.18	26%	0.25
NH Black	49	0.05	12	0.11	39%	0.16

Winestone, ASH Annual meeting, 2020

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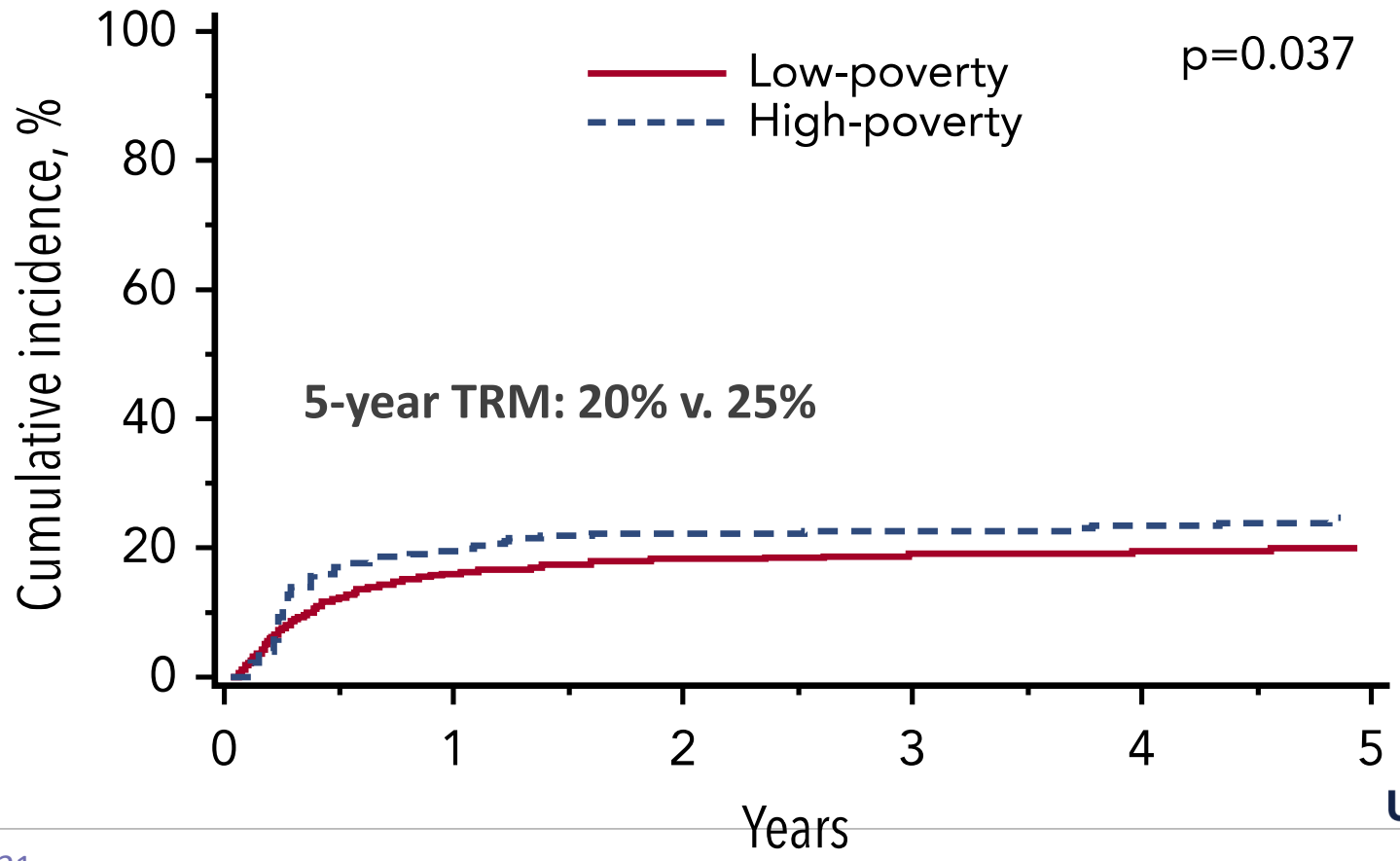
Neighborhood poverty impacts transplant-related mortality



Bona, Blood, 2021

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Black Race is Associated with Worse Survival

	Overall Survival HR (95% CI)*	Treatment-related Mortality HR (95% CI)**
White	ref	ref
Black	1.47 (1.20-1.81)	1.65 (1.26-2.17)

* Adjusted for nSES, insurance, performance score, disease, disease status, donor/graft source, CMV, year

** Adjusted for nSES, insurance, performance score, donor/graft source, CMV, age

Bona, Blood, 2021

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Summary of Disparities

- Minority patients:
  - are more likely to relapse
  - are less likely to be referred from outside for CAR T cells
  - are more likely to not receive CAR T product (despite pheresis)
  - Are more likely to experience high grade CRS
  - are less likely to undergo stem cell transplant
  - are more likely to die following receipt of stem cell transplant

Future Considerations

- Should we be testing approaches to improve access or simply implementing them?
- Who ‘should’ be referred for consideration of CAR-T cell therapy?
  - How does this vary by indication and disease?
- What is the role of telehealth in improving access?
- What is the late effect profile of CAR-T and are there disparities?
- What mechanisms underlie described disparities in CRS and relapse?

First steps

- Referral and Screening Logs (including reason if not enrolled)
- Sociodemographic Data Collection
- Develop Consensus/Resources to Share Best Practices Approach to Addressing Payor Issues and Financial Burden of Travel

Where do we go from here?

1. Collect detailed information about social determinants of health
2. Apply precision medicine approach to health of population to identify mechanisms
3. Leverage existing infrastructure to evaluate interventions to address disparities

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Discussion/Questions?

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