The Making of the COMPARE-Pediatric IBD Study

Michael D. Kappelman, MD, MPH

University of North Carolina at Chapel Hill

Overview

- What is PCORnet®
- What is a PCORnet® Study
- Background, Rationale, and Design of the COMPARE Pediatric IBD study
- Use of PCORnet in the COMPARE study
- Study progress to date

pcori®

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Cycle 1 2024 Funding Cycle

Broad Pragmatic Studies
PCORI Funding Announcement

Maximum Project Budget (Direct Costs)	• Category 1: Less than or equal to $5 million in direct costs • Category 2: Greater than $5 million; up to $10 million in direct costs • Category 3: PCORnet® Studies up to $10 million in direct costs At the time of contract execution, PCORI sets aside all the funds associated with an awarded project to be made available throughout the contract's period of performance. The maximum budget includes all research- and peer review–related costs. For Category 2 and Category 3, projects may request up to $12 million in direct costs with certain justifications as described within the PFA, with PCORI approval required at the LOI stage, before application submission. Project budgets that exceed the $10 million in direct costs maximum without prior PCORI approval conferred at the LOI stage will be administratively withdrawn. PCORI approval to exceed the direct cost limit in applications for Category 2 or Category 3 does not guarantee funding of the application nor funding of the additional costs.

Use of the PCORnet resources to improve the efficiency or quality of the patient-centered research conducted (e.g. Common Data Model, single institutional review board, engagement resources)

So What is PCORnet?

One PCORnet® — Many Possibilities

PCORnet is a **national resource**, funded by PCORI, that enables insights from **high-quality health data**, **research expertise**, and **patient partnership** to deliver trustworthy answers that advance health outcomes.

Research Powered by PCORnet®

- Clinical Effectiveness Research
- Population health research
- Health systems research
- Implementation science research
- And more

More Than a Data Network

Access to patient partners and **thousands of clinicians** with expert knowledge of PCORnet-enabled data = meaningful research targets and faster answers.

The PCORnet® Common Data Model

- Standardized, structured EHR across health systems
- Frequent data curation

Ready for Research

Demographics	**Diagnoses**	**Procedures**
Vital Signs	**Labs**	**Clinical Observations**
Social Drivers of Health	**Medication Orders & Administrations**	**Patient-Reported Outcomes**

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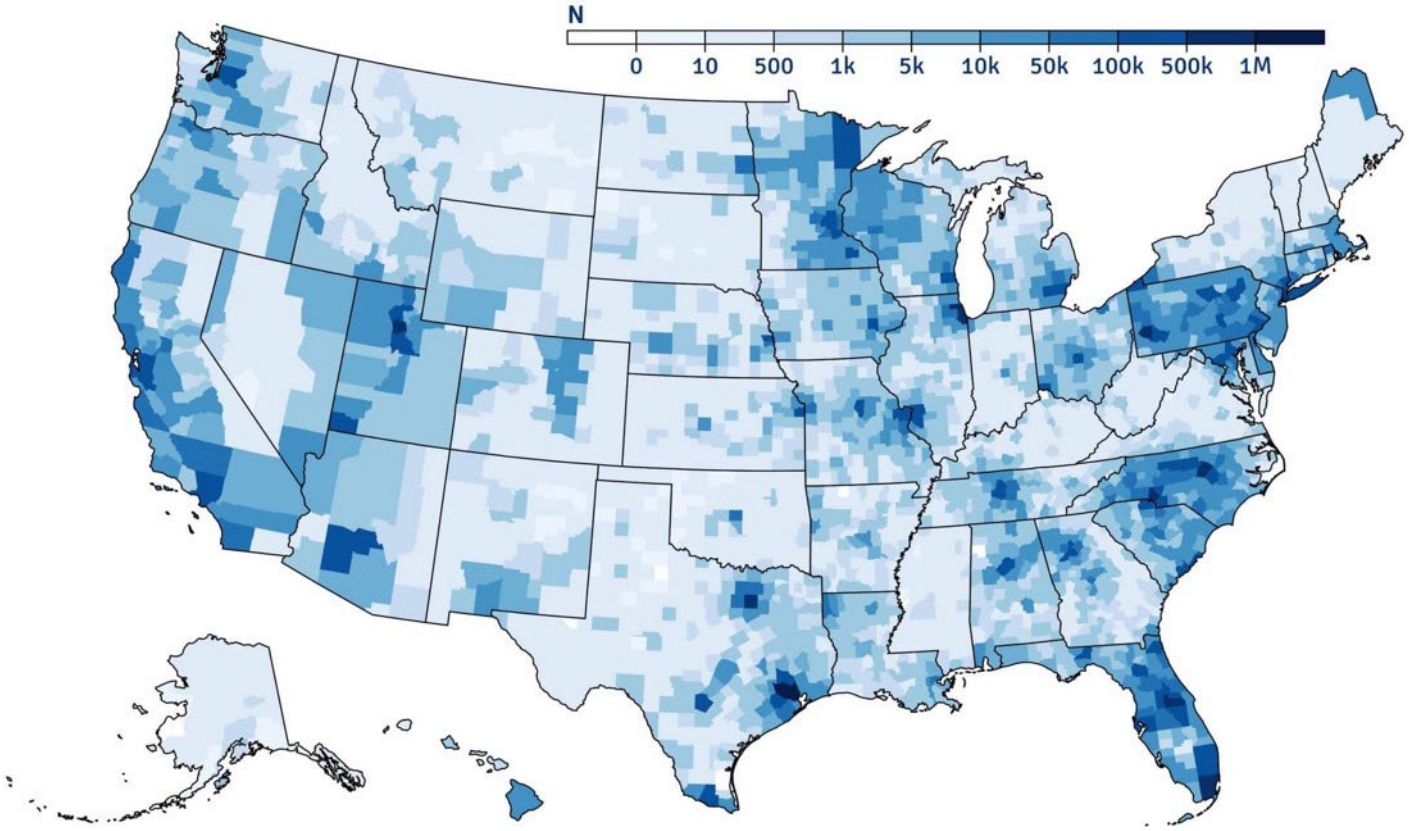
The National Patient-Centered Clinical Research Network

Scope of PCORnet-Accessible Data

PCORnet represents data from **everyday health care encounters** with more than **47 million people** annually across **all 50 States**, enabling large-scale, innovative, patient-centered health research



The data density map illustrates single addresses that are associated with individual PCORnet® Network Partner encounters.

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The National Patient-Centered Clinical Research Network

What is a PCORnet® Study?

PCORnet® Studies represent a deep level of partnership to advance patient-centered comparative clinical effectiveness research and other national-scale research.

PCORnet® Studies are committed to:

1. Collaborating with **two or more** PCORnet® Clinical Research Networks (CRNs)
2. Ensuring **stakeholders** are engaged throughout the project lifecycle
3. Broadly **disseminating findings** and returning study results to participants
4. **Sharing** study progress, performance metrics, and best practices with the network regularly
5. Leveraging PCORnet® resources (e.g., PCORnet® Common Data Model, Master Agreements, etc.) as appropriate

57

Active PCORnet® Studies

991+

Publications about PCORnet®

$644M

PCORnet® Study Funding

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The National Patient-Centered Clinical Research Network

COMPARE Study Background (for the non-Pediatric GI)

- **Inflammatory Bowel Disease (IBD),** including **Crohn's disease (CD)** and **ulcerative colitis (UC),** are chronic, immune-mediated gastrointestinal conditions with no cure
- Affects ~ **100,000 youth** in U.S, with increasing prevalence in recent decades
- **Gastrointestinal symptoms** include **abdominal pain, diarrhea, blood** in stool, and urgency/incontinence
- Profound impact on **nutrition, growth, physical, and psychosocial development**
- Up to 25% of patients may require **surgery** (and possibly ostomy) in first year from diagnosis
- Treatment can be very **costly**, often $20-30K per patient per year

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Background II

- Anti-TNF biologics are first-line therapy
  - Only FDA-approved advanced therapies for children
- Approximately ~30% experience treatment failure within 1st two years
  - Urgent need for additional therapies
- IBD treatment armamentarium continues to grow
- Many new therapies targeting different mechanisms of action FDA-approved for adults
  - Frequently used off-label in children
- No Comparative Effectiveness Research to guide treatment decisions for children for whom anti-TNF fails

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Aims

Aim 1. In children with **Crohn's disease** refractory to anti-TNF therapy, we will:

A) Compare the effectiveness of IL 12/23 inhibitors (ustekinumab, risankizumab, etc.), vedolizumab, upadacitinib and other emerging therapies;

B) Characterize the **safety** of these treatments by analyzing adverse events and laboratory abnormalities; and

C) Explore **heterogeneity of treatment effects (HTE)** across subgroups of clinical interest: age, time from diagnosis, baseline disease severity, number of prior anti-TNF therapies, and disease phenotype.

Aim 2. In children with **ulcerative colitis** refractory to anti-TNF therapy, we will**:**

A) Compare the effectiveness of IL 12/23 inhibitors (ustekinumab, risankizumab, etc.), vedolizumab, JAK inhibitors (tofacitinib and upadacitinib), and other emerging therapies;

B) Characterize the **safety** of the above treatments; and

C) Explore **HTE** across subgroups of clinical interest.

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Study Design

- **Parallel multi-center, <u>prospective</u> cohort studies** (CD and UC) developed with multi-stakeholder input that focus on comparative clinical effectiveness
- **<u>Retrospective</u> cohort studies using de-identified EHR data that focus on safety**
  - Larger sample size with longer follow-up

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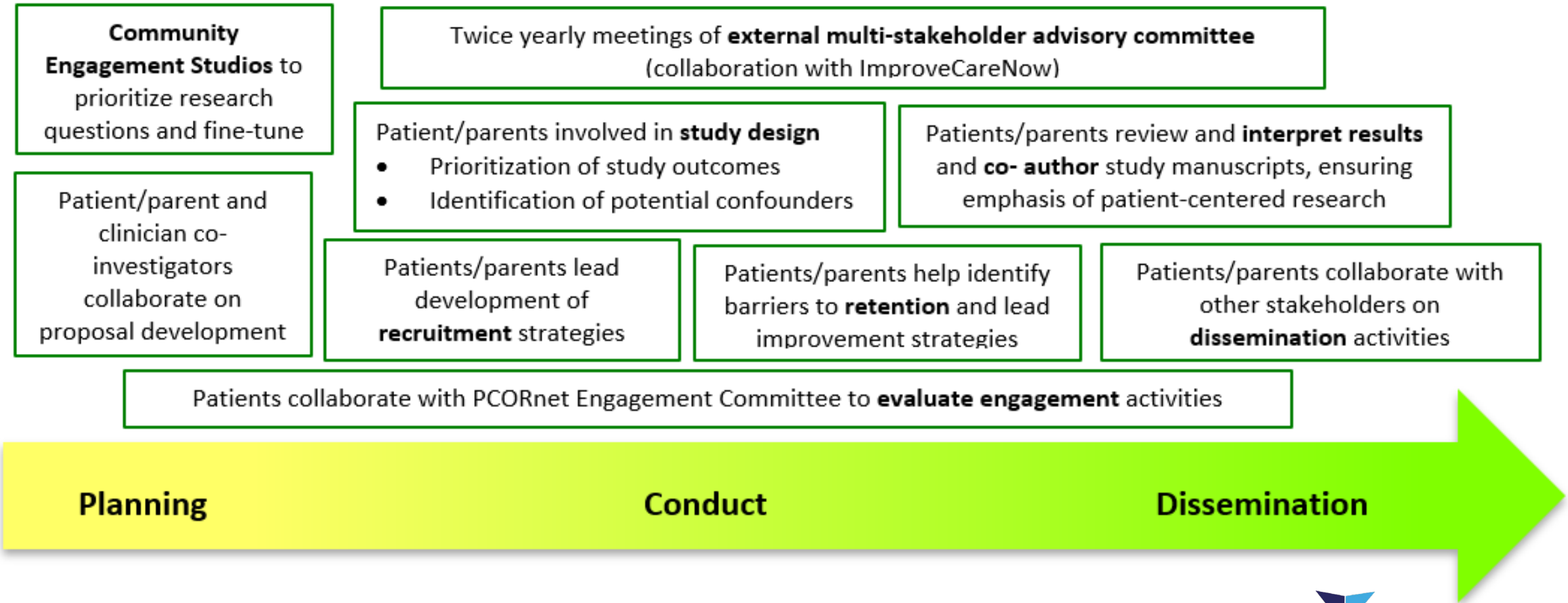
Engagement

Figure 3: Stakeholder Engagement across Project Lifecycle



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Prep-to-Research Engagement: Community Feedback Sessions

- 8 parents, 4 adult patients, and 4 clinicians
- Goals:
  - Pressure test importance of research question
  - Consider overall study design
  - Identify primary and secondary study endpoints

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Overall Study Design-verbatim from proposal

- "The pros and cons of these **alternative study designs were discussed with patient, parent, and clinician stakeholders."**
- **"**During the engagement studios, **100% of stakeholder participants strongly agreed or agreed that a prospective cohort study was the most appropriate design,** given the pros/cons of alternative designs."
  - 71% strongly agreed and 29% agreed that a prospective cohort would "**provide high quality data** that addresses this important knowledge gap"
  - 64% strongly agreed and 36% agreed that this study design would "**produce results that patients and providers can depend upon** in making clinical decisions."

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Study Outcomes

intestinal inflammation [e.g., fecal calprotectin (FC), c-reactive protein (CRP)], and 5) safety endpoints. A primary focus of our multi-stakeholder engagement studios was a detailed discussion of the strengths and limitations of these general classes of outcome measures as well as specific candidate measures within each class. Nearly all participants believed that a PRO should be either a primary or secondary outcome. Most participants believed that a clinical DAI and/or an endoscopic DAI should also be a co-primary or secondary outcome. Therefore, we propose co-primary endpoints of 1) a PRO and 2) a clinician-reported DAI. FC and endoscopic DAIs will be considered as secondary outcomes.

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Use of PCORnet® in COMPARE

Research done differently

- **Study sites**
- **Prep-to-Research Queries**
  - Demonstrate current, real-world use of comparators in population of interest
  - Feasibility of recruitment at participating centers
- **Administrative efficiencies**
  - Use case for PCORnet® Clinical Research Collaboration Agreement
  - sIRB
  - Research Readiness Coordinators and other levers
- **PCORnet® Common Data Model**
  - Support recruitment
  - Supplement chart review and manual data entry
    - Ease site burden; minimize human error
  - Low-touch monitoring
  - Assess representative of study population
  - Expanded safety analysis-larger cohort, enrolled and unenrolled participants

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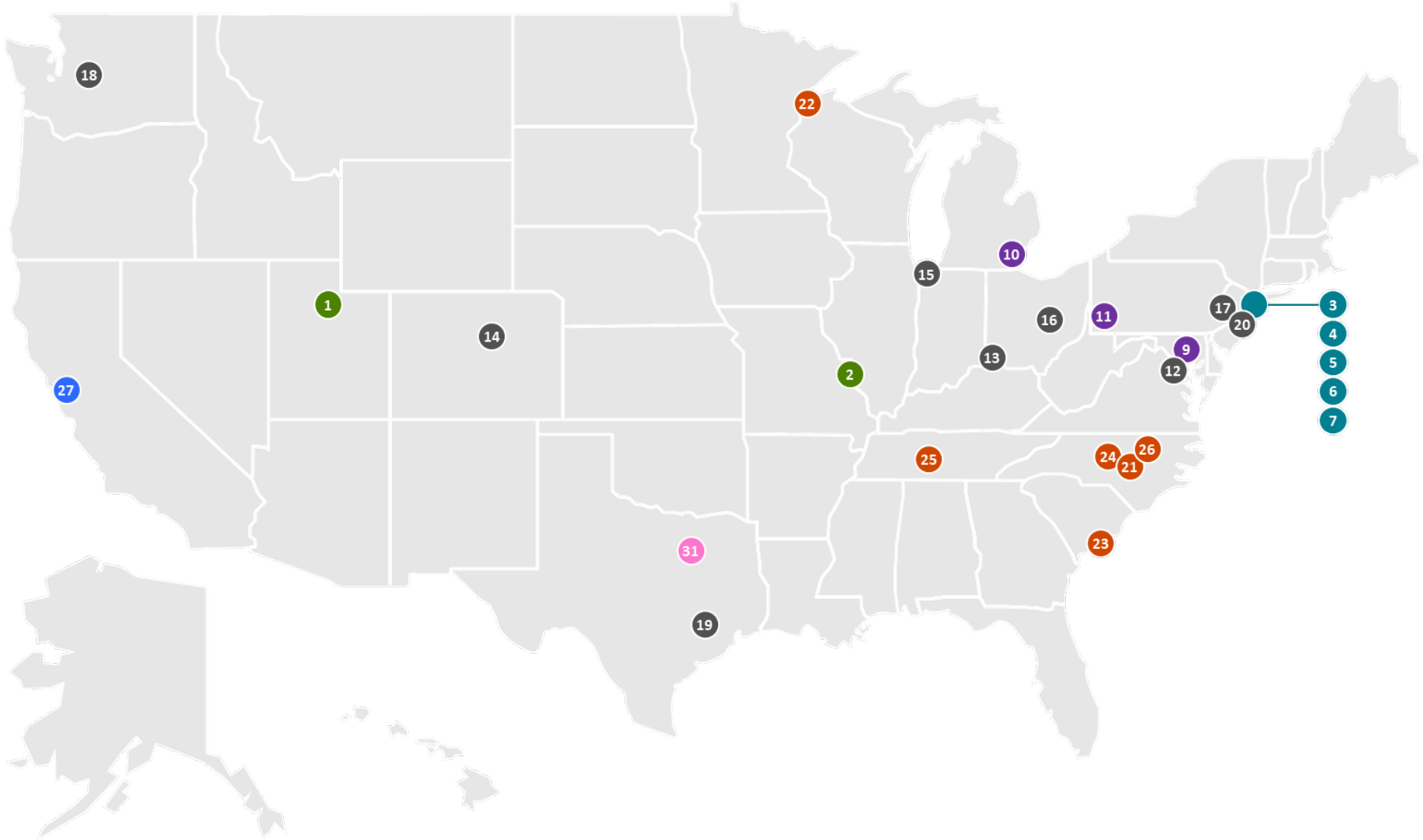
COMPARE Sites & Corresponding PCORnet® Clinical Research Network Locations



GPC
1. University of Utah
2. Washington University in St. Louis

INSIGHT
3. Columbia University Irving Medical Center
4. Montefiore Einstein
5. Mount Sinai Health System
6. NYU – Langone Health
7. NYU – Lake Success
8. Weill Cornell Medicine

PaTH
9. Johns Hopkins University
10. University of Michigan
11. University of Pittsburgh

PEDSnet
12. Children's National Hospital
13. Cincinnati Children's Hospital
14. Colorado Children's Hospital
15. Lurie Children's Hospital
16. Nationwide Children's Hospital
17. Nemours Children's Health
18. Seattle Children's Research Institute
19. Texas Children's Hospital
20. The Children's Hospital of Philadelphia

STAR
21. Duke University
22. Mayo Clinic
23. Medical University of South Carolina
24. University of North Carolina
25. Vanderbilt University Medical Center
26. Wake Forest University School of Medicine

REACHnet
27. University of California, San Francisco

Non-PCORnet Sites
28. Penn State University (Penn State Health Children's Hospital)
29. Indiana University (Riley Hospital for Children)
30. Emory University (Children's Healthcare of Atlanta)
31. UTSW (Children's Medical Center, Dallas)

Prep-to-research work using PCORnet resources

PCORnet prep to research query

Table 1. Demographic characteristics of ant-TNF experienced patients with PIBD initiating emerging biologic and small molecule therapies		
	CD (n=983)	**UC (n=524)**
Mean age (years)	13.6	13.7
% Female	48%	50%
White race (%)	73%	76%
Black race (%)	8%	9%
Other race/missing (%)	19%	15%
% Hispanic	9%	14%

Table 3. Comparator Agents and frequency of use in PIBD	Percent of CD patients using agent after prior anti-TNF	Percent of UC patients using agent after prior anti-TNF
Vedolizumab (α4β7 integrin antibody)	25%	49%
Ustekinumab (anti-IL-12/23 antibody)	72%	37%
Risankizumab (selective IL-23)	<1%	<1%
Tofacitinib (small molecule JAK)	3%	12%
Upadacitinib (selective JAK 1 inhibitor)	<1%	<1%
Ozanimod or etrasimod (sphingosine 1-phosphate receptor modulators)	<1%	<1%

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Use of the PCORnet® Common Data Model

- Plan to send quarterly queries to all sites
  - Same query, updated regularly
- Uses of query
  - Supplement chart review and manual data entry
    - Ease site burden; minimize human error
  - Support recruitment
  - Low-touch monitoring
  - Expanded safety analysis
  - Assess representativeness of study population

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PCORnet® CDM to supplement chart review and manual data entry

- Pull high-quality, discrete data that don't require manual review directly from EHR
  - e.g. height, weight, vitals, many labs, etc.
- Also built eCRF forms for these values as not all test results are included as discrete data
  - Outside labs that are scanned documents, etc.

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PCORnet® CDM queries to support recruitment

- PCORnet® CDM query will identify participants in site DataMarts that appear to have met eligibility criteria
- Compare this with actual enrolled participants
- Generate report for sites

Recruitment Opportunity Report

Patient ID	PARTICIPANTID	Enrollment Status	Index Comp Agent	Index Date	Most Recent Dx (UC/CD)	Most Recent DX Date (UC/CD)

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PCORnet® CDM queries for low-touch monitoring

- Identify events of interest in enrolled participants
- Use as a reminder for sites to complete chart abstraction and eCRF entry as needed

Emergency Visits (enc_type = 'ED)

PARTICIPANTID	Patient ID	Enrollment Date	Admit Date	EncounterID	DiagnosisID	Diagnosis Type	Encounter Type	DX

Hospitalizations (enc_type = 'EI', 'IP', 'OS', vs. 'IS')

PARTICIPANTID	Patient ID	Enrollment Date	Type	Admit Date	Discharge Date	DiagnosisID	Diagnosis Type	DX

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PCORnet® CDM queries for low-touch monitoring (2)

Outpatient Oral Steroid Use (based on data in the PRESCRIBING, DISPENSING and EXTERNAL MEDS tables; see Medications for of qualifying drugs)

PARTICIPANTID	Patient ID	Enrollment Date	Med ID	CDM Table	Rx Date	Drug Name

Infections or Cancer (see Diagnoses for list of qualifying diagnoses)

PARTICIPANTID	Patient ID	Enrollment Date	Diagnosis ID	Diagnosis Date	Diagnosis Concept

Abnormal Liver or Kidney Tests (based on a quantitative result outside of the normal range for the test, regardless of the unit of measure. See Labs for list of qualifying lab tests)

PARTICIPANTID	Patient ID	Enrollment Date	Lab Result _ID	Lab Date	Lab Test Name	Numeric Results	Result Modifier	Result Unit	Normal range

Comparator Agent Use (based on medications in the PRESCRIBING, MED_ADMIN, PROCEDURES, EXTERNAL_MEDS, or DISPENSING table after the enrollment date. If there are multiple records for the same drug name only list the first record. See Medications for list of qualifying drugs)

PARTICIPANTID	Patient ID	Enrollment Date	Med ID	CDM Table	First Rx Date	Drug Name

PCORnet® CDM for retrospective safety studies

- Comparator agents have been used in this population for a decade
  - Demonstrated by preliminary data
- Not all patients who start comparator agents over next 3 years will be enrolled in the prospective cohort
- Many of the safety events of interest can be readily identified in EHR data
  - Malignancy, serious infections, venous thromboembolic events
- Advantages of analyzing EHR data
  - Larger sample size
  - Longer follow-up
  - Don’t need to wait 5 years for an answer

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PCORnet® CDM to evaluate representativeness

- **Super unique opportunity**
- We know who ***could be enrolled***
- We know who is ***actually enrolled***
- We can compare their “baseline characteristics”
  - **And outcomes**

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Administrative efficiency

- Use case for PCORnet® Clinical Research Collaboration Agreement
- sIRB
- Leveraging Research Readiness Coordinators, PCORnet® CRN PIs, and PCORnet® CRN site PIs

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Startup metrics-contracts

- All 31 site contracts fully executed (~7 months)
- First site: 34 days; last site: 196 days
- Median days to contract execution: 95.5 days
- Variation by CRN (median days)
  - STAR (89 days)
  - PEDSnet (94 days)
  - PaTH (118 days)
  - INSIGHT (129 days)
  - GPC (86 days)

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IRB reliance

- 23/31 sites approved (7 months)
- On track for all sites to be approved by end of Feb
- Variation by CRN (% sites IRB approved by 7 months)
  - STAR (100%)
  - PEDSnet (78%)
  - PaTH (75%)
  - INSIGHT (33%)
  - GPC (75%)

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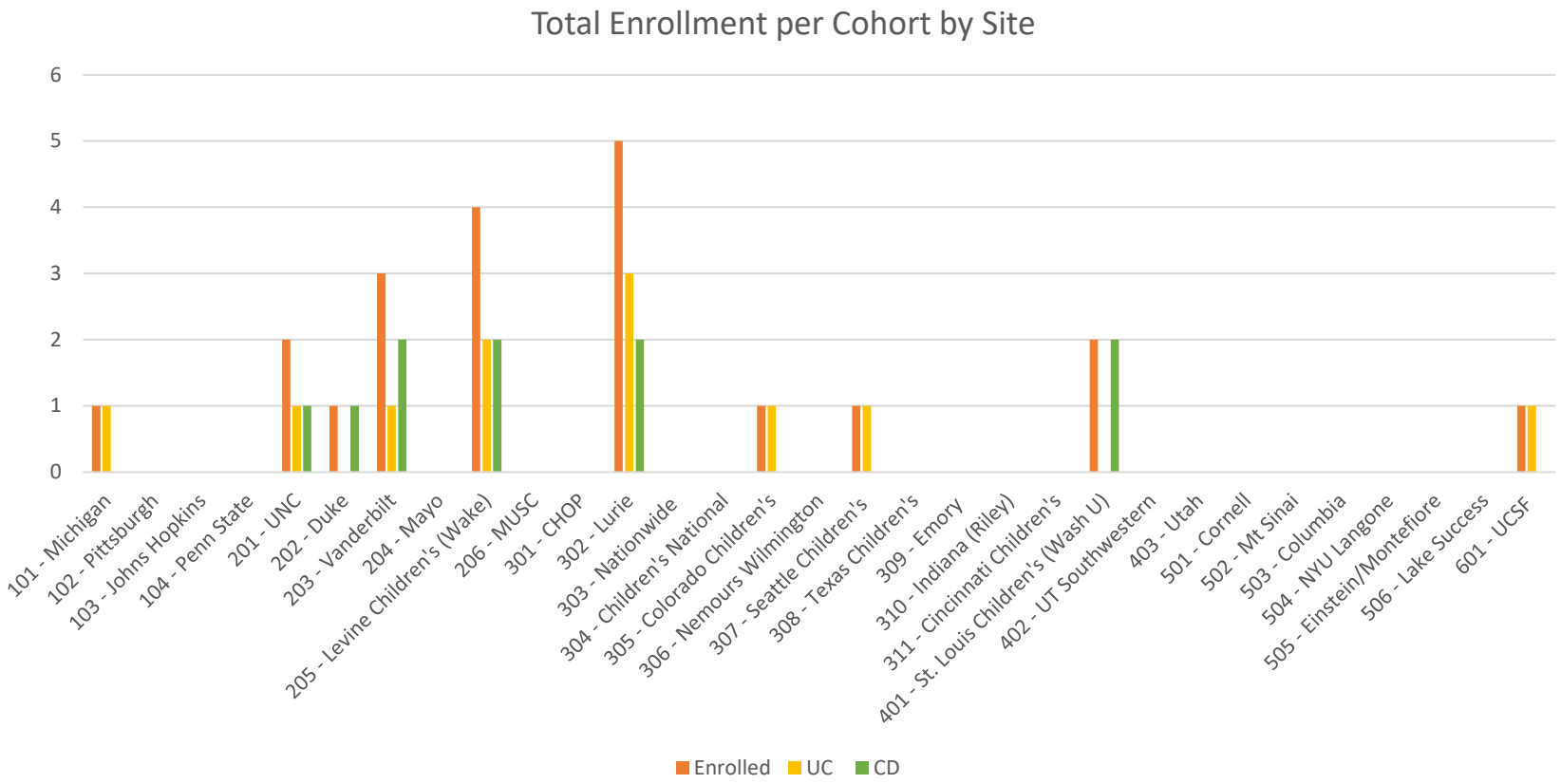
21 Participants Recruited across 9 Sites

- Lurie
- UNC
- Michigan
- Wake Forest/Atrium
- Seattle Children’s
- Vanderbilt
- Colorado
- Duke
- UCSF



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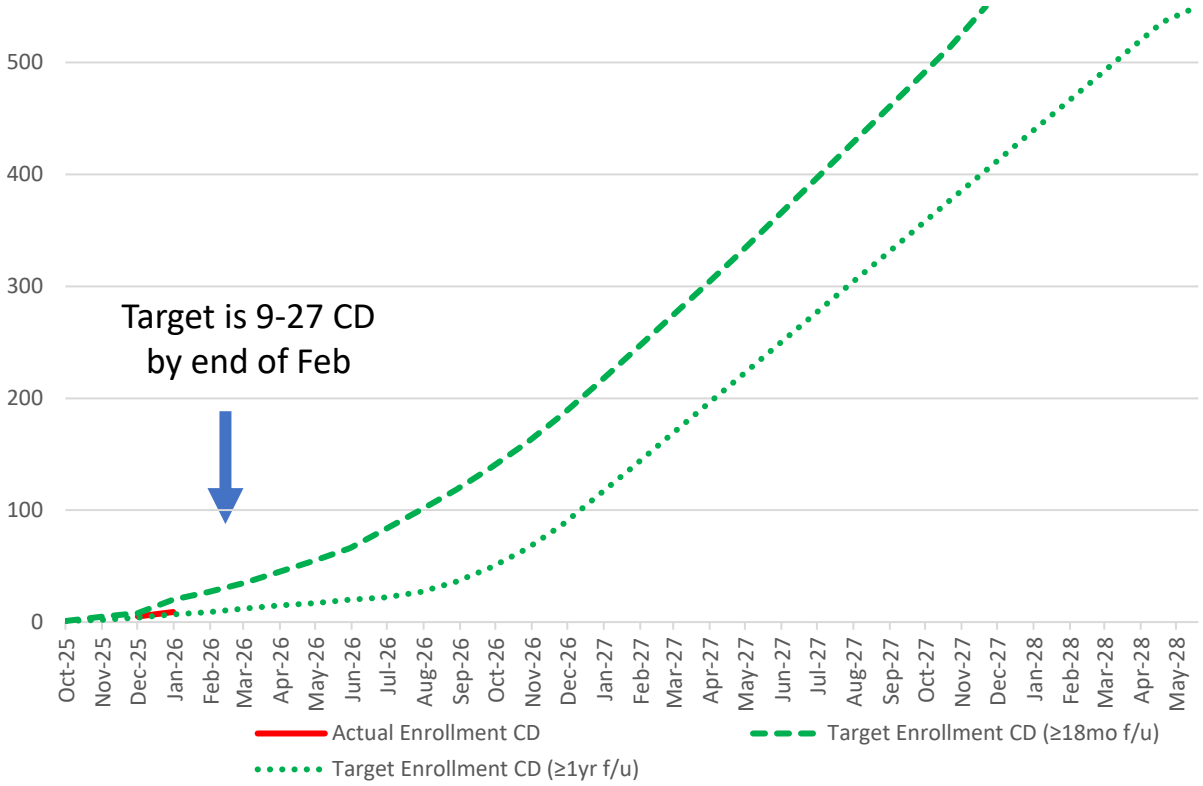
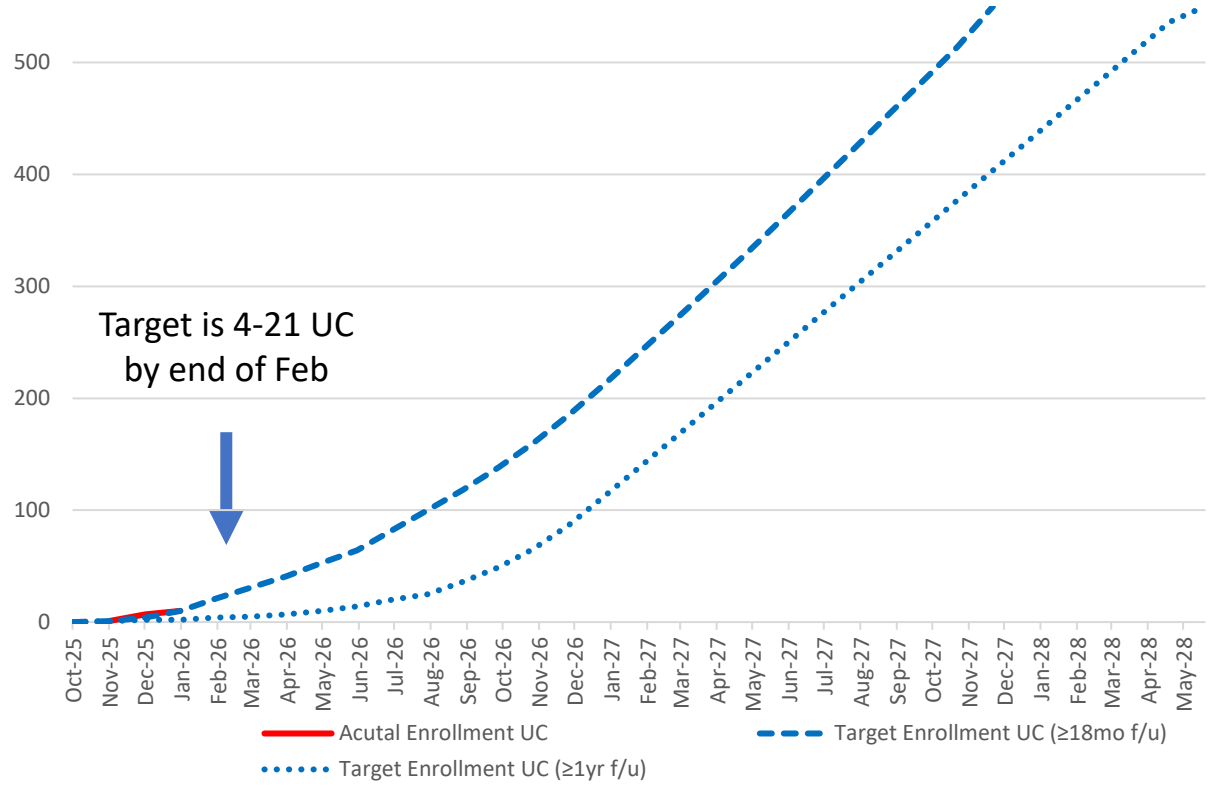
Recruitment

Crohn's disease (n=10)



Ulcerative Colitis (n=11)



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Summary

- Pressing need for CER in Pediatric IBD
- PCORnet® can facilitate ***Research Done Differently*** (and better)
  - special funding opportunities for PCORnet® Studies
- Planning a PCORnet® Study is a lot of work (and takes time)
  - Start the process early
  - Benefits may be on the back-end even with more effort up front
- Use PCORnet Prep-to-Research Queries wisely
- Be aware that use of PCORnet adds complexity (and likely cost)
- Don’t forget about Engagement (including Prep-to-Research)

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The PCORnet® Front Door

The access point for PCORnet resources and services

A “knock” on the PCORnet® Front Door can support:

STUDY DESIGN

Preliminary data for proposals, effect sizes, and potential study power

DATA NETWORK REQUEST

- Get data insights from PCORnet® Clinical Research Networks
- Obtain aggregated results for informing research project development

CONNECTIONS TO NETWORK COLLABORATORS

- Partners to co-design research
- People with specific expertise

PCORnet® STUDY SUPPORT

Deeper partnership with PCORnet provides access to best practice sharing, patient engagement, and transparent quality improvement initiatives

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