Choosing ImmunoSuppression regimens in renal Transplant by Efficacy and Morbidity 2 (CISTEM2)

David Axelrod, MD, MBA, Transplant Surgeon, Health Services Research, University Hospital Cleveland
Vikas Dharnidharka, MD, MPH, Pediatric Transplant Nephrologist, Rutgers University

R01DK139339
https://github.com/gpcnetwork/r01_cistem2_study

University of Missouri

Background

University of Missouri

Background

- The transplant recipient's immune system recognizes new kidney transplant as foreign and attacks it
- Multiple medicines (i.e., immunosuppresants, IS) suppress the immune system but does not always work perfectly
- Therefore, transplant recipients susceptible to life-threatening infections
- Each IS medicine we use has some potentially major side effects; they can add up
- **Q: How do we choose which IS medicines, and how do we adjust over time?**

First Study: CISTEM1

- **Evaluated association of *initial immunosuppression regimen* with key clinical outcomes**
  - Patient and kidney transplant survival
  - Development of cardiometabolic complications (e.g. diabetes)
  - Infectious complications
- **Data sources**
  - Transplant Registry (SRTR) data on donor and recipient outcomes
  - Medicare FFS claims
  - Pharmacy claims
- **Results and Contribution**
  - Recognize that the choice of IS varies markedly across centers, even those serving nearly identical populations in the same region in the U.S.
  - Developed and piloted a free web-based application for kidney transplant
    - https://neph-calc-i2-wustl.azurewebsites.net/
    - Shared decision making
    - Improve discussion of options with patients
  - Utilize data sources beyond SRTR to assess outcome
    - SRTR/Medicare data to assess long term outcomes

University of Missouri

First Study: CISTEM1

- **Limitations**
  - Medicare claims lack detailed clinical data on kidney function and meaningful outcomes
    - Patients with advanced CKD are equivalent to patients with normal function
    - E.g., serum creatinine levels/eGFR, tacrolimus drug levels, measures of viremia and viruria, malignancy diagnoses, and rehospitalization events
  - Selection bias of patient cohort
    - Only assessed patients with Medicare primary insurance
    - Medicare pays > 60% of transplants but has fewer living donor recipients
  - Paucity of longitudinal data and responsive outcomes
    - How should immunosuppression be adjusted after an episode of rejection

Objective and Aims

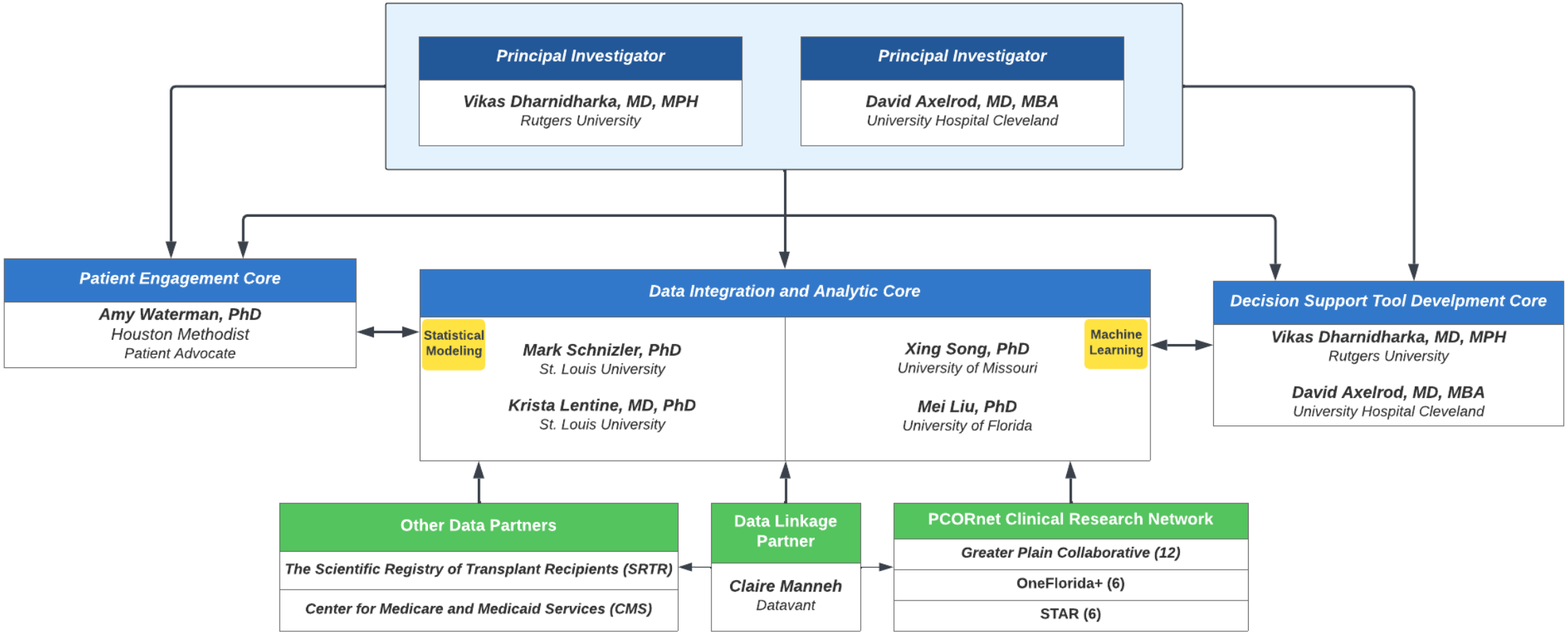
Aim 1: establish a novel, robust and curated database (CISTEM2 Database) **integrating transplant registry data with multi-site EHRs, claims and social determinants of health** data for KT recipients, leveraging the PCORnet infrastructure.

Aim 2: develop longitudinal machine learning (ML) algorithms to dynamically suggest immunosuppression (IS) strategies that optimize renal allograft function (at 1-, 3- and -5-years post-KT), reduce cost, and limit IS comorbidities.

Aim 3: validate and fine-tune the temporal-aware ML models to determine reliability in predicting long-term graft function in by additionally incorporating data from other two PCORI networks.

University of Missouri

Study Team



University of Missouri

Participating Sites

Transplant Hospital/ Health System	PCORnet CRN	#KTx 2012-23
University of Missouri (DCC)	GPC	179
Allina Health System	GPC	290
Intermountain Healthcare	GPC	1078
Medical College of Wisconsin	GPC	728
University of Iowa	GPC	836
University of Kansas Medical Center	GPC	1383
University of Nebraska Medical Center	GPC	1448
University of Utah	GPC	1276
UT Southwestern Medical Center	GPC	989
Washington University in St. Louis	GPC	2526
UT Health Science Center at Houston	GPC	637
GPC Total		***11,370***
Vanderbilt University Medical Center	STAR	2286
Duke University Medical Center	STAR	1497
Mayo Clinic Arizona	STAR	3407
Mayo Clinic Rochester	STAR	2171
Mayo Clinic Florida	STAR	1673
University of Florida	OneFlorida+	970
University of Miami	OneFlorida+	3726
Advent Health	OneFlorida+	1592
Emory University	OneFlorida+	2766
Tampa General Hospital	OneFlorida+	2749
University of Alabama at Birmingham	OneFlorida+	2620
Houston Methodist	Insight	??
Total (GPC/STAR/One Florida/Insight)		***36,827***

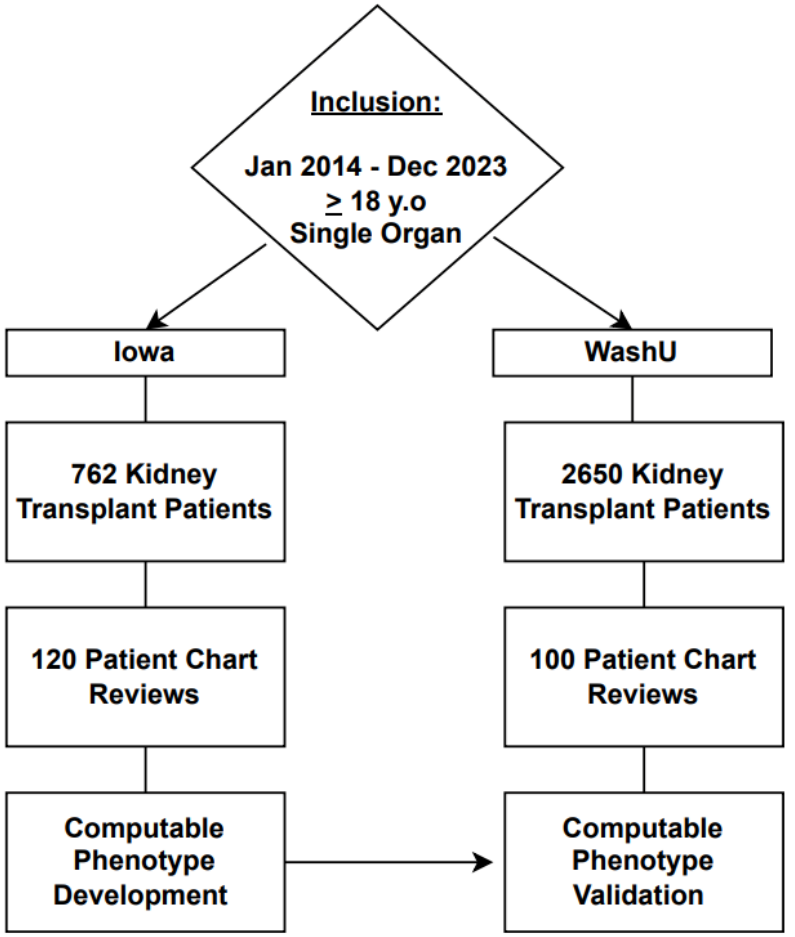
Missouri

Computable Phenotype Validation

Computable Phenotype Validation

Study Design

- 10-year retrospective cohort study across two transplant centers – *University of Iowa* and *University of Washington St. Louis*
- 220 / 3412 patient charts manually reviewed to identify true positive IS related complications
- Computable phenotype were developed comparing Iowa chart review results to PCORnet-coded data.
- Computable phenotypes were validated against WashU data.



University of Missouri

Computable Phenotype Validation (Cont.)

Acute Rejection

- ≥ 1 ICD Rejection diagnosis code within 12 months of transplant date
- **And** Renal biopsy procedure after transplant
- **And** Treatment with standard anti-rejection therapies

Classification	Code list	Codes
Renal Rejection	ICD9	996.81
	ICD10	T86.11

Medication class	Generic names	RXNORM_CUI
Methylprednisolone	Solumedrol	6902, 314099, 1743704, 1743729
Anti-Thymocyte Globulin	Thymoglobulin	107044, 107050
Rituximab		121191, 2472332

Procedures	Code List	Codes
Plasmapheresis	CPT	36514
Renal Biopsy	CPT	50200

	ICD Only	Iowa - CP	WashU - CP
PPV	57%	84%	97%
NPV	100%	100%	100%
Sensitivity	100%	100%	100%
Specificity	85%	96%	98%

New Onset Diabetes after Transplant (NODAT)

- ≥ 1 ICD diagnosis code for diabetes of any type after transplant date
- **And** 0 ICD diagnosis of diabetes of any type before transplant date

Classification	Code list	Codes
Diabetes Mellitus	ICD9	250.*
	ICD10	E09, E10, E11, E13

	ICD Only	Iowa - CP	WashU - CP
PPV	40%	75%	62%
NPV	90%	98%	100%
Sensitivity	97%	97%	100%
Specificity	15%	96%	95%

Myocardial Infarction

- ≥ 1 Diagnosis code for Myocardial infarct of any type after date of transplant
- **And** must be in-patient encounter type (EI or IP)

Classification	Code list	Codes
Myocardial Infarction	ICD9	410
	ICD10	I21; I22
	Encounter_Type	IP or EI

	ICD Only	Iowa - CP	WashU - CP
PPV	65%	100%	100%
NPV	100%	100%	100%
Sensitivity	100%	100%	100%
Specificity	95%	100%	100%

University of Missouri

Data Management Plan

University of Missouri

Dataflow

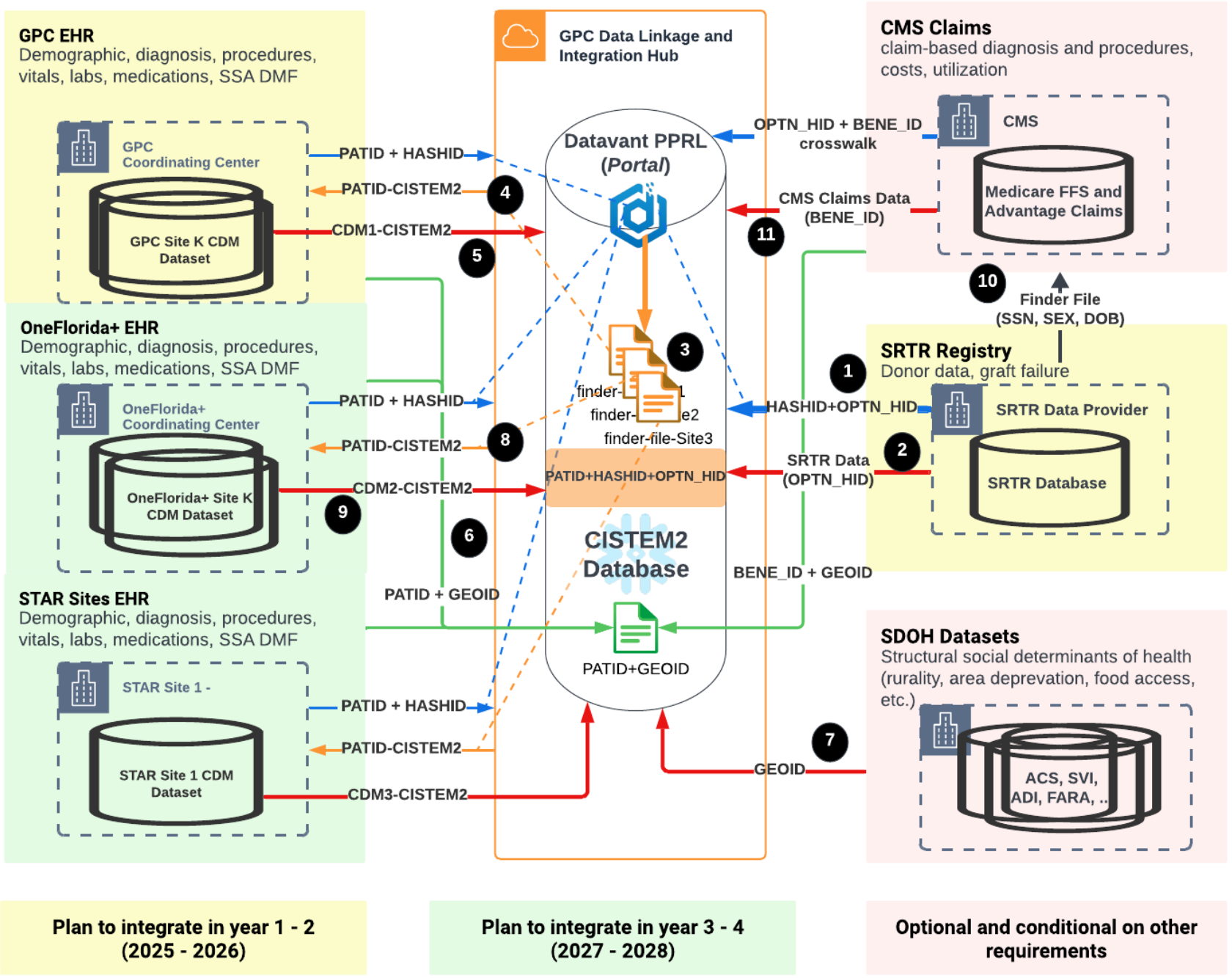
1. SRTR generate CISTEM2 study-specific tokens (HASHID)

2. Participating sites receive finder file from Datavant portal

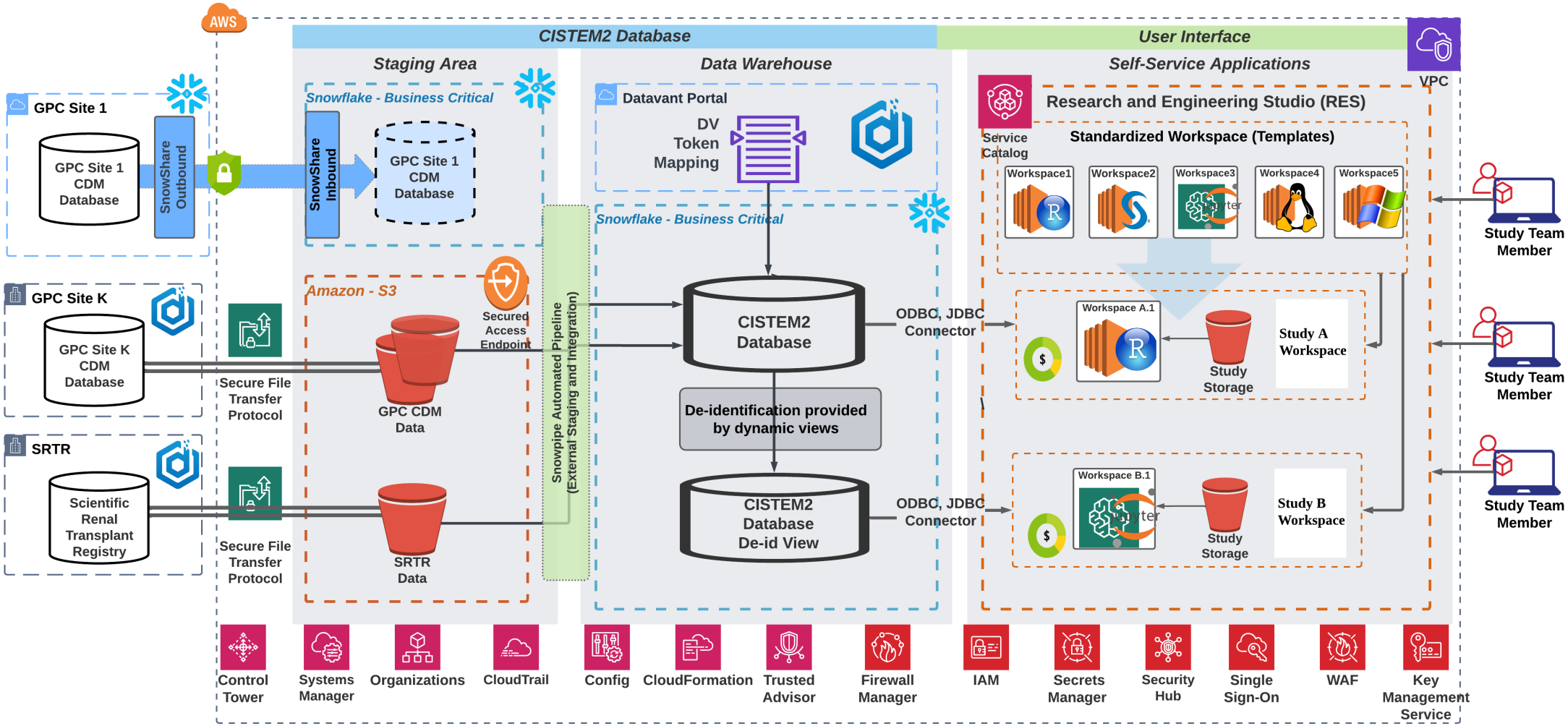
3. Reidentify patients from CDM by mapping to PATID via HASHID

4. Extract CDM tables for the CISTEM2-eligible, kidney transplant patients

5. Submit data to DCC



Data Enclave Architecture



University of Missouri

Site SOW and Budget

University of Missouri

Site SOW

Administrative Readiness

- IRB or Non-Human-Subject Determination
- Study-specific DUA

Technical Readiness

- Datavant local client: for generating study-specific hash tokens
- Datavant portal access: for downloading finder file generated from SRTR data
- LDS CDM extraction and submission

Analytical Participation

- Open github repo: https://github.com/gpcnetwork/r01_cistem2_rutgers
- Publication policy will be published

University of Missouri

Site Budget

Site Total budget: $28,762 (proposed)

Budgetary Items:

- Administrative and Startup costs (including small PI oversight effort)
- Hash token generation and linkage
- Site CDM Data-as-a-Product
- Other (e.g., infrastructure cost recovery, PM effort)

University of Missouri

Timeline (New)

University of Missouri

Milestones

Milestones	Target Date
Transfer grant awarded	10/01/2025
Medicare Claims reuse application submission	11/01/2025
CISTEM2 Data Enclave Phase I (Pilot GPC sites + full SRTR data)	12/01/2025
CISTEM2 Data Enclave Phase II (All GPC sites + full SRTR data)	04/01/2026
Non-GPC network administrative readiness	06/01/2026
CISTEM2 Data Enclave Phase III (All participating sites + full SRTR data)	11/01/2026

Engagement Efforts

University of Missouri

Patient Engagement Effort

- Conducted literature review of medication side effects; created plain-language explanations with *physicians*.
- Designed multiple *patient focus group* guides to address patient confusion in weighing preferences.
- Collaborated with *patient & qualitative advisory boards* to develop transplant-related preference questions.
- Final guide being piloted with *patients and physician*-reviewed before IRB submission; patient-friendly slides in development.
- Two *patient focus groups* scheduled at Houston Methodist within six months.

Amy D. Waterman, PhD, FAST
Director, Patient Engagement
Professor of Outcomes Research in Surgery,
Houston Methodist Academic Institute
Full Member, Houston Methodist Research Institute
Professor of Population Health Sciences in Surgery,
Weill Cornell Medicine
Deborah C. and Clifton B. Phillips Centennial Chair
for Clinical Research in Transplant Medicine

University of Missouri