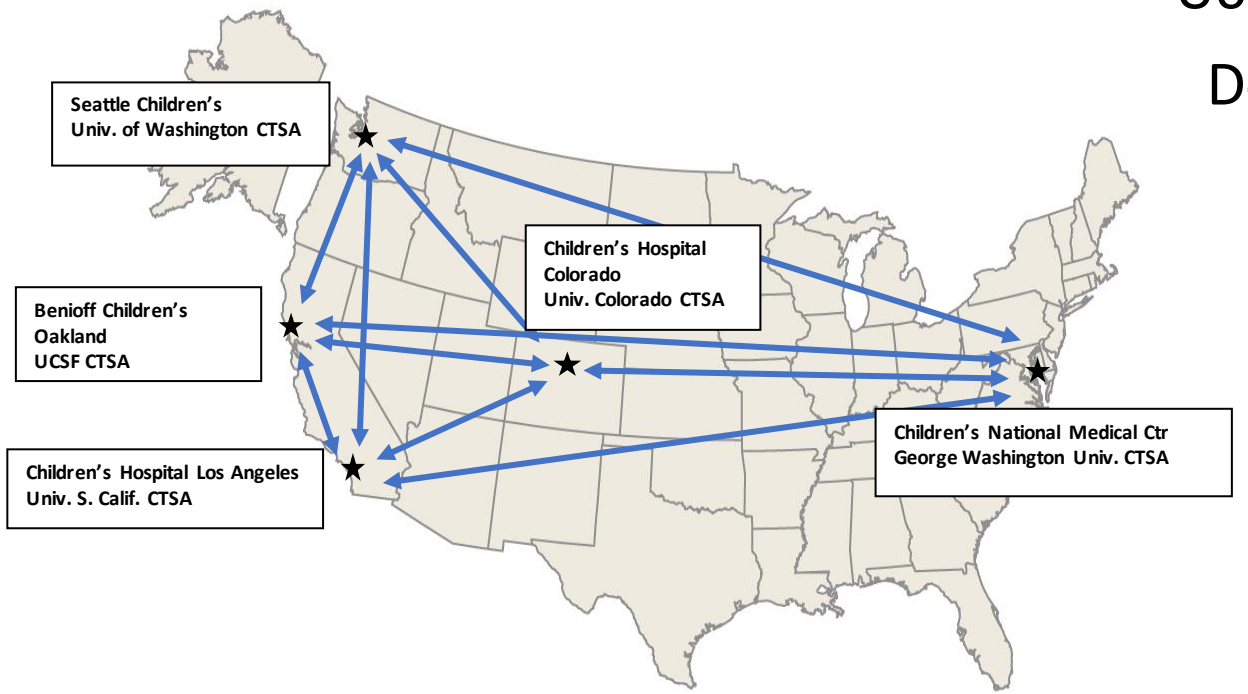
Consortium of Pediatric Cellular Immunotherapy

U01 Annual Meeting

December 6, 2018



Goals for the CPCI 2018 Annual Meeting

- Understand the objectives of the U01 grant
- Review what we plan to accomplish in the next 5 years
- Establish how we are going to accomplish our objectives
- Understand governance that will be in place to facilitate these accomplishments

- Acronym and Logo competition (dinner activity)

General U01 Objectives

- Accelerate the development of novel cellular immunotherapies for pediatric disease including cancer, infection and immune tolerance
- Develop and disseminate resources to enhance the development and implementation of novel cellular immunotherapy
- Expand patient access to novel cellular immunotherapy

Why CPCI now?

- Scientific discovery has provided unprecedented window of opportunity
- Need to establish efficient and effective framework to move from single center Phase 1 to multi-center Phase 2; ultimately setting the stage for large Phase 3 multi-center trials
- Need leaders in the field to create the translational pathway
- NCATS wants to break down translational barriers

How will CPCI accomplish goals?

- Develop a consortium with the specialized expertise to conduct novel cellular immunotherapy multi-institutional trials for pediatric disease
  - Aligned through cGMP cell manufacturing facilities, clinical research infrastructure and reference correlative endpoints laboratories
- Inform therapy for pediatric disorders through collaboration within the CTSA network
  - Extend these novel cellular immunotherapies to pediatric and adult patients across the US CTSA network
- Establish standard processes and procedures that can be easily disseminated
- Train clinical, manufacturing, research, and regulatory teams capable of advancing cellular immunotherapy for a wide range of pediatric disorders

Important Clarifications

- We will develop trials beyond those for cancer or those investigating CAR T cells
- We are not mandating use of a centralized coordinating center and biorepository for all clinical trials
  - Not all CPCI sites will have access to all trials
  - Could be a long term outcome of this U01
  - Adequate funding will be mandatory
- We are not proposing a single manufacturing center
- We are not in competition with existing consortia

Pathway to success: Develop resources to accelerate use of cellular immunotherapy to cure pediatric disease

- Share knowledge
- Share patient resources
- Share biologic specimens
- Share data

SA1: Expand manufacturing capabilities of cellular immunotherapy products

- Define and align best practices across GMP facilities
- Expand distribution of cellular therapeutics to sites of patient care
- Expansion of available GMP facilities across CTSA

SA2: 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

SA3: Expedite the assessment of key biologic correlates uniquely associated with cellular immunotherapy.

- Develop reproducible sample collection and process standards for use across consortium trials
- Apply a web-based data integration 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

SA4: Facilitate sustainable access to the most promising cellular immunotherapies for children

- Sustain through extramural grant funding and pharmaceutical collaborations
- Establish an organizational model to develop a sustainable infrastructure

Table 3. Abbreviated Evaluation Plan and Timeline			
Aim	**Activities**	**Outputs and Metrics**	**Outcomes**
1) Develop the infrastructure to expand manufacturing capabilities of cellular products developed for treatment of pediatric disease	Expand distribution and manufacturing capabilities	Y1: Developed consensus re:best practices on cGMP manufacturing, cell product acquisition and cell product shipment; Y2: Enabled cross site assessment of utilization of best practices Y5: Established capabilities at all consortium sites for multi-site distribution	Increased pediatric patient access to cellular immunotherapeutics
Aim	**Activities**	**Outputs and Metrics**	**Outcomes**
2) Expand the clinical development of cell-based therapeutics for pediatric diseases with high unmet needs.	Implement the Consortium Coordinating Center to monitor clinical trial conduct	Y1 - Y2: Opened at least 2 multi-site clinical trials at > 2 consortium sites	Export single center cellular immunotherapy clinical trials to multiple sites throughout North America and increase patient access to cellular immunotherapy for a variety of pediatric diseases
	Develop immunotherapy specific training modules	Y1-Y2: Developed training modules to assess toxicity, reporting and analysis for 2 cellular immunotherapy trials	
	Develop Tools for Cohort Recruitment	Y3: Developed and implemented tools to assess site accrual and data reporting	
Aim	**Activities**	**Outputs and Metrics**	**Outcomes**
3) Enhance rigorous assessment of key biologic correlates uniquely associated with cellular immunotherapy mechanism(s) of action in conjunction with safety and outcome metrics.	Establish best practices for sample collection and processing	Y1: Established GCLP standard for sample collection and processing Y3: Establish GCLP standards across the consortium	Improve the reliability and timeliness of safety and efficacy measurements
	Establish assays to assess safety and efficacy	Y3:Established and implemented assays that lead to increased safety and efficacy	
	Apply IT platform for sharing of data	Y4: Implemented LabKey for at least 3 multi-site trials	
Aim	**Activities**	**Outputs and Metrics**	**Outcomes**
4) Develop infrastructure and collaborations to facilitate sustainable access to the most promising cellular immunotherapies for children.	Obtain Grant Funding	Y1: Obtain grant funding for 2 trials	Sustain access to cellular immunotherapy for pediatric disease
	Develop pharmaceutical collaborations	Y3: Established at least 2 pharmaceutical collaborations linked to clinical trials	
	Develop CureWorks	Y3: Developed business structure of CureWorks and engage at least 3 sites	

Agenda

- Thursday AM
  - CTSA Integration – Bonnie Ramsey/Nora Disis
  - Governance and Committee Structure – Julie Park
  - Lunch and cGMP facility tour
- Thursday PM
  - Aim 1 – Mike Jensen/Catherine Lindgren
  - Aim 2 – Julie Park/Cristin Gordon-Maclean
  - Dinner
- Friday AM
  - Aim 3 – Ashley Wilson
  - Aim 4 – Julie Park/Mike Jensen
  - Wrap-Up

Dr. Mary (Nora) Disis, MD

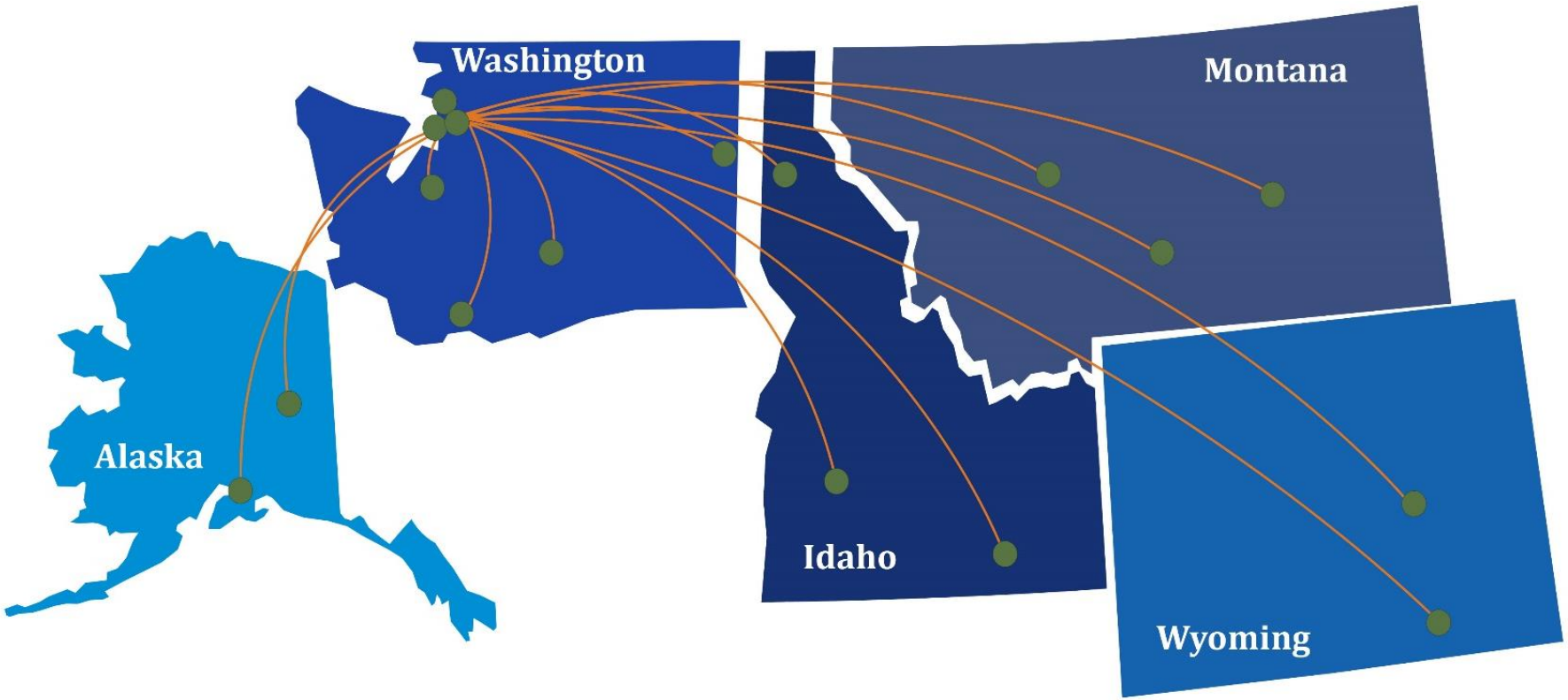
As principal investigator for the ITHS, Dr. Disis sets the strategic direction for the Institute

Other roles and accomplishments include:

- Associate Dean for Translational Health Science at the UW School of Medicine
- Professor of Medicine and Adjunct Professor of Pathology and Obstetrics and Gynecology
- Director of the UW Medicine Cancer Vaccine Institute
- Editor in Chief for JAMA Oncology
- Expert in breast and ovarian cancer immunology, with an interest in developing vaccine and cellular therapy
- Several patents in the field of targeted cancer therapy

The Institute of Translational Health Sciences

is dedicated to speeding science to the clinic for the benefit of patients and communities throughout Washington, Wyoming, Alaska, Montana, and Idaho (the WWAMI region).



Local, regional, and national engine for clinical and translational research

Turning Observations into Interventions



Lab → **Clinic** → **Community**

Accelerate science to the clinic for the benefit of patients and communities by:

- ❑ Fostering innovative research
- ❑ Cultivating multi-disciplinary research partnerships
- ❑ Ensuring a pipeline of next-generation researchers through robust education and career development programs

Regional Research Accelerator

BENAROYA RESEARCH INSTITUTE Virginia Mason · KAISER PERMANENTE · NWABR.ORG Northwest Association for Biomedical Research · UNIVERSITY OF MONTANA

Seattle Cancer Care Alliance · UAF UNIVERSITY OF ALASKA FAIRBANKS · BOISE STATE UNIVERSITY · Billings Clinic

UNIVERSITY of WYOMING · UAA UNIVERSITY of ALASKA ANCHORAGE · KootenaiHealth · MONTANA STATE UNIVERSITY

University of Idaho · MultiCare Institute for Research & Innovation · PROVIDENCE Health Care

IDRI · WASHINGTON STATE UNIVERSITY · VA U.S. Department of Veterans Affairs

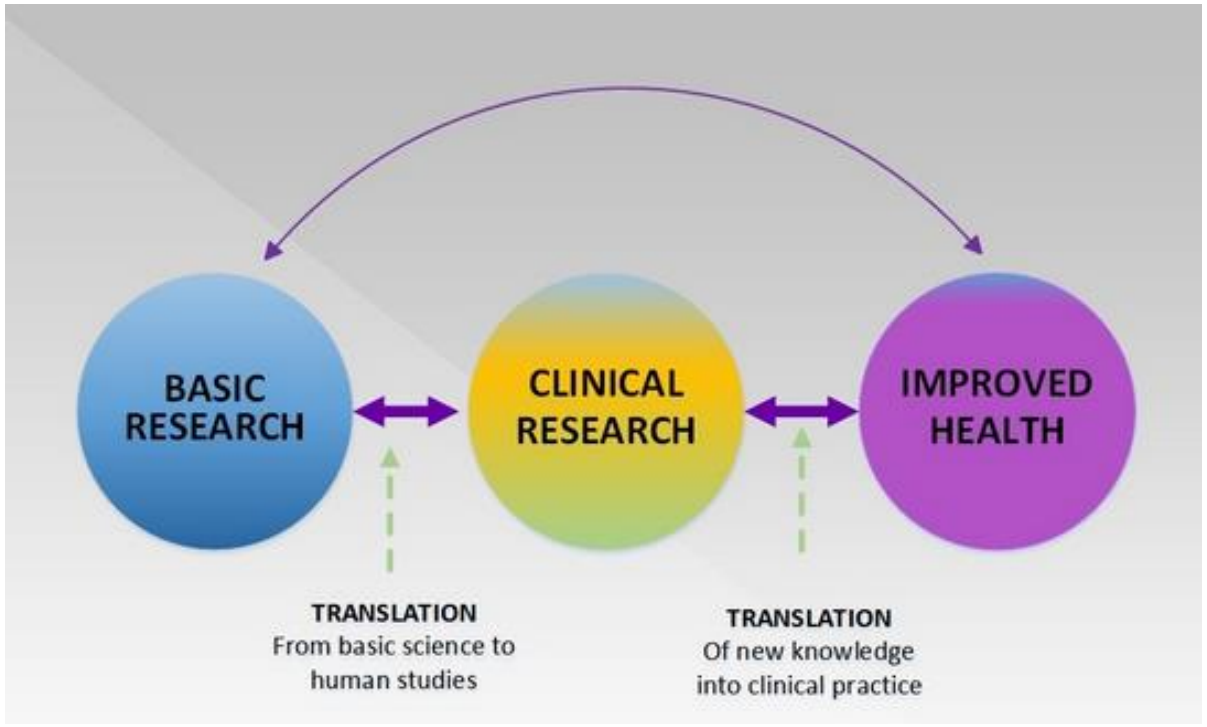
427	5078	242	2474
COLLABORATING ORGANIZATIONS	ACTIVE ITHS RESEARCHERS	EDUCATIONAL PROGRAM GRADUATES	ITHS SUPPORTED PUBLICATIONS

as of Dec. 2018

ITHS Overall Strategic Goals

Workforce Development	Develop and provide comprehensive role-specific training that can be continuously accessed to evolve a highly competent, collaborative, and diverse translational and clinical workforce.
Collaboration/ Engagement	We have developed lasting local, regional, and national collaborations that are project-based and aimed at advancing translational and clinical research in our region.
Integration	Identify and overcome barriers to participation in translational and clinical research for minorities, populations with lifelong disease, and individuals at the extremes of their lifespan.
Methods/ Processes	Discover and support innovative approaches to improve the quality and efficiency of translational and clinical research with the goal of facilitating more rapid dissemination of health innovations to our communities.
Informatics	A shared vision of the integration of health care and research and common and communicating informatics platforms across our partner institutions will be the basis of a “learning healthcare system” in our region.

Research on Translational Research



Nearly 100 Publications about Improving the Process…

Partnership-driven Resources to Improve and Enhance Research (PRIMER): A Survey of Community-engaged Researchers and Creation of an Online Toolkit. *Clinical and Translational Science*

LC Data QUEST: A Technical Architecture for Community Federated Clinical Data Sharing. *AMIA Summits Translational Science Proceedings*

Developing a practice-based research network by integrating quality improvement: challenges and ingredients for success. *Clinical and Translational Science*

A model for incorporating patient and stakeholder voices in a learning health care network: Washington State's Comparative Effectiveness Research Translation Network. *Journal of Clinical Epidemiology*

A survey of informatics approaches to whole-exome and whole-genome clinical reporting in the electronic health record. *Genetics in Medicine*

The association between use of a clinical decision support tool and adherence to monitoring for medication-laboratory guidelines in the ambulatory setting. *Applied Clinical Informatics*

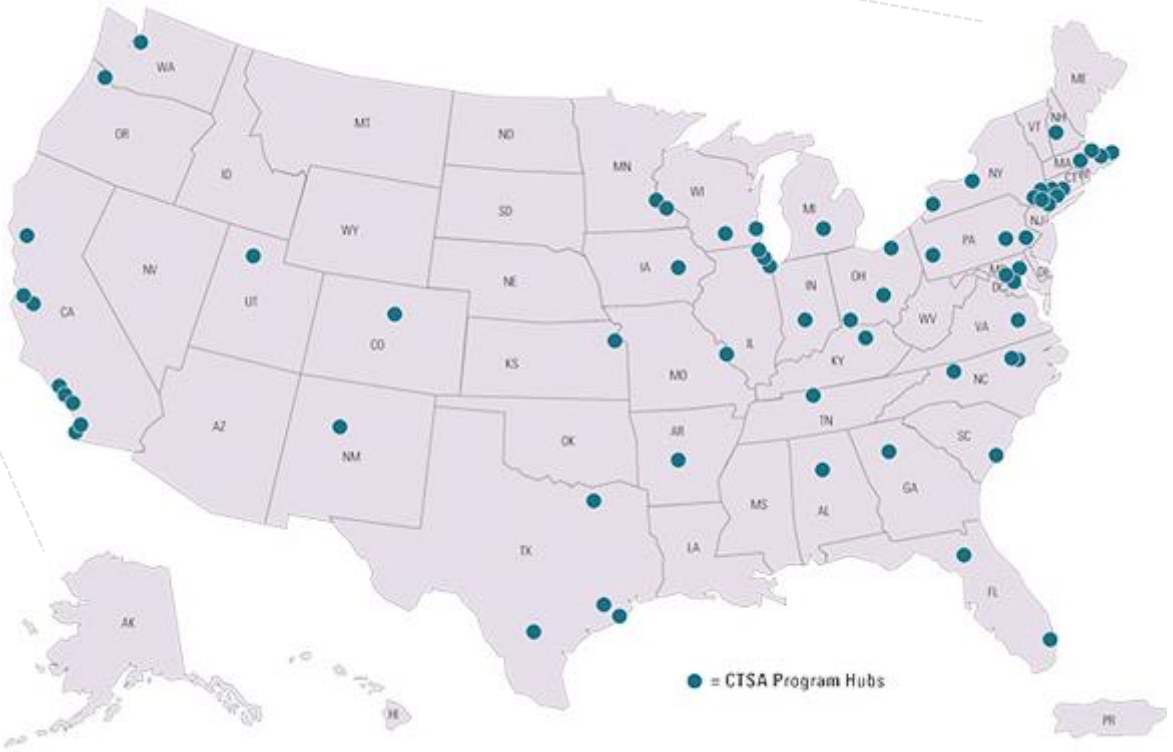
Governance strategies for conducting text messaging interventions in clinical research. *Clinical and Translational Science*

Use of mobile health (mHealth) tools by primary care patients in the WWAMI region Practice and Research Network (WPRN). *Journal of the American Board of Family Medicine*.

Attitudes Toward Risk and Informed Consent for Research on Medical Practices: A Cross-sectional Survey. *Annals of Internal Medicine*

Authors: ITHS faculty

From Regional to National



Develop lasting **local, regional, and national collaborations** that are project-based and aimed at advancing translational and clinical research nationally.

Emphasis on Dissemination and Implementation tools and science

National CTSA network collaborations

Standard practices that can be exported to other sites

ITHS | Inst
Acce

Discover and support innovative approaches to **improve the quality and efficiency** of translational and clinical research.

Methods and training to ensure quality and safety

Export novel approaches nationwide

A model to follow for the CTSA network

Engage diverse populations of every age to participate in clinical and translational research.

Develop methods to ensure every individual has the ability and access to participate in research.

Create tools tailored for both participants and their surrogates which will enhance the consent process

Feasibility of high risk/high gain therapies in special populations

ITHS is Here to Help

Linking the Consortium for Pediatric Cellular Immunotherapy (CPCI) to Other Clinical-Translational Programs – NCATS and CF TDN

Bonnie Ramsey, MD

CF Endowed Professor of Pediatrics and Vice Chair of Research, UWSOM
Director, Center for Clinical and Translational Research, Seattle Children's Research Institute
Co-PI, UW Institute of Translational Health Science

December 6, 2018

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

Financial disclosures

I have received grant funding from Vertex Pharmaceuticals in the past 10 years.

I currently receive funding from Cystic Fibrosis Foundation and National Institutes of Health.

U01TR002487 UL1TR002319 1P30DK089507

RAMSEY03Y0 CFFT-OBSERV13K0 CFFT-OBS-226

Seattle Children's HOSPITAL • RESEARCH • FOUNDATION

UW Medicine UW SCHOOL OF MEDICINE

Why establish a clinical trials network?

Advantages

- Large participant pool permitting more generalizable results
- Enhanced training and expertise across sites
- Broad expertise and unique perspectives from membership
- Standardized processes to enhance data quality and reduce variability

Why establish a clinical trials network?

Disadvantages

- Loss of autonomy for each participant site
- Ineffective resolution of competing interests (e.g., IP)
- Potential for unequal recognition of accomplishments
- More difficult for junior faculty to get recognized and achieve academic success

Why did the CFF and NIH (NCRR) establish TDN in 1998?

- Scientific discovery was providing unprecedented window of opportunity
- CF community had long history of single-site, underpowered studies
- Looked at success of pediatric oncology CTNs
- Wanted to capture “leaders” in field to establish necessary infrastructure, outcomes, study designs
- NCRR was interested in partnering to establish an electronic network (eCRFs, e-tracking, etc.).

Why is CPCI forming in 2018?

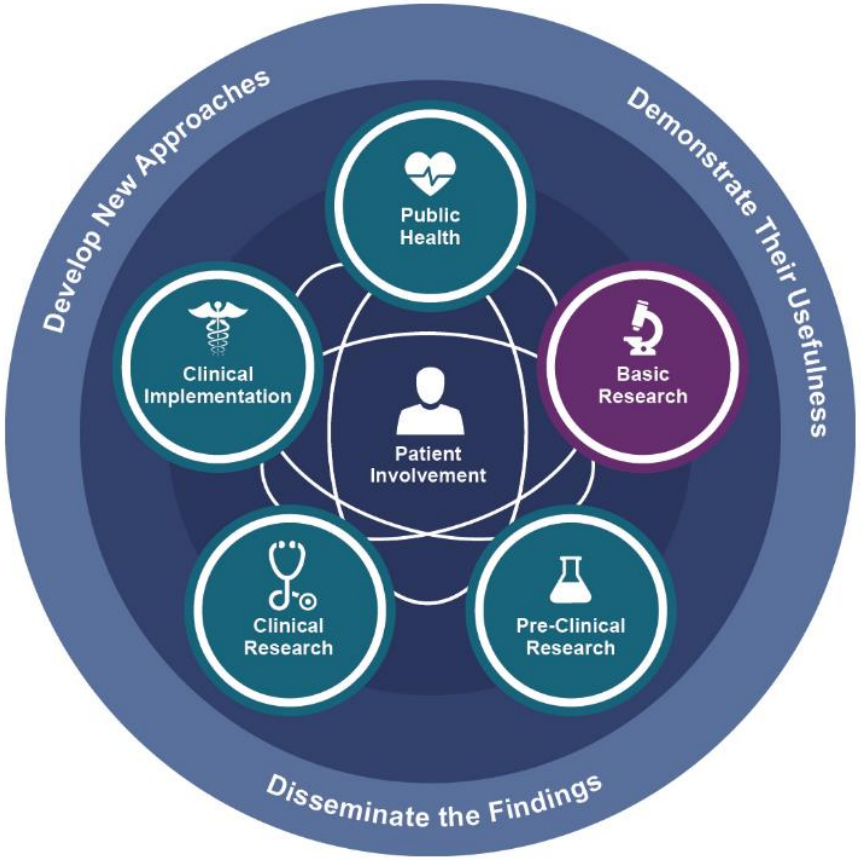
- Scientific discovery is providing unprecedented window of opportunity
- Need to move from Phase 1 to Phase 2 multi-center trials
- Need leaders in the field to create the translational pathway
- NCATS (replaced NCRR) wants to break down translational barriers

Why link with the National Center for Advancing Translational Sciences (NCATS)?

Mission: get more treatments to more patients more quickly

"The CTSA Program is designed to develop innovative solutions that will improve the efficiency, quality and impact of the process for **turning observations in the laboratory, clinic, and community into interventions that improve the health** of individuals and the public."

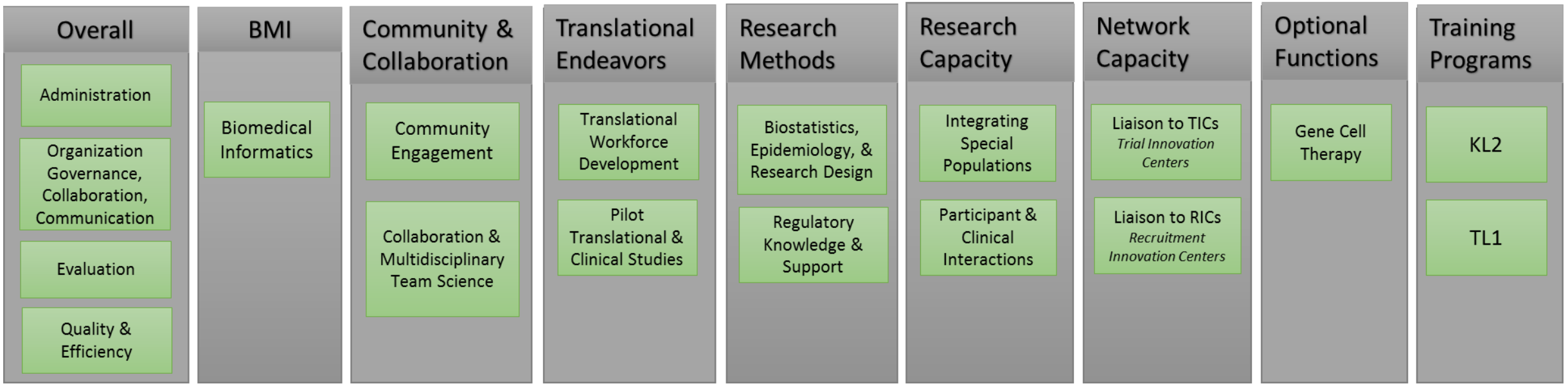
Source: https://ncats.nih.gov



What can the NCATS program provide the CPCI?

- CTSA program infrastructure
- Collaborative Innovation Award (CCIA)
- Other national efforts (SMART IRB)

CTSA Program Areas



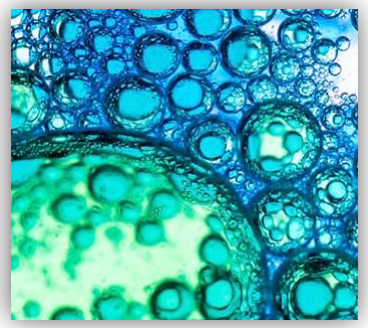
Research resources and services available at each CTSA

Biomedical Informatics

Biostatistics
SCH & UW

Data and Safety Monitoring

Education and Training



GMP Production Facility

Research Navigation

Preclinical Consulting

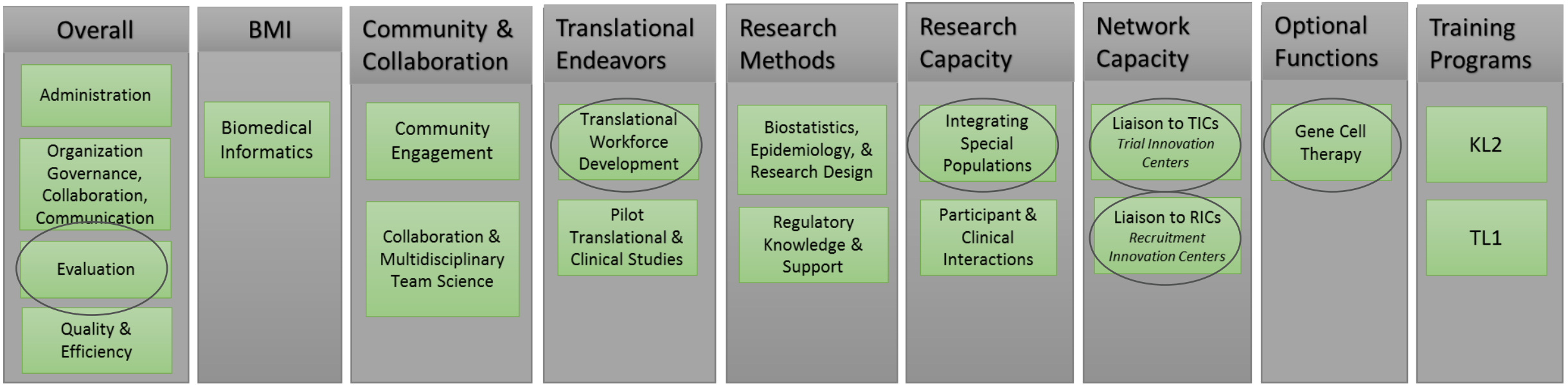
Research Coordination

Regional Collaboration

Adult, Pediatric, Dental Translational Research Units

ITHS | Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

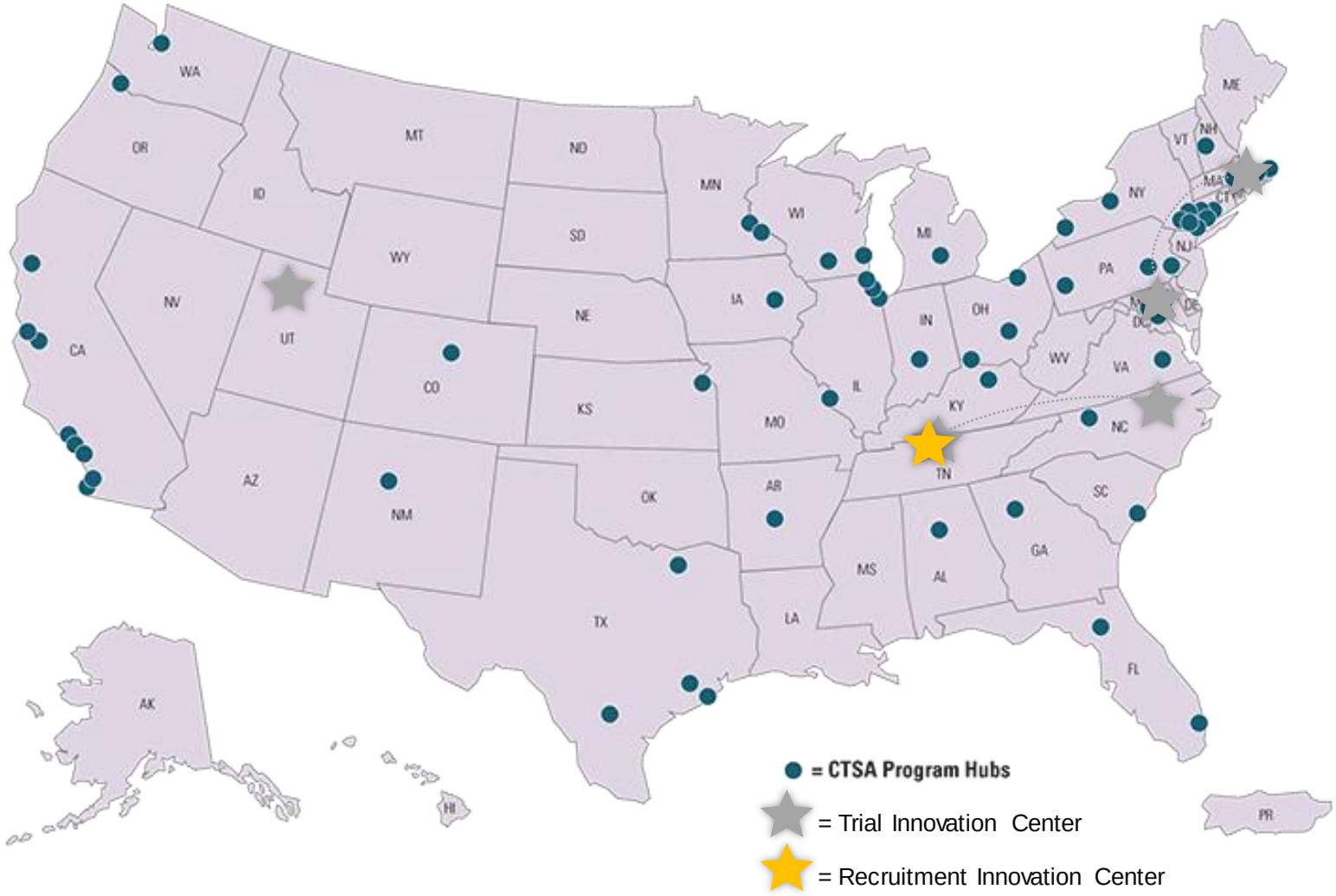
UW ITHS Programs Linked to the CPCI



CPCI collaboration with ITHS

- Integrating Special Populations (Faculty Lead – Tumaini Coker)
  - Representation on Patient Advocacy Committee
- Training of Workforce (Faculty Lead – Larry Kessler)
  - Utilizing ITHS self-directed learning center (SDLC) for developing and posting training curricula
- Evaluation (Director – Julie Elworth)
  - Established outputs and metrics for current four specific aims (Table 3 of U-01)
  - Helping to establish tracking system to collect metrics
  - Re-evaluate metrics as work progresses

Trials Innovation Network



Local Faculty Leads

- Chris Goss, Medical Director
- Ann Melvin, ITHS Recruitment Support Service

ITHS | Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

SMART IRB

A master agreement between institutions' Human Research Protection Programs / IRB offices to allow for single IRB review.

- CTSA supported
- Clearly defines roles and responsibilities
- Eliminates the need to sign reliance agreements for each study
- Supports small and large studies, regardless of funding
- > 500 institutions have signed on
- Onboarding support available via SMART IRB Ambassadors

Accelerated Clinical Trial Agreement (ACTA)

- CTSA Initiative
- Sets forth regulatory and contractual obligations
- Industry or NIH sponsored multi-center clinical trials
- Pharmaceutical and academic collaboration
  - Including Children's National
- Template language serving as a starting point to contract negotiations

CTSA Collaborative Innovation Awards (CCIAs)

- U01 awards initiated in 2016 (we are in the 3rd funded cohort)
- Goal
  - Focus on team based research (≥3 CTSAs)
  - Develop, demonstrate and disseminate innovative experimental approaches to overcome translational roadblocks
- Our aims address roadblocks in translation of cellular immunotherapy: manufacturing, distribution of cGMP products, clinical trials, correlative endpoints, sustainability

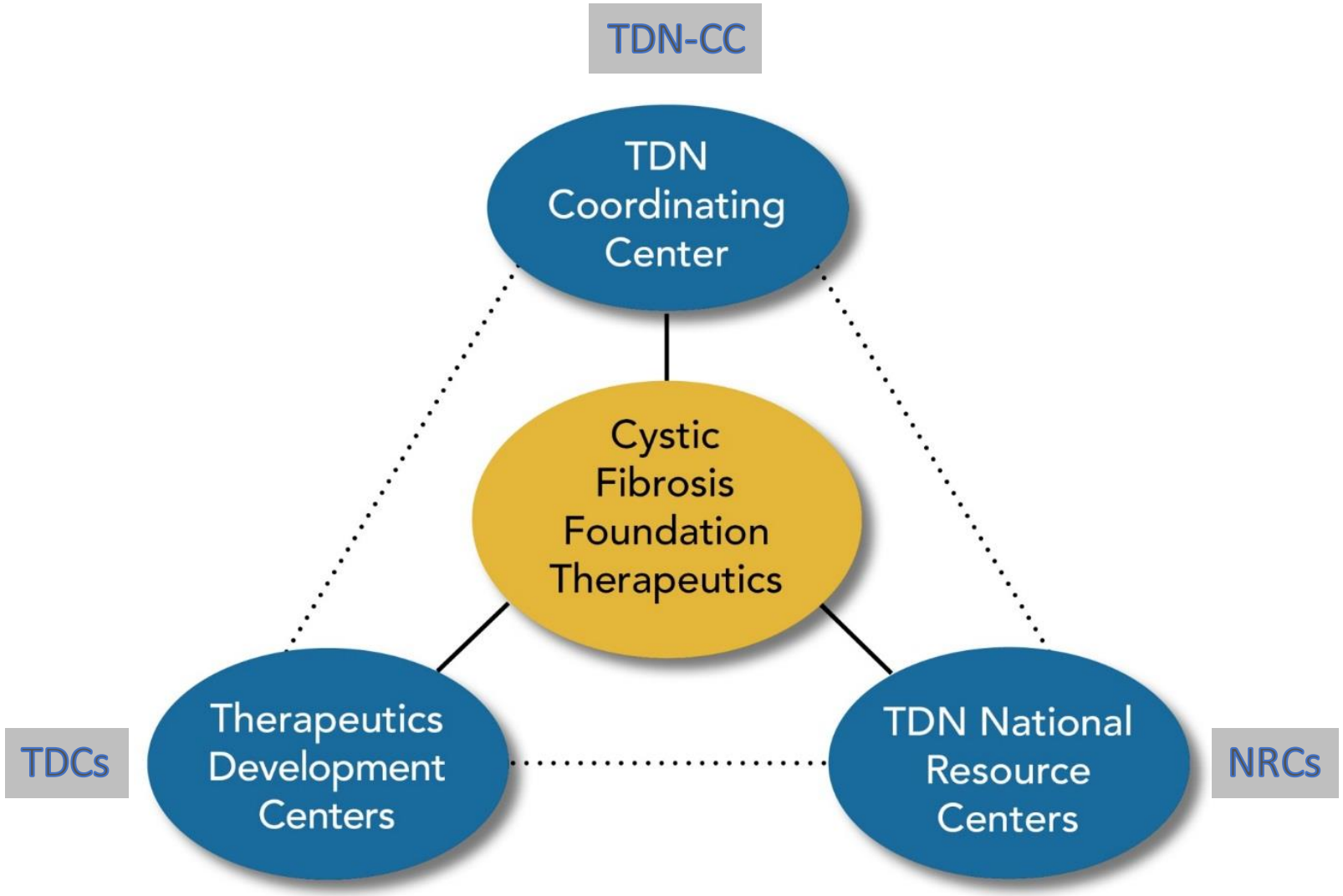
CTSA Collaborative Innovation Awards (CCIAs), cont'd

- Our deliverables
  - Training modules
  - SOPs (cGMP, clinical, laboratory)
  - Tracking of metrics
  - Efficient and safe conduct of trials
  - Sustainability (grants, Cureworks model)

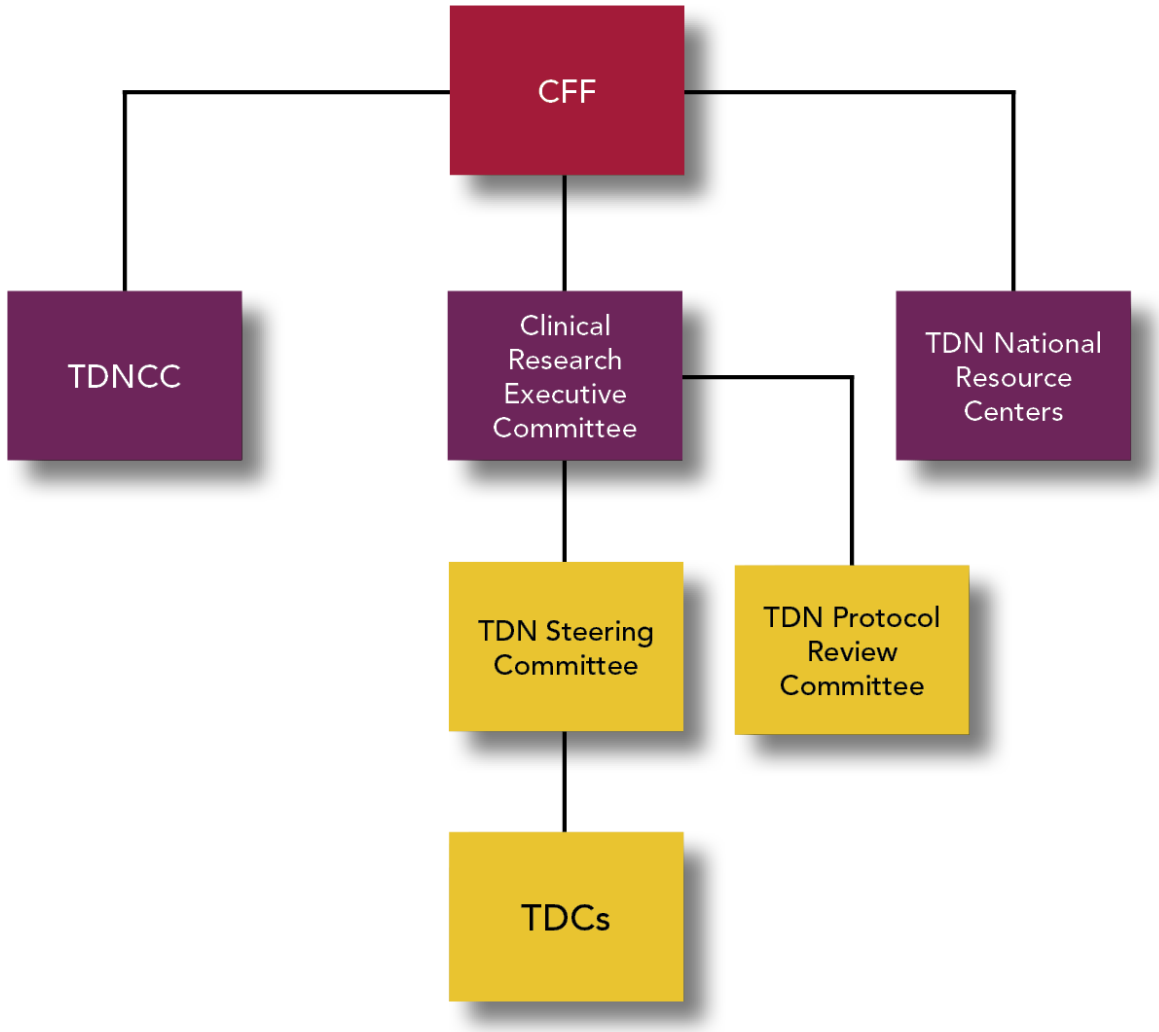
How can the Cystic Fibrosis Therapeutics Development Network (CF TDN) support the CRCI?

- Share 20 years experience and tools
- Training manuals, tracking system, best practices
- Already assisted coordinating center in establishing systems

The CFTDN Organizational Structure



TDN Governance Structure



Protocol Review Committee

- Charged with evaluating all interventional multicenter (>3 sites) CF protocols
  - Industry and Academic
- Critically reviews & critiques final draft protocols prior to trial enrollment
  - Enable a level playing field across numerous sponsors and vetted compounds to maximize opportunity for multiple successful CF therapies
  - Ensure effective use of the limited patient population available for clinical trials to assure possibility of advancement of multiple new therapies simultaneously

CFF Data Safety Monitoring Board

- The DSMB is charged with protecting the safety and welfare of people participating in clinical trials sanctioned by the Therapeutics Development Network (TDN) and ensuring the scientific integrity of those trials
- Though both the TDN and DSMB are sponsored by the CF Foundation, the two entities are organizationally separate from each other and the Foundation
- DSMB and CREC work in collaboration to ensure that the DMC Charter reflects expectations for safety oversight, as well as expectations for interim futility analyses, for example
- Includes patient representatives on DMC

Patient and family involvement

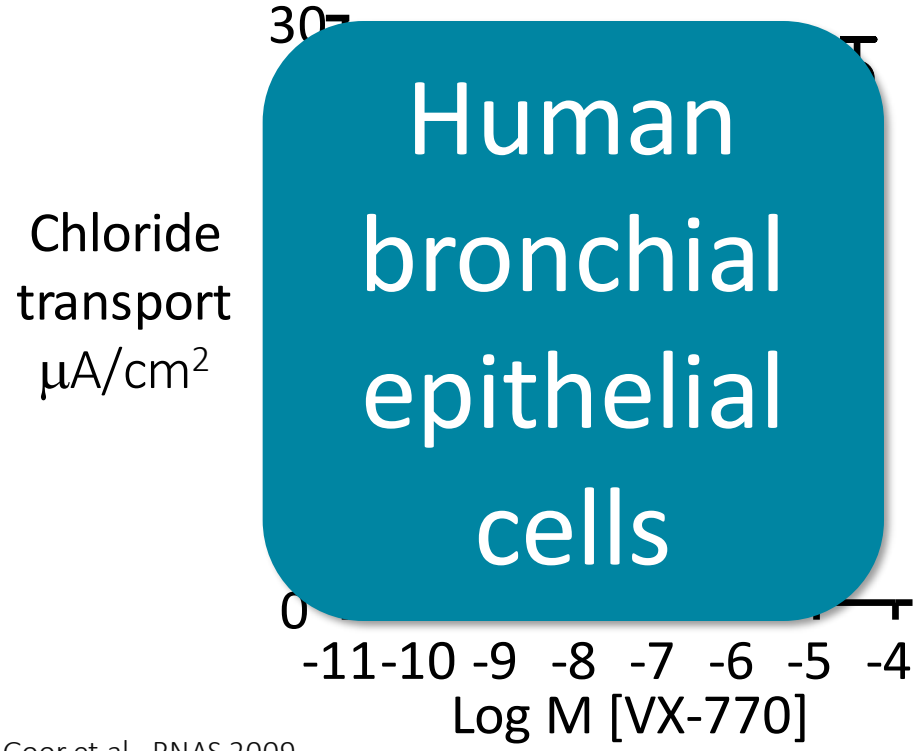
- CF Community Insights Advisors
  - Group of 12 individuals with CF and parents of children with CF
  - Experience participating in clinical trials, trained in drug development and reading a protocol
  - Under confidentiality
  - Can provide feedback to Sponsors on scientific relevance, eligibility criteria, procedural burden, and patient facing clinical trial communication materials
- PRC and DSMB
  - Individuals with CF and parents of children with CF participate as reviewers of protocol and trial

Lessons learned from TDN

- Kept sites engaged through ancillary (correlative endpoint) studies; successful focus of network
- Wrote grants together (TDN served as CCC and DCC)
- Common approach to industry trials (“herd effect”)
- Gradual expansion of network based upon need

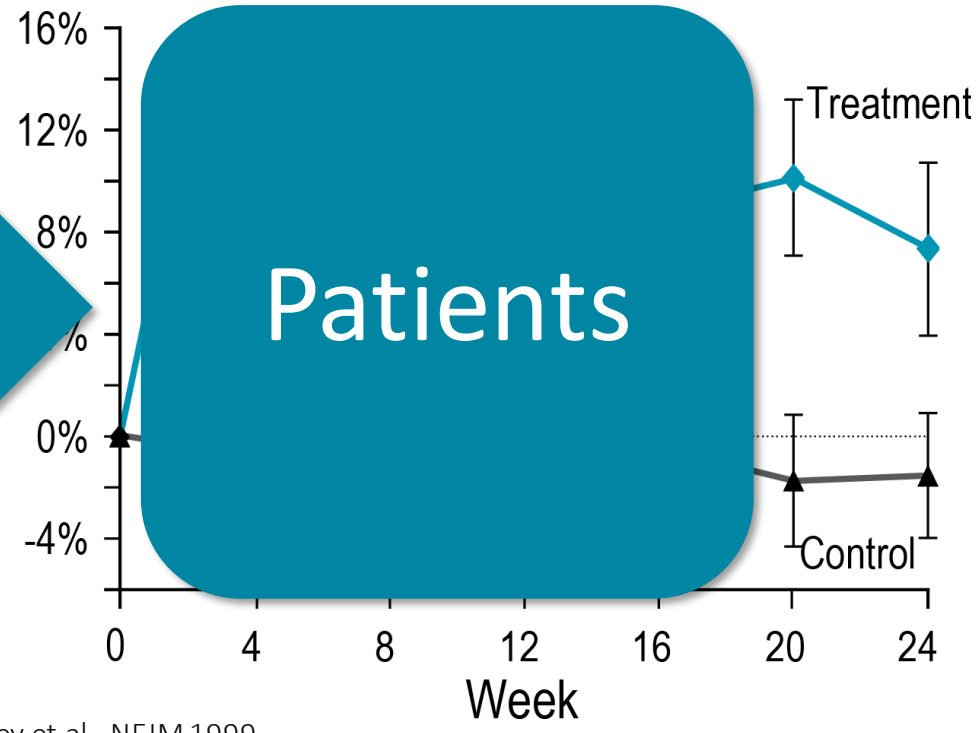
Critical contributors to CFTR modulator development: Preparing for the first human trials, 2000-2007

- Genotyping of the global CF population
- Bridging between laboratory findings and validated clinical endpoints with biomarkers of CFTR-dependent ion transport



Human bronchial epithelial cells

?



Patients

Van Goor et al., PNAS 2009

Ramsey et al., NEJM 1999

Critical contributors to CFTR modulator development: Preparing for the first human trials, 2000-2007

- Genotyping of the global CF population
- Bridging between laboratory findings and validated clinical endpoints with biomarkers of CFTR-dependent ion transport

Sweat chloride

Gold standard for CF diagnosis

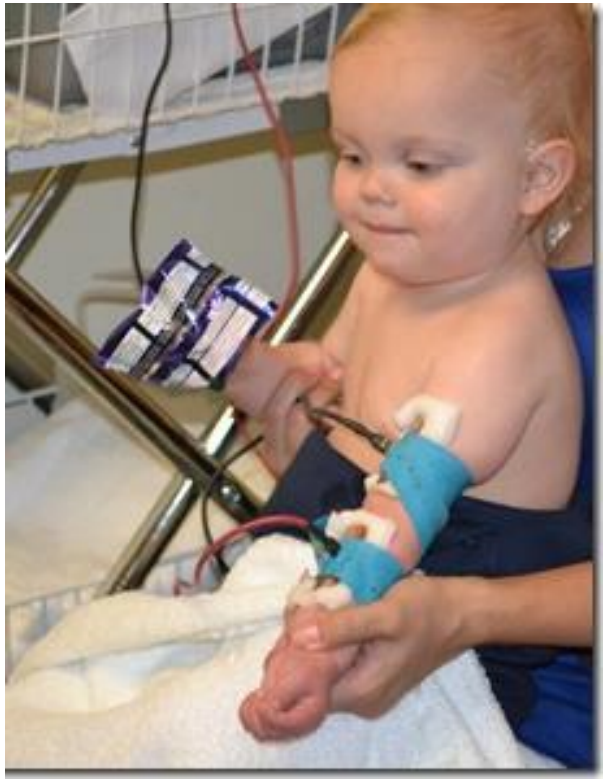
≥60 mmol/L

Direct measure of CFTR activity

Routine, non-invasive

Reproducible, low variance

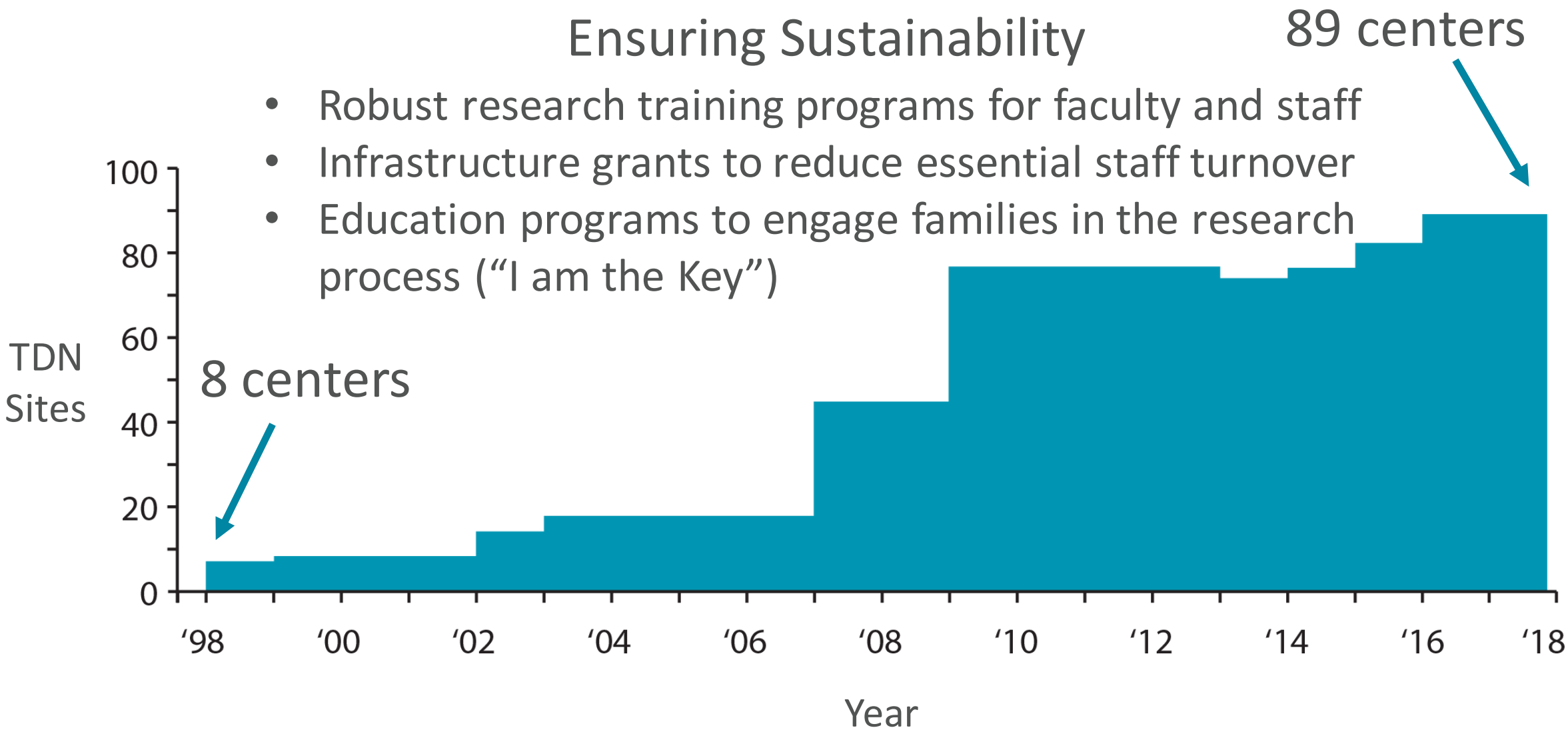
Much smaller sample size requirements to detect CFTR function change *in vivo* than other proposed biomarkers



Expansion of TDN capabilities: 1998 to present

Ensuring Sustainability

- Robust research training programs for faculty and staff
- Infrastructure grants to reduce essential staff turnover
- Education programs to engage families in the research process (“I am the Key”)



Advice Today

- Choose 1-2 active studies to “run through system” – PCR, Steering Committee, SOPs, etc.
- Choose 1-2 potential topics for NIH grants

Thank You

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

Translational Innovation Network (TIN)

- TIN Hub at each site available to assist site PIs and staff
- SMART IRB (NCATS Streamlined, Multisite, Accelerated Resources for Trials IRB Platform)
  - Developed to meet June 2016 NIH policy requiring NIH-supported clinical trials to use single IRB ethical review
  - May be one central IRB or different single IRB designated for each study
  - SMART has already provided authorization and “joinder” agreements across all CTSAs
  - In grant, Seattle Children’s designated as central IRB of record but could be changed for specific studies as long as SMART platform used

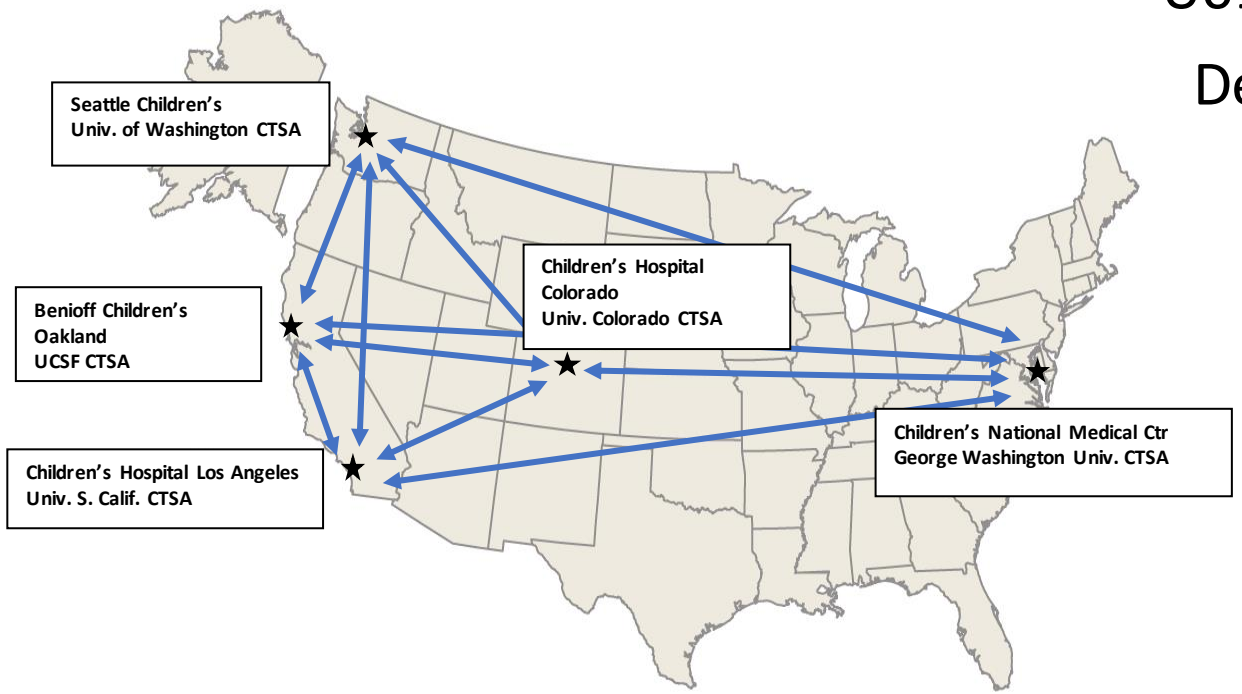
Translational Innovation Network (TIN), cont'd

- Master Contracting Agreements (ACTA)
  - All CTSA sites have agreed to utilize the same template and common terms (e.g. publication policy, intellectual property, etc.)
  - Does not pertain to existing contracts (e.g. PLAT studies)
  - Going forward, encouraged to start with ACTA language and follow "spirit" of the template
- Patient Recruitment Hubs (RICs)
  - Utilize tools for patient identification

Consortium of Pediatric Cellular Immunotherapy

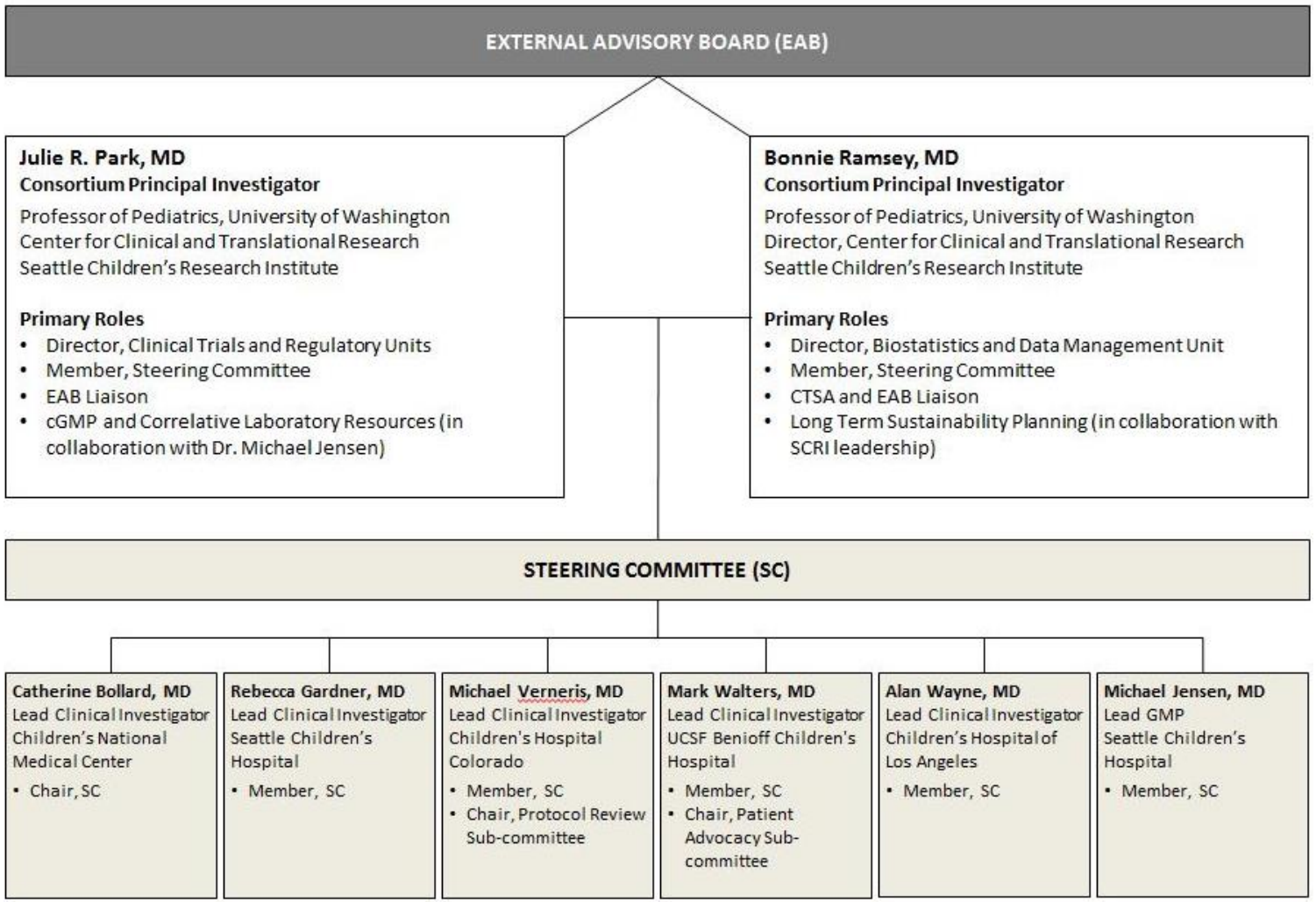
U01 Annual Meeting

December 6, 2018



Governance and Committee Structure

Roles and Responsibilities



Steering Committee

- Membership: Chair (Dr. Bollard) and Co-Chair, Voting Member from each site
- Responsibilities: Provide scientific oversight and prioritization. Oversee operations
- Term Limits: 5 years

Patient Advocacy Committee

- Membership: Chair (Dr. Walters), Site investigators (2); Site's CTSA Institute of Special Populations reps (2); patient advocates (2)
- Responsibilities: Ensure input from families and participants on all aspects of the therapeutic development process
- Term Limits: 3 years, staggered starting at year 2

Protocol Review Committee

- Membership: Chair (Dr. Verneris); CTU manager; Statistician; Site investigators (2); Clinical research assistant or research RN (2); patient advocate.
- Responsibilities: Critically review, critique, and rate protocols in the areas of scientific merit, feasibility and study design.
- Term Limits: 3 years, staggered starting at year 2

External Advisory Committee

- Membership: 3 members with experience in CTSA network, pediatric translation and clinical research.
- Responsibilities: annual performance review

Figure 2. Consortium for Pediatric Cellular Immunotherapy Governance Structure. The Steering committee will set scientific priorities and oversee operations of the consortium including oversight of the subcommittees, Patient Advocacy and Protocol Review Committees.

External Advisory Board

- An External Advisory Board will be composed of 3 members including a chair with CTSA network leadership experience, a senior laboratory or translational scientist with pediatric hematology/oncology or immunology expertise and a senior clinical scientist with expertise in pediatric clinical research
- The board will convene annually to review the Consortium progress including protocol development, implementation and dissemination and provide input on scientific prioritization
- Proposed Members
  - Leslie Kean – translational scientist (accepted)
  - Bruce Blazer – CTSA leader
  - Don Kohn – clinical scientist

Steering Committee

- The Steering Committee will provide scientific oversight and oversee operations
  - Set scientific priorities and will assign a scientific fit rating for protocol concepts
- Establish network-wide policies and procedures, review site performance
- Provide oversight of subcommittees including approval of subcommittee chairs
- Review proposals for use of archived data in ancillary studies
- Review manuscript and presentation submissions
- Identify and seek extramural funding opportunities

Steering Committee

- Membership: one voting member from each participating site, the cGMP lead, a Chair and co-Chair (?), U01 PIs.
- Chairs will be chosen by a voting process of site principal investigators. Term limits of 5 years will be applied to Steering Committee Members and Chairs.
- Members:
  - Chair – Cath Bollard
  - Sites – Wayne, Walters, Verneris, Gardner
  - GMP lead – Jensen
  - U01 PIs – Park and Ramsey

Patient Advocacy Committee

- The Patient Advocacy committee will ensure input from families and participants on the therapeutic development process including study design and implementation, patient accrual, patient diversity and dissemination of study results.
- Membership: Chair, Site investigators (2), Patient advocates (2), CTSA Institute of Special Populations. 3 year term, staggered starting at year 2
- Members
  - Chair: Mark Walters (U-BCHO)
  - Patient Advocates: Dana Dornsife; (Gianna McMillan, Bioethicist Loyola Marymount)
  - CTSA ISP: Tumaini Coker + ?
  - Site investigators: Kirsten Williams? + ?

Protocol Committee

- The Protocol Review Committee will critically review, critique and rate each protocol submitted for conduct within the Consortium in the areas of scientific merit, feasibility and study design.
  - Provide recommendations for protocol templates
  - Provide recommendations for standard data capture
  - Facilitate use of central IRB
  - Recommend standard processes for Conflict of Interest

Protocol Committee Membership

- Membership: chair, statistician, the CTU manager, a patient advocate, site investigators (2) and clinical research staff (2). 3 year, staggered starting at 2 years
- Members:
  - Chair: Michael Verneris (Colorado)
  - Statistician: Vicky Wu
  - CTU manager: Leslie Elliott
  - Research Staff (2): SCH + other site?
  - Patient advocate: ?
  - Site Investigators (2): Rebecca Gardner + ?

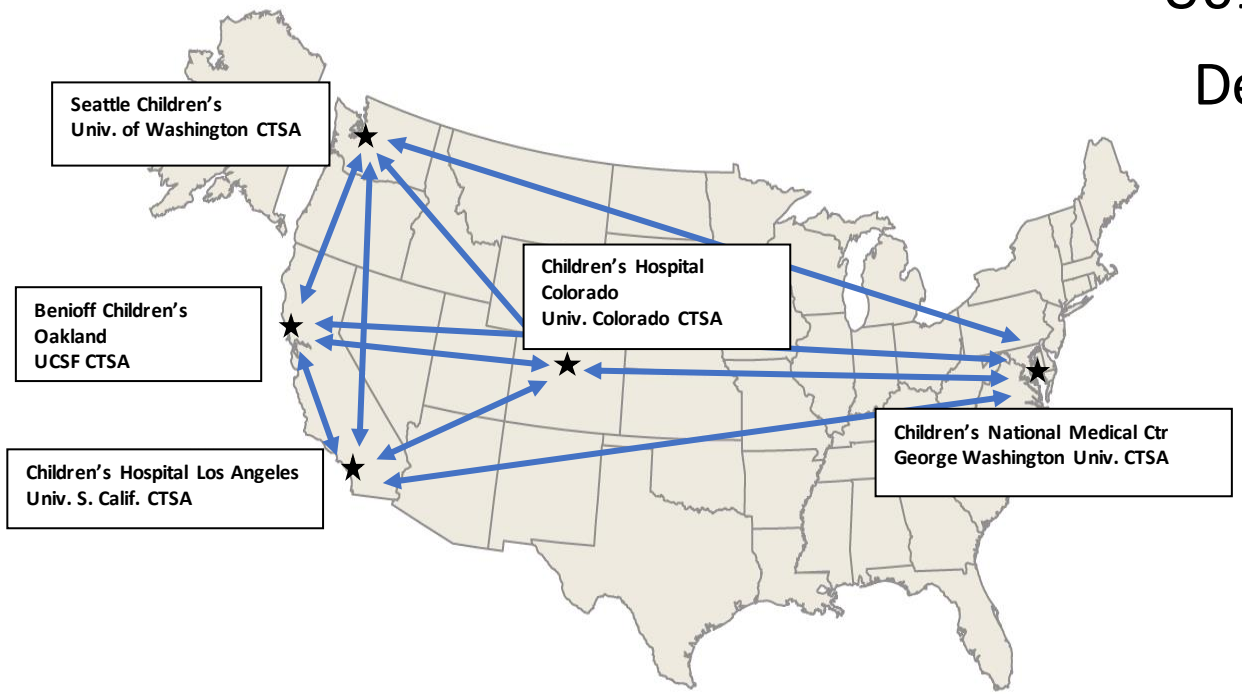
Site Responsibilities

- Participate in established U01 metrics
  - Staff or PI participation in the establishment of SOPs and training materials
  - Share knowledge
- Identify clinical trials for the consortium
- Recruit and/or refer patients for enrollment onto consortium trials
- Ensure patient safety
- Follow set CPCI guidelines for protocol conduct
- Foster education and training of staff

Consortium of Pediatric Cellular Immunotherapy

U01 Annual Meeting

December 6, 2018



SA1 Overview:

Expand a cGMP cellular therapeutics manufacturing program focused on single center trials to provide capacity and expertise to ensure state-of the-art cellular immunotherapy for multi-center clinical trials.

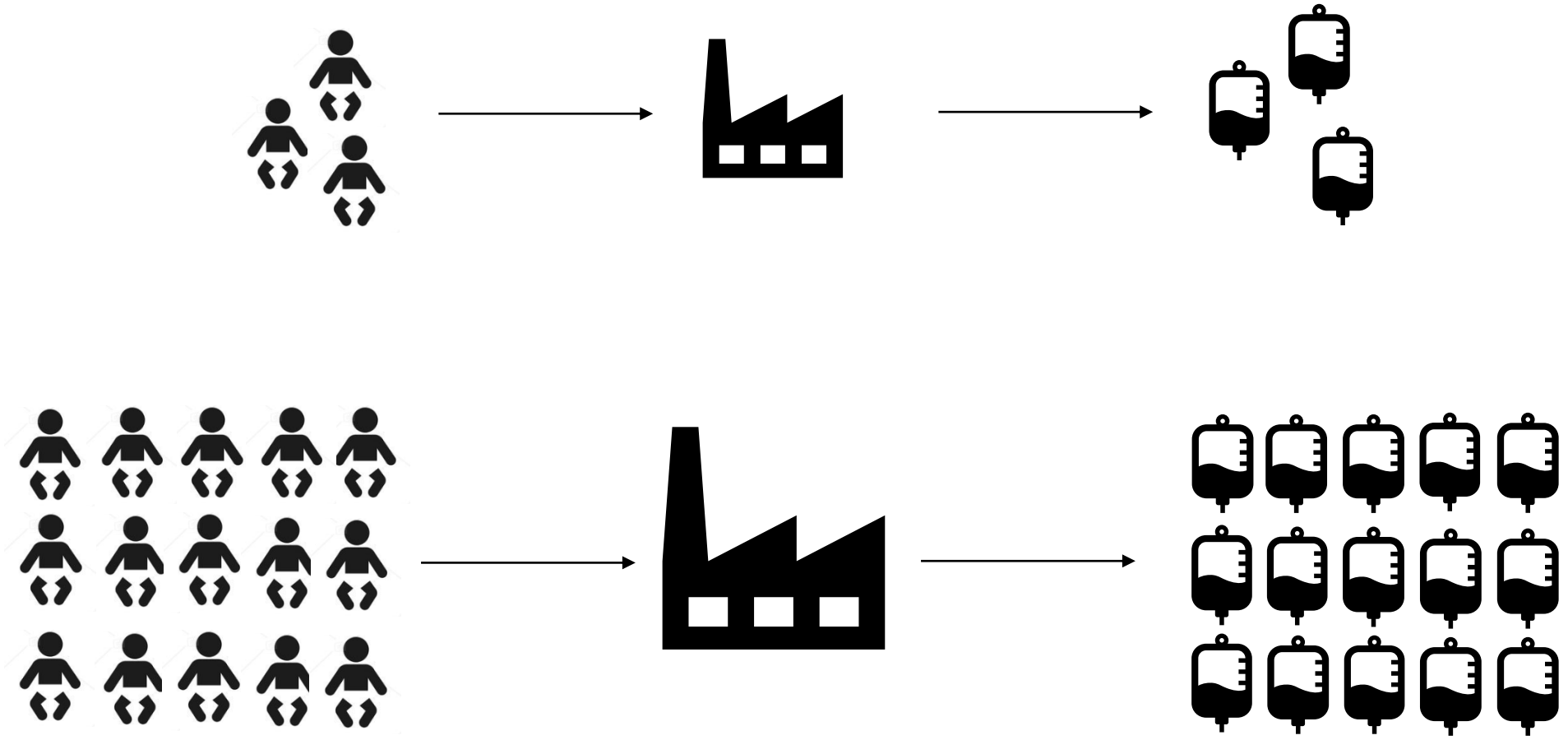
Subaims-

SA1A. Develop a work flow that can be scaled to provide cellular products across the consortium.

SA1B. Produce a series of standard operating procedures (SOP's) covering the manufacture and shipment of cellular products.

SA1C. Provide consultation to enhance the transfer of cGMP technology to other sites for use in establishment of additional cGMP facilities.

SA1A. Develop a work flow that can be scaled to provide cellular products across the consortium.



SA1a

Develop GMP workforce training modules and proficiency tests

- GMP regulations
- Aseptic training and assessment
- Manufacturing process training
- Quality control training
- Operator and verifier training
- Competency (written and practical assessment)

SA1b

Training group with representatives from consortium sites will align and train on best practices

- Product cryopreservation
- Mononuclear cell collection and shipment
- Final product shipping and receipt
- Preparation for infusion
- Manufacturing logistics
- On-site storage

SA1c

Subject matter experts across consortium will provide consultation services to other sites for:

- Facility design
- Vendor sourcing
- Supply chain confirmation
- Budget and cost assessments
- Process optimization
- Qualification and validation
- Development of manufacturing and testing SOPs

Strategy to get started

Year 1 -- Consensus meeting

Purpose: Define best practices

Potential areas of collaboration and alignment between sites:

- Annual proficiency/competency testing of cGMP staff
- Manufacturing and testing process optimization 
- Regulatory compliance
- Staff training

Desired outcome:

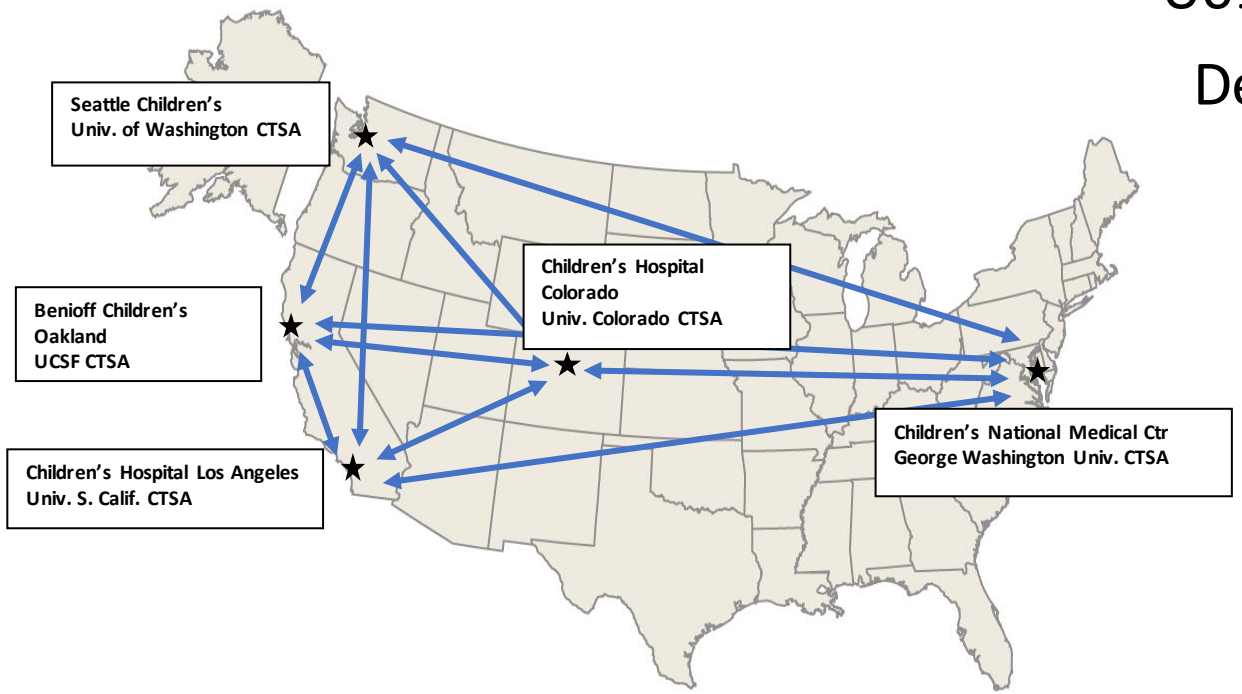
- Gap analysis
- Development of SOPs
- Training modules

- **Ongoing regular planned visits between sites**
- **2 consensus meetings a year**

Consortium of Pediatric Cellular Immunotherapy

U01 Annual Meeting

December 6, 2018



SA2: Expand the clinical development of cell-based immunotherapy

SA2: 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
  - Develop a clinical trials coordinating center with expertise in the development of cellular immunotherapy clinical trials
    - Tools for efficient clinical trial development and implementation
    - Resources for SOP and training modules for clinical trial implementation
    - Resource for monitoring
    - DSMB
    - Smart IRB and Accelerated Clinical Trial Agreement
- Utilize clinical trial designs that realize the unique constraints of rare disease-focused clinical trials in pediatric populations
  - Designs will recognize limitation in patient accrual and minimize complexity to increase feasibility of implementation and access to all patients

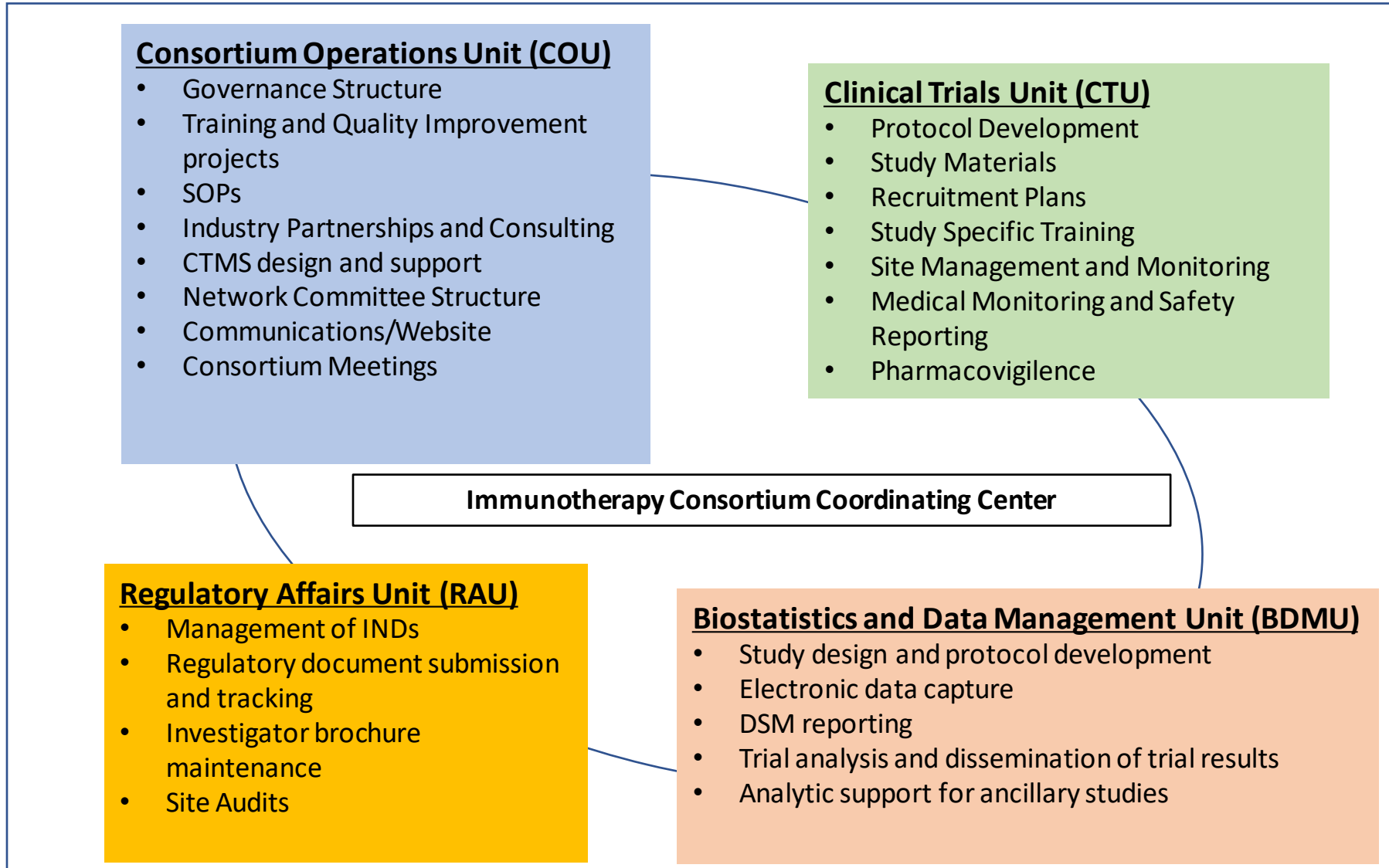
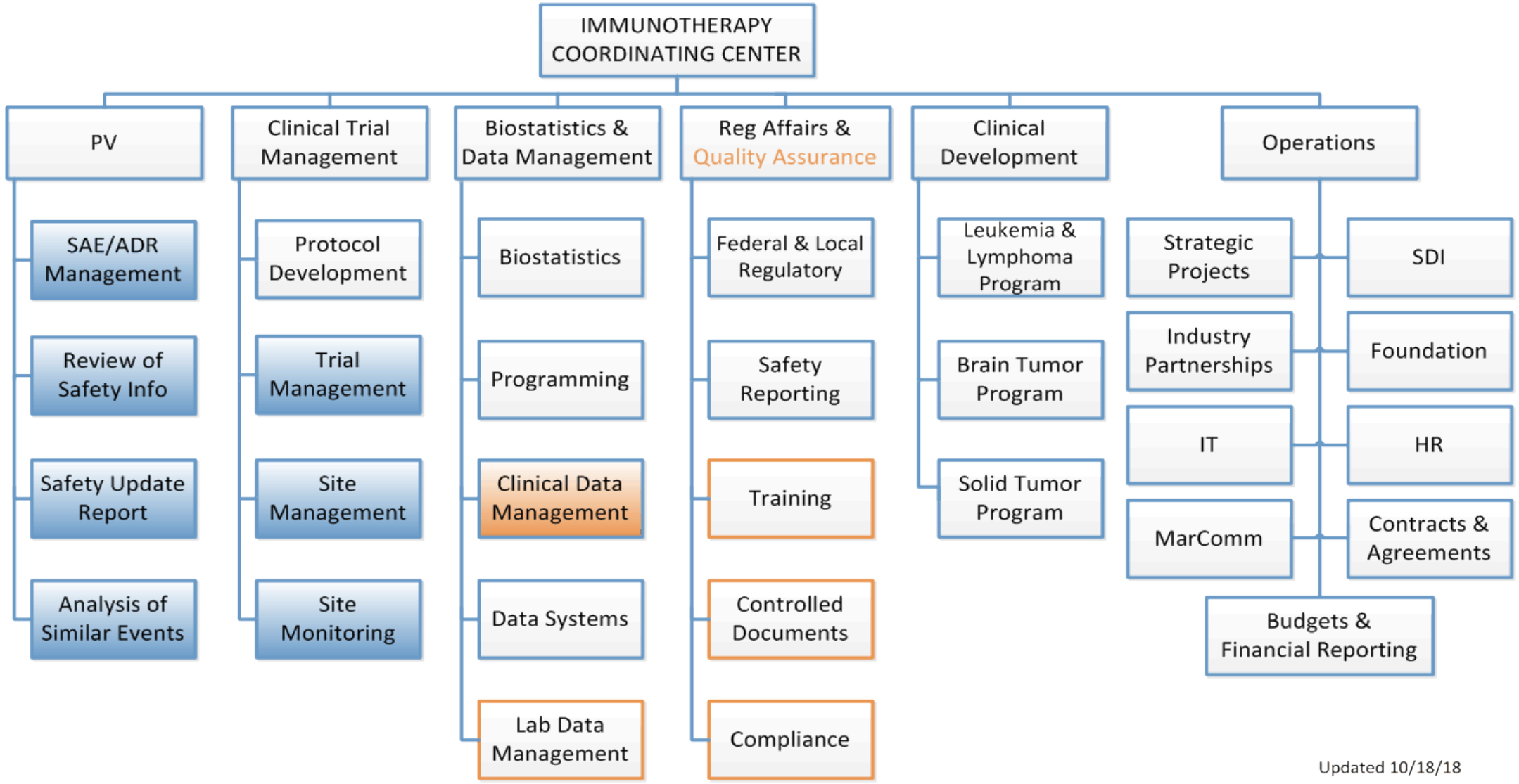


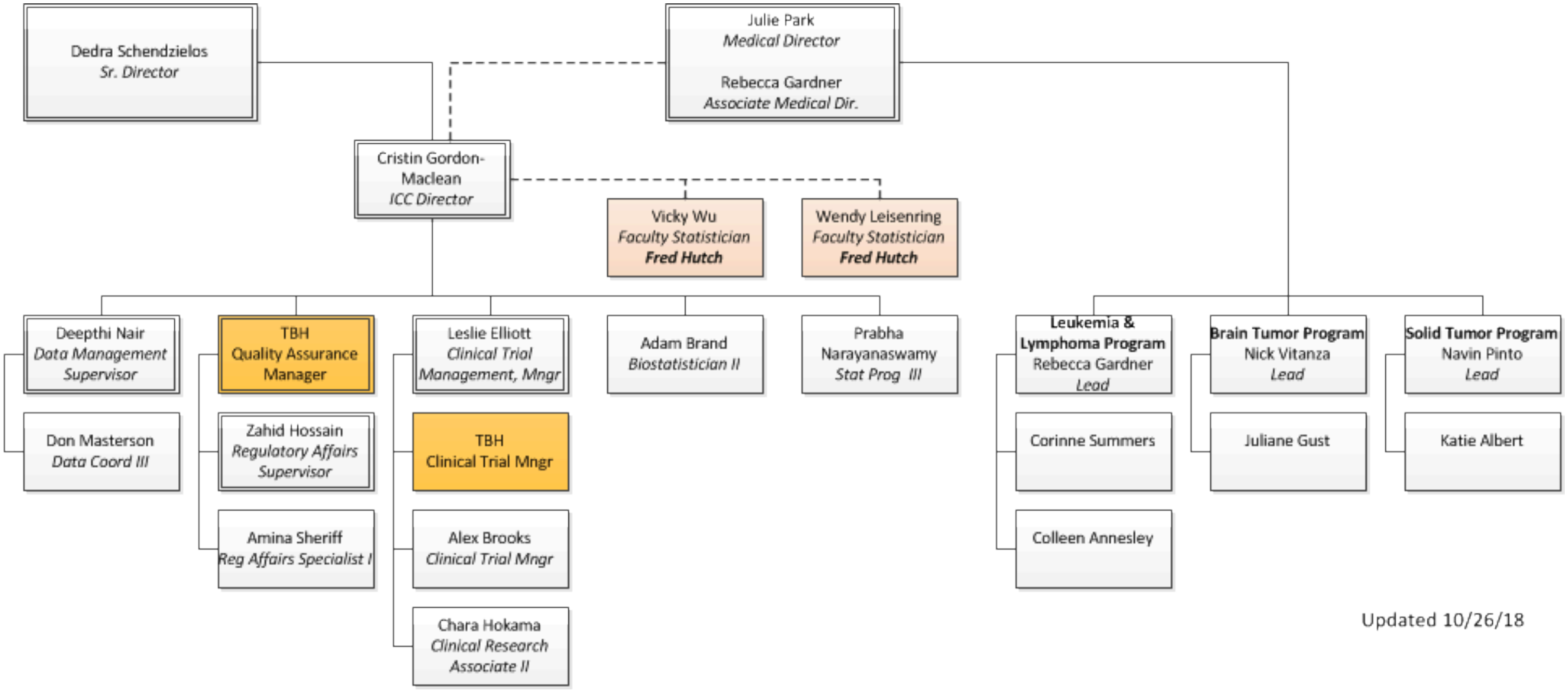
Figure 4. The Immunotherapy Consortium Coordinating Center (ICCC) will be composed of the four units noted above, all working together for implementation of clinical trials. Dr. Ramsey and Park will co-direct the ICCC including oversight of the Operations Unit. Dr. Park will be medical director of the CTU and RAU. Dr. Ramsey will be medical director of the BDMU.

ICC Organizational Chart

Functional Areas

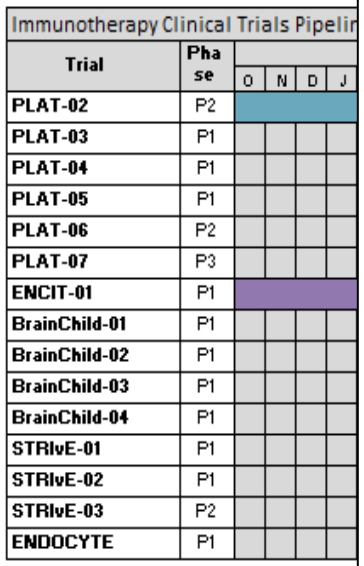


ICC Organizational Chart



Updated 10/26/18

Pediatric Cancer CAR T Cell – Clinical Trial Pipeline



PLAT - Pediatric Leukemia Adoptive Therapy

- PLAT-02: CD19CAR T Cell
- PLAT-03: CD19CAR T Cells + CD19t + T-APC's
- PLAT-04: CD22CAR T Cells for CD19neg Antigen Escape ALL
- PLAT-05: CD19x22 Bispecific T cells
- PLAT-06: huCD19CAR T Cell

ENCIT - Engineered Neuroblastoma CAR ImmunoTherapy

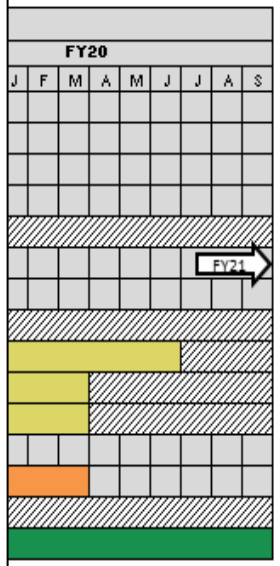
- ENCIT-01 Phase 1 L1CAM CAR G2 vs G3)

BrainChild - Locoregional CAR Immunotherapy for Pediatric Brain Tumors

- BrainChild-01: HER2CAR T Cells
- BrainChild-02: EGFRCAR T Cells

STRIvE - Solid TumoR ImmunothErapy

- STRIvE-01: EGFR806 basket trial



Process Improvement: Immunotherapy Clinical Trial Timeline and Dependencies

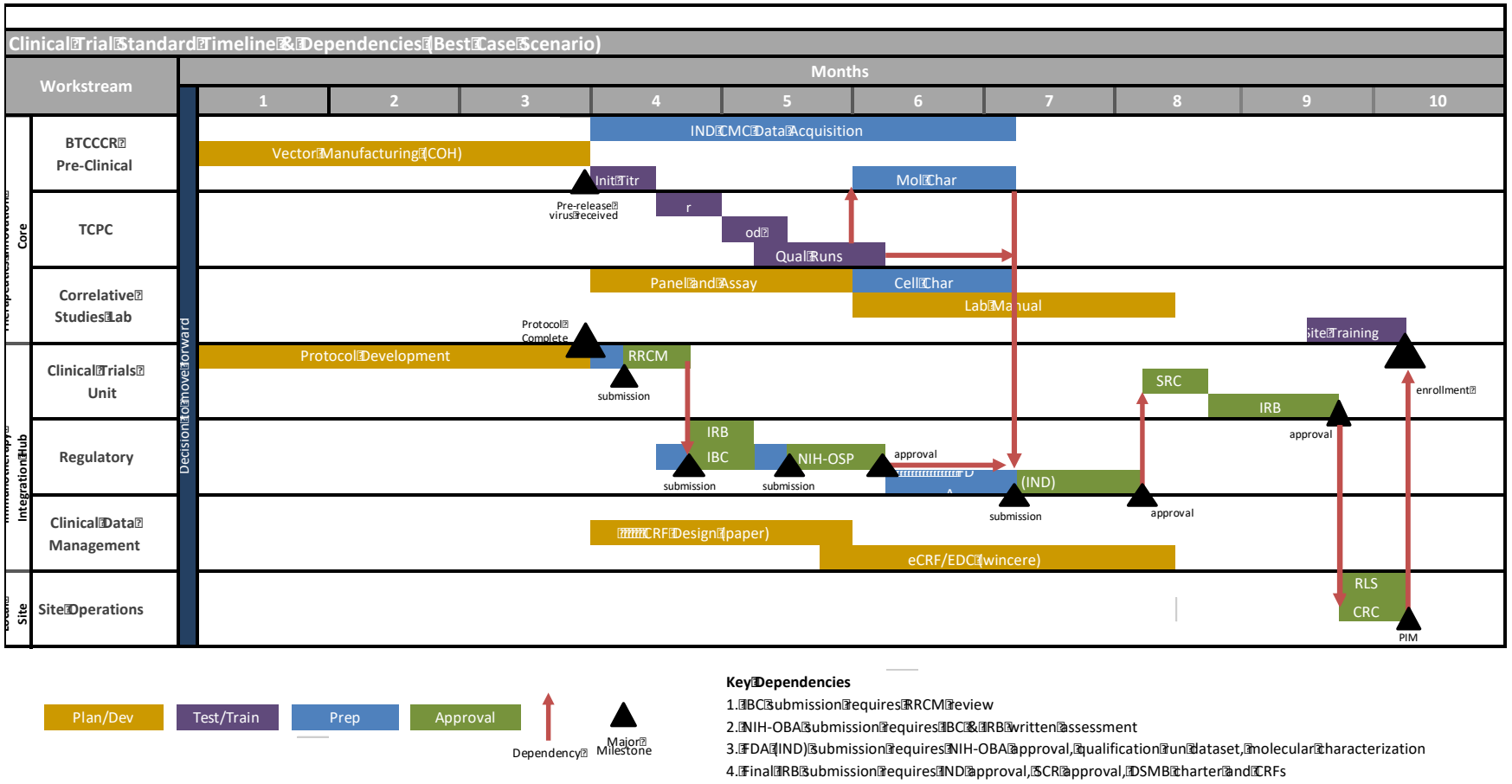


Figure 5. Lean methodologies will be employed to maximize efficiency of study development, implementation and analyses. Timelines and dependencies between protocol and cellular product development have been developed for CAR T cell trials (Figure 5) will be used to formulate similar dependency timelines for other forms of cellular immunotherapy. Such tools will be disseminated to throughout the CTSA using SDLC.

Additional potential ICC resources

- Protocol Template
- Standardized supportive care for toxicity
  - Pre-emptive treatment of CRS
- Staff training resources for CD19 CAR T cells
- Lean methodologies for process improvement
- Prioritization for which resources are developed for U01
- CPCI website?
  - Sharepoint with active trial materials
  - Teaching resources

Clinical development of cellular immunotherapies

- Ensure equitable access of all participants who may directly or indirectly benefit from cellular immunotherapies clinical trials.
  - Collaborate with the Patient Advocacy Committee (and Integrating Special Populations (ISP) Services at each of the CTSA hubs)
  - Recruitment efforts will also be enhanced by web-based outreach techniques (successfully employed by UCSF CTSA),
    - Social media advertisement linked to the pertinent study website.
    - External website?
      - Outreach
      - Study specific information about enrollment and contact?
      - CPCI website?

SA2 Outcome

- Develop an infrastructure to promote efficient and effective implementation of clinical trials, unsurpassed multidisciplinary care, education of site medical personnel to ensure safe implementation of cellular immunotherapy clinical trials.
- Export single center cellular immunotherapy clinical trials to multiple sites and increase patient access to cellular therapy for a variety of pediatric disease

SA2 Activities and Metrics

- Implement the Consortium Coordinating Center to monitor clinical trial conduct
  - Y1-2 Opened at least 2 trials in > 2 sites
- Develop immunotherapy specific training modules
  - Y1-2 Develop training models to assess toxicity reporting and analysis for 2 trials
- Develop tools for recruitment
  - Y3: Develop and implement tools to assess site accrual and data reporting

CAR-T Cell Cancer Immunotherapy

Trial	Clinical Target	Product	Phase	Site	Status	FY18	FY19	FY20	FY21	FY22
ENCIT-01	Neuroblastoma	L1CAM CAR T cells G2 vs G3	Phase I	SCH	Recruiting					
PLAT-02	ALL & NHL	CD19CAR T Cells	Phase I/II	Multi-site	Recruiting					
PLAT-03	ALL	CD19CAR T Cells + CD19t T-APC's	Phase I	SCH	Recruiting					
PLAT-04	ALL	CD22CAR T Cells	Phase I	SCH	Recruiting					
PLAT-05	ALL & NHL	CD19x22 Bispecific T Cells	Phase I	Multi-site	Recruiting					
STRIvE-01	Solid (non-CNS) Tumors	EGFRCAR T Cells	Phase I	SCH	Recruiting					
BrainChild-01	Brain & CNS Tumors (excl. DIPG)	HER2CAR T Cells	Phase I	SCH	Recruiting					
NCT02772679	18 – 45 years with type I DM (U-BCHO)	Polyclonal Tregs + IL-2 (TILT) – (UCSF)		U-BCHO						
NCT02244801	Therapy in Renal Transplantation: A ONE Study Clinical Trial (DART) (UCSF) 18 – 70 yrs (U-BCHO)	Donor-Alloantigen-Reactive Regulatory T Cell (darTreg)		U-BCHO						
NCT02203903	PRAME/WT1/Survivin-specific T cells for AML	T cells		CNMC						
NCT03180216	Virus specific T cells (CMV/EBV/Ad/Paraflu/HHV6/BKV) for pediatric patients after BMT	Virus specific T cells		CNMC						

CAR-T Cell Cancer Immunotherapy

Trial	Clinical Target	Product	Phase	Site	Status	FY18	FY19	FY20	FY21	FY22
PLAT-06	ALL & NHL	huCD19 CAR T Cells	Phase I/II	Multi-site	Recruiting					
BrainChild-02	Brain & CNS Tumors (excl. DIPG)	EGFRCAR T Cells	Phase I	SCH	Recruiting					
	AML	Ex vivo expanded NK cells		Colorado						
	PRAME/MAGE/Survivin-specific T cells with nivolumab for Hogdkins Lyphoma	PRAME/MAGE/Survivn T cells		CNMC						
	Anti EphB4 CART Cells for Pediatric Hematologic Malignancies and Solid Tumors	EphB4 CAR T cells		CHLA						
BrainChild-03	Brain & CNS Tumors (incl. DIPG)	B7H3CAR T Cells	Phase 1	SCH	In process					
STRIvE-02	Solid (non-CNS) Tumors	B7H3CAR T Cells	Phase 1	SCH	In process					
	Dinutuximab, IL-15 and Memory NK cells for GD2 expressing solid tumors	Memory NK cells		Colorado						
	Childhood Leukemia and Neuroblastoma	Antigen-presenting cell; a natural killer (NK)-derived Exosomes, CAR T Cells		CHLA						
BrainChild-04	Brain & CNS Tumors	IL13Ra2CAR T Cells	Phase 1	SCH	Planning					

SA2: Working Group

- Training Module
  - Topics?
  - Members?