PART I: EXECUTIVE SUMMARY

The Greater Plains Collaborative (GPC) is currently a network of ten leading medical centers in seven states committed to a shared vision of improving healthcare delivery through ongoing learning, adoption of evidence-based practices, and active research dissemination. Partners by state are: KS, the University of Kansas Medical Center (KUMC); MO, Children’s Mercy Hospital; IA, University of Iowa Healthcare; WI, the University of Wisconsin-Madison, the Medical College of Wisconsin, and Marshfield Clinic; MN, the University of Minnesota Medical Center; NE, the University of Nebraska Medical Center; and TX, the University of Texas Health Sciences Center at San Antonio and the University of Texas Southwestern Medical Center. For Phase 2, these ten sites will be joined by Indiana University /Regenstrief Institute (IU Health and Eskenazi Health) and the University of Missouri Health Care.

The GPC is strongly committed to PCORnet and providing the structure to develop and support diverse research with meaningful patient involvement. Current GPC capabilities have led to funded projects as well as protocols under development, including the following impressive list: “Midwestern Collaborative for Treating Obesity in Rural Primary Care (PCORI: Befort, KUMC; collaborations with Marshfield, Nebraska), “Identifying breast cancer patients receiving autologous fat grafting in the Greater Plains Collaborative” (Holden Cancer Center: Saftlas and Chrischilles, Iowa), “Comparative Effectiveness Study of Treatment of Sialorrhea in Patient with Amyotrophic Lateral Sclerosis” (Barohn, KUMC), “Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure” (Solomon and Vardeny, Harvard and Wisconsin), “A Pragmatic Clinical Trial of Nighttime Dosing of Anti-Hypertensive Medications” (Vander Weg, Iowa), “Finding Fractures and Osteoporosis Using Native Data from Computed Tomography” (Jarvik, Washington; GPC coordination by Neuner at MCW), inter-Clinical Data Research Network (CDRN) collaboration on Sickle Cell Disease (GPC, Mid-South, PEDSnet, Louisiana), “Research Literacy: Empowering Patients as Research Team Members” (Kimminau, KUMC; DeVoe, OCHIN; Wallace, OSU) and a Centers for Disease Control proposal (NEXT-D: GPC and CAPriCORN). The GPC IRB reliance agreement process also is being used to streamline approvals for current PCORI multi-site study “Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations” (Barohn, KUMC).

During Phase 1 the ten GPC partners developed three cohort surveys (breast cancer, amyotrophic lateral sclerosis – ALS, and obesity), participated in task forces, and provided methodology expertise to the ADAPTABLE1 trial (DeMets, Pollock) as well as support from all adult sites to participate in this first PCORnet-wide trial. The GPC has delivered required data dictionaries, established PopMedNet nodes, conducted tests queries with the PCORnet Coordinating Center, and fully instantiated enterprise-wide PCORnet Common Data Model tables at the majority of its sites. While based in our medical centers’ Clinical and Translational Science Awards and Institutes (CTSA), the GPC’s incorporation of standardized cancer tumor registries at all its sites creates a unique resource for extending comparative effectiveness research (CER) in support of Cancer Centers. All GPC sites participated in the development and signing of an IRB master reliance agreement and master data sharing agreement that provide the network foundations for observational and interventional research. GPC investigators participated with and engaged patients in our developmental activities (e.g., developing SOPs, and confidentiality agreement statements, reviewing/contributing to cohort survey development.) We also held a successful Learning Engagement Kickoff in August2 for patients, investigators and other stakeholders to have the opportunity to interact face-to-face. A pre-LEK “boot camp” was held the day before to help our patient partners become familiar with PCORnet and the GPC so that they could participate more meaningfully in the LEK and going forward. The GPC also has actively promoted PCORnet at AMIA, the Epic Research Forum, the i2b2 Academic User’s Group Workshop, with EHR vendors (Cerner and Epic), and entrepreneurs and nonprofits at the Kauffman Foundation3.

In Phase 2 the GPC offers broadened network leadership and productive partnerships across CDRNs and Patient Powered Research Networks (PPRN). We will create enhanced data resources to support observational and interventional research by adding record linkage and duplication analysis capabilities with new data partners and deploying free text note de-identification and processing to support advanced computable phenotyping at vast scale across our enterprise data warehouses (hundreds of millions of notes; over ten million patients). We are transitioning from building to operating a new governance structure ensuring full stakeholder participation, especially by patients, and establishing new approaches to research opportunity assessment and integrated pilot programs with our CTSA to develop proficient CER collaborators from every perspective (patients, clinicians, investigators, health system leaders), work with patients, insurers, and private industry to equitably position the GPC as a responsive, sustainable service for advancing PCORnet’s vision for meaningful patient centered outcomes research.
PART II: TECHNICAL PROPOSAL

A. Demonstration of Successful Achievement of Phase I Infrastructure Requirements (Criterion 1)

Goal 1. Engagement, Governance, & Collaboration: As described in our Phase 1 proposal, the GPC Governing Council was initially composed of the site PIs and health systems’ Chief Medical Information Officers as we were focused on establishing the new collaboration and identifying key institutional concerns. Having successfully addressed the initial concerns about data sharing, common infrastructure, and reliance, we are now transitioning to an inclusive governance model (Figure 1) that integrates patients, clinicians, health system leaders, and investigators. This newly formed governance model addresses a broader range of issues as we move from building to operating and enables all stakeholders to play key roles in strategic planning and decision making. All parts of this governance model will be fully implemented prior to the start of Phase 2. The Governance Council convenes monthly via conference call, includes the GPC site PIs and two patient representatives, and reviews and approves: (1) GPC policies and standard operating procedures (SOPs); (2) new institutional members; (3) partnership relationships with PPRNs and external organizations; (4) budgetary allocation; (5) GPC core activities; and (6) strategies for long-term sustainability.

The Governance Council is advised by three stakeholder committees, each of which includes one representative from each GPC site and meets every other month. The Patient Advisory Council is composed of patients who participate in GPC working activities, such as data request oversight and research opportunity assessment, and other patients interested in the overall mission and activities of PCORnet. They share information from their respective GPC involvement, review GPC policies and SOPs, and provide input on strategies for using GPC data and engaging patients with proposed study development. The Health Systems Advisory Council provides input on strategies for effectively engaging health system leaders and demonstrating the value of the GPC for developing learning health systems. The Clinical and Translational Science Advisory Council includes the PIs of the eight CTSA programs in the GPC and translational science program directors at non-CTSA institutions. It is charged to identify synergies between CTSA and PCORnet agendas and leverage resources afforded by these two initiatives. The Governance Council also oversees several central GPC functions related to: (1) assessing the suitability of new research opportunities; (2) data queries,
analysis and requests; (3) long-term sustainability of the GPC, including pricing of GPC services; and 4) progress reporting on both achieved milestones and completed deliverables as well as monthly dashboard updating.

The Governance Council also oversees the two core GPC agendas – CDRN data and informatics infrastructures (directed by Dr. Waitman) and collaborator engagement (directed by Dr. Rosenthal). **CDRN infrastructure** functions involve: (1) managing interactions with current and new data partners (e.g., GPC institutions, CMS, state health information exchanges, private insurers), the PCORnet Distributed Research Network, and GPC staff to maintain data infrastructures; and (2) directing several key functions, including data standardization and interoperability, software engineering, quality control analytics, EHR-based interventional informatics, and data security. **Collaborator engagement** functions involve: (1) facilitating interactions among clinicians, patients, and investigators; (2) developing a shared IRB model and providing input on ethical issues in research; (3) coordinating biospecimen collection; (4) implementing innovative patient recruitment strategies; (5) prioritizing potential research questions; and (6) providing study design consultation. In addition, the GPC develops research agendas for three disease cohorts – ALS, breast cancer, and obesity – and manages interactions of the disease cohort work groups with the CDRN infrastructure and collaborator engagement functions. It is additionally planned that the GPC’s collaborations include attendance/participation at Steering Committee meetings (targeted at 90%+) and participation in subcommittee work.

**Expectations of Sites:** Each site is required to abide by PCORnet-wide policies and adopt the GPC Data Sharing Agreement (DSA) that allows sharing of data from a locally i2b2 database warehouse and PCORnet Common Data Model. Sites must maintain certain elements in their data warehouse and must approve the GPC’s IRB reliance agreement and SOPs for conducting observational studies and pragmatic trials (see Goal 3, below). Sites participate in GPC committees and national PCORnet workgroups. Sites also must implement credible approaches to engage patients and other stakeholders. Meeting these expectations is required to be in good standing. The GPC Governance Council specifies corrective actions for sites that fall short of expectations or PCORnet-wide policies, and has procedures for terminating and reviewing new memberships. Additionally, the GPC will meet the milestones of 50% of Network Affiliates having signed the PCORnet DSA by year 1/month 5 and 100% having signed the DSA by year 1 month 10. Further, GPC sites will sign on to the PCORnet streamlined IRB agreement and streamlined contracting agreement within the targeted timeline (year 1 – month 10).

**Patient engagement** occurs at the central GPC governance level and at individual sites. Five **engagement circles** (Figure 2 in the Appendix) infuse the patient voice throughout the GPC. At each engagement circle, patients have the same roles, responsibilities and voting rights as all other members of the team or committee. The model represents a work-in-progress and evolves as we continue to learn what works to ensure our ultimate goal of full partnership.

The engagement model emerged from a successful Learning Engagement Kick-off meeting (LEK) in August 2014 in Kansas City that brought together patients, patient advocates, team members from all 10 GPC sites, and senior PCORI staff (J. Selby, M. Zirkle, and JB Smalley). A special session “boot camp” exclusively for patients was held the day before the meeting to prepare them to participate more fully in the group discussions. In addition to providing a forum for face-to-face interaction, the LEK reviewed: (1) the use of EHR data for advancing research to improve health; (2) the critical role of patients for ensuring that studies address questions and concerns of relevance to them; (3) issues related to research in the ALS, breast cancer, and obesity cohorts; and (4) data sharing agreements and data governance. The disease cohorts used the LEK to engage patients face-to-face and to facilitate their participation in subsequent monthly conference calls. For example, at the ALS and breast cancer sessions’ patients identified specific data elements of concern to them for best capturing patients’ own experiences.

Other examples of meaningful patient engagement include: (1) inclusion of patients on the GPC Governance Council; (2) inclusion of two patients on the Data Request Oversight Committee (DROC) and their drafting of the first version of the GPC data confidentiality agreement; (3) attendance by two GPC patients at the PCORnet Patient Retreat in February 2015; (4) patient involvement in the initial Patient Engagement Work Group that is transitioning to the afore mentioned GPC-wide Patient Advisory Council; (5) representation by Ms. Cheryl Jernigan on the PCORnet Patient Council; and (6) development of a new patient engagement officer role at each GPC site to facilitate site-level patient engagement and recruitment for individual studies.

**Health system engagement** is critical to promote supportive climates for practice-based research and for integrating
the knowledge garnered from such research into practice. Initially, site PIs held one-on-one and small-group meetings about the goals and value of PCORnet with key institutional leaders at their sites (e.g., deans, health system CEOs, CIOs, Chief Quality Officers). Each site is now identifying a Health Systems Advocate (typically a Chief Medical Officer or Chief Medical Informatics Officer) with the institutional authority and credibility to garner support for PCORnet and to serve on the GPC’s Health Systems Advisory Council. The Health System Advocates are charged with promoting opportunities for leveraging the GPC’s data infrastructure for healthcare improvement and ACO population management. They also assist site PIs with engaging clinical services needed for PCORnet studies. Notably, the GPC arranged for CEOs and other health system leaders from several sites to attend two meetings convened by the Institute of Medicine on how participation in PCORnet could be leveraged to promote learning health systems at their institutions.

**Clinic engagement** has targeted clinicians whose patients are the focus of studies. The GPC chose not to broadly engage all clinicians because of the enormous effort that requires and because of the importance of managing clinicians’ expectations in the absence of specific information about the trials PCORnet will support in the future. To date, clinicians have been actively involved in the three GPC disease cohort work groups, serving as clinician “opinion leaders” at each site to garner support from other physicians and staff. For example, the ALS work group includes neurologists who are responsible for the care of ALS patients at each site. These stakeholder work groups (on ALS, Breast Cancer, and Obesity) hold conference calls monthly to receive input on the patient survey, develop a standard approach for administering the survey, and discuss strategies for developing a long-term research agenda that engages patients and families. Similarly, for the upcoming ADAPTABLE trial comparing low and high dose aspirin for the secondary prevention of cardiovascular events, participating GPC sites identified a lead cardiologist and primary care provider to serve as local advocates for the trial and to spearhead recruiting clinicians and patients.

Lastly, the GPC binds together our patients, clinicians, health systems leaders, clinicians, infrastructure cores, and investigators through twice monthly Global Call webinars that are open to all members of our community and potential collaborators outside the GPC. The agendas and minutes are shared publically. The calls address key milestones and discuss cohort activities, trial opportunities, and regulatory/infrastructure needs and accomplishments. To augment and strengthen these virtual connections across our geographically separated sites, we will hold an annual in-person meeting Learning Engagement Kickoff (LEK; following our successful Learning Engagement Kickoff) described further in Phase 2 Goal 5. In sum, the GPC has engaged patients, clinicians, and health systems leaders in its early development and has made structural and process changes in response to ‘lessons learned’ to more fully integrate all stakeholders in all PCORnet activities.

**Goal 2. Phase 1 Data Infrastructure and Analysis-Ready Data Requirements**: The GPC now has a scalable standardized data infrastructure that includes data communication and management resources compliant with PCORI Data Standards, Security, and Network Infrastructure (DSSNI) requirements for semantics and transaction processing. The GPC strives to make compliance with the PCORnet common data model (CDM) and other technical innovations transparent to the broader community through communications on our website. All 10 current GPC sites deployed and tested an i2b2 data warehouse and successfully developed shared extract, transform, and load (ETL) scripts that render site data sources including EHR data in both de-identified and identified client environments. Testing of communication client software has been successful within the GPC, and we are awaiting query benchmarks from PCORI for assessment of CDM Version 1 query capabilities.

**Patient Capture and Compliance with CDM Requirements**: The GPC is confident of its ability to provide access to CDM compliant research data on one million patients by completion of Phase 1. All ten sites completed an initial assessment of patient populations with the filing of ETL ADDS to DSSNI in September 2014. Summary statistics from our ten data marts identified 17,330,624 unique patients. Preliminary analyses of the “uniqueness” of individual patients across the ten sites found a low likelihood of record overlap at all sites other than Wisconsin and eastern Minnesota. Based upon guidance from the PCORnet DSSNI Work Group, we explored several different “enrollment” criteria (e.g., patients with health insurance sponsored by GPC institutions, in NCQA certified patient centered medical homes, or with specific levels of repeated care). Based on these assessments, we are confident that 4-8 million unique patients are available within our network depending upon the DSSNI-specified criteria used to define enrollment. The addition to our network of sites at Indiana University and University of Missouri will enhance our potential research study populations. The
University of Missouri will enhance longitudinal data availability for research colleagues in Kansas City, while Indiana University brings experience with HIE technology and access to longitudinal data sets for Indianapolis.

The GPC successfully mapped our i2b2 data to CDM Version 1 and provided quantitative reports that demonstrated that data were extracted and structured properly. We have deployed PCORI metadata models within our i2b2 deployments across the GPC, and have extracted CDM compliant data tables in preparation for responding to PCORI research requests. We await release of data characterization queries from the DSSNI Work Group to validate our data tables at all sites relative to the information model requirements of the CDM. From these data characterizations, we will revisit a deficiency analysis for all sites by June 2015 and develop a network plan for remediation and data quality improvement. In addition, we completed initial analyses related to the implementation of the Version 2 CDM, including deployment of SNOMED CT® problem lists, LOINC® laboratory results, and RxNorm®/National Drug Code medication dispensing data.

A major aspect of assessing readiness is having data in the proper format. All ten current GPC sites have data marts in the GPC’s standard i2b2 format, and six transformed relevant data from i2b2 into full instances of the PCORNet CDM format, housed within their native database software. All ten will have data in CDM format before the end of Phase I. Another aspect of readiness is having the query tool operable. At present, the PopMedNet® Version 5 datamart client is operational at eight of our ten current sites. Moreover, five sites responded within 48 hours to initial queries from the Coordinating Center to test basic processes and connections to verify the presence of expected CDM tables and variables. We expect full compliance with PopMedNet query management at all GPC sites before the end of Phase I.

The GPC is obtaining broad advanced regulatory approval across GPC sites to submit and receive results from PopMedNet queries for quality assurance, data characterization, and study feasibility purposes, using our External Investigator Data Use Agreement (see Appendix) for the PCORnet Coordinating Center. This approval process will include vetting by the GPC Data Request Oversight Committee, with both site and patient involvement. In addition, the GPC is ready to respond to future PCORnet data queries that will run via Structure Query Language (SQL) against native database software. When PCORnet moves to SAS-based query programs, the GPC sites will work with the Coordinating Center to ensure compatibility.

The GPC commits in year 1 to executing 50 pre-research or research queries with submission to the PCORnet Coordinating Center with scaling to 100 queries in year 2 and 200 queries in year 3. The GPC will also update the enrollment tables (referred to as Table 1) for each reporting period and will perform/pass data quality checks as specified by the PCORnet Coordinating Center.

**Longitudinal Data Capture:** The GPC is pursuing multiple initiatives to enhance access to longitudinal patient data because we recognize that patients may receive some care outside the participating GPC sites. The lead GPC institution, KUMC, has had discussions with: (1) the PCORnet program officer and Coordinating Center to provide GPC access to Medicare and Medicaid claims data via the CMS Enclave project; (2) ResDAC to obtain Medicare data; (3) Kansas Department of Health to obtain Kansas Medicaid data; and (4) re-licensing its Social Security Death Master file from the National Institutes of Standards and Technology to provide death records in support of the entire network. Dr. McClay and the UNMC team are working closely with the Nebraska Health Information Initiative (NeHii) to develop collaboration with organizations participating in this statewide health information exchange (HIE). Three important steps have been accomplished. The NeHii governing council approved changes in the data sharing agreement to make the NeHii data available for secondary use for research. NeHii leadership and UNMC worked with the State of Nebraska to submit for additional support from the Office of the National Coordinator to include funding to support data integration extending the comprehensiveness of patient data in the UNMC CDM instance. NeHii and the UNMC team worked to ensure NeHii could report data in the PCORNet Common Data Model. Lessons learned from the Nebraska HIE experience will be shared across the GPC and with PCORnet to expand the national availability of EHR data for CER trials.

Work is underway to establish data linkages with private insurance plans, including Anthem BlueCross and the insurers in the FDA Minisentinel® Program. Marshfield Clinic is a member of Minisentinel program and has a representative (Dr. Greenlee) on the working group tasked with determining the processes that will support individual linkage between Minisentinel and PCORnet distributed databases. This work will require numerous agreements to obtain longitudinal data across all payers for all members of the GPC.
Data Standardization: The GPC is a leader in PCORnet in research data standardization and interoperability. We are deploying a multi-layered data standardization architecture across GPC sites which provides: (1) reference standard metadata for i2b2 employing ONC standard ontologies and terminologies; (2) PCORI CDM SQL tables extracted from i2b2 observation facts for responding to PopMedNet queries; and (3) standard metadata employing reference paths for research queries within and between GPC network researchers who use the i2b2 client. During Phase 1, we disseminated metadata builds for ICD-9-CM, Current Procedural Terminology\(^\text{16}\) (CPT), Healthcare Common Procedure Coding System\(^\text{17}\) (HCPCS), LOINC, RxNorm and are currently testing our release of SNOMED CT in order to align with the Meaningful use standards of ONC and CMS\(^\text{18}\). The GPC submitted new code requirements on behalf of DSSNI for CDM Version 1 to Indiana University and is deploying a CDM Version 1 reference build fully coded with LOINC, ICD-9-CM, CPT, HCPCS and ICD-9-PCS. We are working with our prime vendors, Epic and Cerner, and in close relationship with Marshfield Clinic to disseminate uniform ETL procedures for reference standard code mapping of EHR extract data. Our data element coding consistently employs ONC standard value sets where available and employs many data elements from PhenX\(^\text{19}\) and CaDSR\(^\text{20}\) reference standards.

The CDM Version 2 data model requirements for patient reported and laboratory data will use our current metadata build for LOINC and benefit from the coding of laboratory data that is occurring in all our sites due to Meaningful Use\(^\text{18}\) incentives. We will shortly complete a SNOMED CT metadata build in support of Version 2 compliance and will revise and enhance our metadata build for RxNorm and NDC to ensure Version 2 data compliance for dispensed medications.

Data Security: All 10 GPC institutions signed IRB master reliance and master data sharing agreements in 2014. A GPC Data Request Oversight Committee (DROC), including patients, has been established to review data requests from GPC investigators and external PCORnet investigators. Sites are approving an External Institution Collaborator Agreement that allows investigators outside the GPC to request access to de-identified and limited datasets. Fully de-identified data access developed for all data warehouses will not require IRB approval for use. De-identification protocols were established by our standards development team in 2014 and patient, encounter and data obfuscation algorithms were approved for de-identified dataset build at all data warehouses. SOPs\(^\text{21}\) have been established for executing data sharing agreements, ensuring data quality, human subjects protection, data privacy, and managing research data (including PHI) and biospecimens. A central REDCap\(^\text{22}\) repository tracks all data distribution and access within the GPC.

Cohort Characterization: Patient and researcher work groups for obesity, breast cancer and ALS developed a common understanding of data dictionaries needed for cohort characterization. The teams collaboratively developed surveys for the three cohorts and determined how to ask if eligible patients would be interested in participating in patient centered outcomes research. Preliminary estimates of eligible patients were collated from i2b2 queries and used to guide data collection plans. Efforts to assess the quality of data obtained for all three cohorts will be based on the GPC Data Quality SOP\(^\text{21}\). The GPC also developed and distributed a utility based upon R-Data Builder\(^\text{23,24}\) for use at all GPC data warehouses that constructs identified research data sets in response to an i2b2 data query originated by a network investigator and approved by a network IRB. Investigators may plan their projects using network de-identified data but this utility yields patient-level data that may be merged across sites using REDCap. Importantly, GPC patient partners review all steps including those involving patient identification and data sharing to ensure that we fully address their privacy concerns.

On a broad level, EHR phenotypes for clinical research must be understandable and reproducible. We share our i2b2 ontologies on our terminology clearinghouse – Babel\(^\text{25}\) – to increase awareness of the strengths and limitations of our EHR extracts and understanding of metadata deployment for phenotypic queries. This allows PCORnet collaborators to build a shared EHR data extraction model and develop interoperable i2b2 queries for phenotype identification. Examples include queries for ADAPTABLE trial eligibility, the PI-CONNECT PPRN, and our three GPC cohorts. When we identify data deficiencies for phenotypic characterization, we enhance our network datasets. An example is using estrogen receptor status to improve the pool of identifiable breast cancer patients. The GPC also explored using PheKB.org\(^\text{26}\), supported by the Mid-South CDRN, to assist investigators in intra and inter-CDRN computable phenotyping activities. In addition, we participated in early cross-CDRN efforts to the EMERGE\(^\text{27}\) network’s computable phenotyping knowledge base to facilitate collaboration with PPRNs and have been leaders in efforts to standardize EHR data elements in compliance with the ONC Standards and Interoperability Framework.
**Goal 3. Phase 1 Clinical Trial Infrastructure Requirements:** All sites and their healthcare systems are committed to supporting observational studies and pragmatic clinical trials, as illustrated by the following accomplishments.

1. All GPC sites (including Indiana and Missouri, joining the GPC for Phase 2) will participate in the ADAPTABLE trial. The patient engagement officer, lead cardiologist and lead primary care provider from each participating site will facilitate patient recruitment and clinician participation. The GPC also will participate in the two recently approved observational studies on obesity (comparative effectiveness of bariatric surgery procedures and the impact of neonatal antibiotics). These studies were discussed on several of GPC Global Calls and each site elected to participate after consulting with relevant stakeholders at their respective site. That all GPC stakeholders agreed to participate, while many of the details regarding the studies are not yet fully developed, speaks well of the GPC commitment to PCORnet.

For Phase 2, the GPC will align with the Global Milestones and participate in at least 10 PCORnet observational studies in year 1 and at least 20 in year 2. Additionally, the GPC will participate in 5 PCORnet clinical trials per year.

2. The GPC implemented an IRB reliance agreement based on a “reciprocal deferral model” in which the institution responsible for oversight of a specific research study will vary. Rather than identifying a single central IRB, this model leverages the strengths of GPC members (i.e., the IRB for a given study can be chosen based on the expertise of an institution). The first two prospective patient surveys for the ALS and breast cancer cohorts were reviewed by this mechanism with KUMC and Iowa serving as the lead IRBs, respectively. The obesity cohort survey IRB protocol is being reviewed by San Antonio. Implementing the reliance agreement brought together IRB representatives from all GPC sites for two in-person meetings and multiple conference calls. The rapid execution of the IRB reliance agreement and the development of consent and HIPPA form templates attest to the commitment of the GPC IRBs to streamline IRB reviews and facilitate GPC-sponsored research. In order to assure a high level of human subject protection, GPC institutions were required to have accreditation of their human research protection programs. A benefit of accreditation is it has fostered consistency in IRB policies across GPC institutions and has encouraged institutions to reduce regulatory burden, when possible, without compromising human subject protection. Lastly, the IRB agreement recognizes the unique nature of PCORnet trials comparing standard of care treatments, relative to traditional clinical trials of novel treatments, as well as the importance of making consenting requirements commensurate with risk level of the study.

3. The GPC executed data sharing agreements. The development and approval of the agreements actively engaged attorneys from all GPC sites. The ratification of these agreements by legal counsel at the 10 sites bodes well for the ability of the GPC to efficiently create efficient, streamlined procedures.

4. The GPC is finalizing 14 Standard Operating Procedures (SOPs) for conducting patient centered outcomes research studies. SOP topics include: patient-reported outcomes data collection; patient engagement during study development; data management; data security; study feasibility assessment; patient consent; patient protection and patient rights; preparation of IRB applications; patient recruitment; IRB communications; misconduct and deviations; biospecimen data collection and management; data request oversight; and data integration, standardization, and quality assessment.

The SOPs outline how GPC members share responsibility for study monitoring and delineate study team interactions with the reviewing IRB. All participating institutions are required to have mechanisms in place to ensure that post-IRB approval monitoring of their local study team performance occurs, even if the oversight of the research is ceded to another IRB. The SOPs require identification of a lead team to streamline interaction with the reviewing IRB. The study teams from relying institutions communicate to the reviewing IRB through the lead team. This mechanism helps mitigate challenges study teams face to learn multiple IRB processes and policies, which can lengthen IRB review time, such as occurs with the use of central IRBs (e.g. National Cancer Institute Central IRB, Western IRB and other commercial IRBs.)

5. The ongoing patient cohort surveys demonstrate the capacity to identify and contact patients using data elements that are in the PCORnet CDM. The GPC obtained estimates of potential patient participants for the ADAPTABLE trial using i2b2 because not all eligibility criteria exist in the current version of the CDM. This process has provided feedback to the Coordinating Center regarding relevant data needs for the evolving CDM.

6. The GPC enjoys close collaborations with the 8 CTSA programs at GPC sites (Kansas, Iowa, Wisconsin, Minnesota, MCW, San Antonio, Southwestern, and Indiana). CTSA PIs and co-investigators play key roles in all GPC functions. Moreover, the informatics cores at the affiliated CTSA programs developed the GPC data marts. Given the emphasis on research-practice integration in the recent CTSA funding announcement, GPC and CTSA alignment will only increase.
(7) The GPC collaborates with several PPRNs (see Phase 2 Goal 5), the Midwest Area Research Consortium for Health (MARCH; provided SOPs that served as templates for several GPC SOPs), and insurers and HIEs (see Goal 2, above).

(8) The GPC is highly supportive of the Accelerated Clinical Trials Agreement (ACTA). Five GPC institutions (Wisconsin, Iowa, Minnesota, MCW, and San Antonio) are current signatories, with other institutions actively reviewing the ACTA.

(9) Institutional support letters for this application demonstrate the strong support for PCORnet and for embedded clinical trials by GPC health system leaders. In addition, GPC investigators are engaging patients and clinicians to develop proposals for pragmatic trials that would involve all GPC sites. For example, colleagues at Iowa have an approved letter of intent from PCORI for a pragmatic trial of nighttime dosing of antihypertensive medications to decrease the risk of adverse cardiovascular events.

(10) All GPC sites communicate with patients through patient portals associated with their EHRs (e.g., Epic MyChart, Cerner Patient Portal), and several sites have collected patient-reported outcomes through these portals. In addition, several GPC sites capture EHR “flowsheet” data, which include patient-reported data (e.g., symptoms, functioning). These flow sheet data are incorporated into the i2b2 data marts and can be viewed on the GPC Babel site.

The GPC has been and continues to be extremely active in addressing and accomplishing all Phase 1 Goals. We look forward to continuing to contribute to PCORnet through collaboration among our patients, clinicians, health system leaders, investigators, and data partners across our sites and with those at other CDRNs and PPRNs.
B. Proposed Plans for the Statement of Work in Phase 2

Goal 1. Highly engaged patients, researchers, clinicians, and health systems participate in network governance and research topic generation (Criterion 2)

The GPC will build on lessons learned, successful strategies and activities from Phase 1 (described in Part A), and the new governance model presented in Figure 1 to promote highly engaged stakeholders and investigators. The three Advisory Councils will be key forums for each stakeholder group to generate research topic ideas of interest to them. The sections below highlight other innovative activities that will be initiated in Phase 2 to engage patients, health systems leaders, and clinicians, to overcome barriers to practice-based research, to generate topics for research, to promote the dissemination of findings to stakeholders, and to facilitate the uptake of PCOR in practice. In accordance with the Global Milestones, the GPC will submit its final engagement policies by month 10 of year 1.

Patient engagement will continue to be guided by the engagement circle framework (Figure 2 in the Appendix) that was developed and refined with patient input during Phase 1. The model ensures the patient voice in organizational and procedural issues, in decisions at the GPC and site levels, and in the design of every GPC study. As depicted in the framework, patient engagement also includes active patient involvement on the GPC Governance Council and Patient Advisory Council. A key lesson learned from Phase 1 was the importance of having a dedicated Patient Engagement Officer at each site to oversee engagement efforts for individual projects, support the work of the GPC Patient Advisory Council, track engagement activities by individual sites, identify and disseminate best practices across sites, build and populate the patient part of the Collaborator Database described in Goal 5 below, and assist investigators in developing and implementing patient engagement plans for new PCOR studies. The GPC Patient Engagement Officer will work with research coordinators and established patient engagement programs at their individual site. For example, the University of Iowa CTSA program recently hired a coordinator to direct a new patient engagement consultation service for investigators designing their initial PCOR studies and that person will work closely with the Iowa Patient Engagement Officer. Similarly, KUMC is creating a new patient engagement role within their CTSA program.

The GPC also will better integrate CTSA community engagement functions. One critical lesson from Phase 1 was the differences between “patient” engagement and “community” engagement. While this led to our change from primarily working with community engagement programs to our current model of patient engagement officers, we believe there are important opportunities for integrating principles of community engagement and community-based participatory research with the GPC patient engagement model and for translating PCOR study findings into routine practice.

In addition to engaging patients as collaborators and full members of the GPC team, GPC patient engagement will address mechanisms for engaging patients as participants in research studies. Several GPC sites currently use EHR portals, such as Epic’s MyChart and Cerner’s Patient Portal, and dedicated registries, such as the Frontiers and Pioneers Research Participation Registries at KUMC1,2, to alert patients to currently enrolling studies and to inform them about their eligibility for these specific research studies. For example, to date over 30,000 patients have signed up for the Frontiers Registry (limited to KUMC patients) indicating their willingness to be contacted for participation in a research study. Prior research confirms patients desire to be informed about research opportunities. A 2013 survey of 743 Iowans found that: (1) 82% were interested in participating in research; (2) 63% expected their physicians to inform them of clinical trials opportunities; and (3) 79% would travel up to 50 miles to participate in trials. Unfortunately, such expectations are under-appreciated by clinicians. Thus, new strategies for communicating opportunities directly to patients, such as the Frontiers and Pioneers Registries and EHR-based portals that enable patients to interact with clinicians and investigators asynchronously at their convenience, and further efforts to engage clinicians in study participant recruitment is warranted and will be developed during Phase 2.

The GPC has allocated funding for compensating patients/participants and will provide reporting to PCORI beginning in Year 2.

Clinician engagement in Phase 2 will target clinicians and clinical services relevant for individual studies, as opposed to a broader, less focused strategy. Given our three selected cohorts, a special focus will continue to be specialists caring for patients with ALS, muscular dystrophy, and breast cancer, and generalists who deliver the large proportion of care to obese patients. GPC clinician leaders also will serve as point persons for recruiting other clinicians at their sites when...
opportunities for participating in studies in their specialty areas arise. Such participation may range from collaborating on the development of specific studies to assisting with recruiting patients as participants in a particular study.

As introduced above, our Phase 2 initiatives explicitly recognize the importance of recruiting patients as study participants at the point of care. However, asking clinicians to engage patients, initiate discussions about their participation in research, and obtain informed consent, when needed, interrupts clinic workflows. Current physician compensation models are based on clinical productivity (i.e., numbers of patient visits) and cumbersome informed consent processes for trials evaluating standard of care treatments create barriers to practice-based research. While we will implement EHR point of care alerts to assist in recruiting patients who are eligible for specific trials, initiating discussions with patients about their participation in such trials requires time. To address the time constraints faced by clinicians and to overcome barriers to clinician involvement in research we will implement several strategies.

One strategy involves the design and use of novel informatics tools. For example, the University of Iowa developed an *interactive online informed consent module*\(^3\) to improve the efficiency of obtaining consent for pragmatic trials. This module was designed with extensive patient input and usability testing to address complaints about the cumbersome and confusing nature of standard consent documents. In an initial evaluation, patients using the module for a mock study had greater (p<.01) knowledge of the protocol and greater (p<.01) satisfaction with the consent process than those completing a paper-based consent form. The module was used in the planning phase for a NIH Health Care Systems Collaboratory trial and is being further tested in three active trials through an NIH R21 award. The module also is being used to obtain consent for collecting biospecimens and is being proposed for use in a PCORI application for a large pragmatic trial of nighttime dosing of antihypertensives that would be conducted through the GPC. During Phase 2 the GPC will consider how this module might be adapted and adopted by other GPC sites, with the long-term goal of disseminating it across PCORnet. A further strategy that will be piloted at the University of Iowa is to provide clinicians with economic credit (through *research RVUs*)\(^4\) for engaging patients in discussions about enrolling in trials for which they are eligible. An additional incentive for clinician engagement in research would be the consideration of clinician involvement in subject recruitment as a criterion for academic promotion for Clinical Track faculty.

Other GPC strategies for engaging clinicians in research focus on demonstrating the value of this research for their practices. We have found that the i2b2 warehouse, which have intuitive user interfaces and provide clinicians the ability to run queries of their own patient panels, can be a powerful tool for garnering clinician interest—enabling clinicians to ask questions of their own patients that can lead to the generation of hypotheses and preliminary data for future PCOR studies. PCORnet and the GPC have the potential to convert interest into action and understanding by providing a community of clinicians, health services researchers, and informaticians who provide richer data characterization, training, and inter-institutional capacity to validate findings that in isolation may lead to skewed results from novice use or limited sample size.

**Health system engagement** during Phase 2 will be driven by a vision of establishing learning health systems across the GPC. The commitment of our collaborating systems toward this vision is clearly expressed in their letters of support. It is also evident from their participation in the IOM meetings to support PCORnet and in the AAMC’s *Research on Care Community* initiative\(^5\). The latter seeks to disseminate best practices in using research to improve healthcare delivery. GPC leaders will promote awareness that research-practice integration and providing patients with opportunities to participate in research is an effective way for participating health systems to differentiate themselves in local and regional healthcare markets. The GPC also is developing use cases for how the i2b2 data warehouses can provide normative benchmarks to support institutional initiatives in quality and efficiency (e.g., decreasing utilization of laboratory and radiology tests for patients admitted for common diagnoses or utilization of blood products during surgical procedures) and in population management\(^6\) (e.g., patterns of post discharge healthcare utilization). Indeed, an important lesson that emerged from discussions with our health systems leaders was that health system engagement will be most effective if PCORnet studies address pressing issues faced by health systems (e.g., alternative bundled payment models, reducing readmissions and hospital acquired complications, adoption of meaningful use standards), in addition to studies comparing the effectiveness of treatments to improve long-term outcomes, such as ADAPTABLE. The Health Systems Advisory Council also identified support for internal rapid-cycle quality improvement projects as an area of need for health systems that could be supported through GPC data and analytical infrastructures.
**Solicitation of Research Topics and Support for Innovative PCOR:** In addition to efforts described above to ensure that GPC and PCORnet research topics address key needs of patients, clinicians, and health systems, the GPC is planning a unique pilot grant program in collaboration with participating CTSA programs and translational science programs at non-CTSA institutions. This program will support cross-institutional projects that would: (1) test innovative approaches to conducting PCOR (e.g., integrate novel registries, web-based patient recruitment, collection of patient reported outcomes using mobile devices, development of new instruments to support observational studies using instrumental variable analysis to decrease selection bias); (2) provide preliminary data to support the feasibility of health system or clinical interventions to be tested in subsequent randomized PCOR trials; or (3) assess patient or clinician preferences for certain study designs in broader populations of stakeholders than are represented on our Advisory Councils.

Requests for proposal topics would be disseminated to all stakeholder leaders at participating sites, to our partnering PPRNs, and to the GPC Advisory Councils. A request for proposals based on these topics would then be disseminated to GPC investigators who will be required to include patients, clinicians, and if relevant, health system leaders on their study team. Proposals would be reviewed using a process similar to PCORI reviews with patient and other stakeholder reviews as well as scientific assessments. This review process would capitalize on existing pilot grant review committees of CTSA programs with the addition of our important stakeholder reviewers. Projects that build on the disease cohort surveys being conducted in Phase 1, involve topics identified by PCORI as national priorities, or draw on unique capabilities of our partnering PPRNs (e.g., DuchenneConnect has eight years of experience collecting longitudinal patient-report data) will be of particular interest to this pilot program. We also view this pilot program as an opportunity to standardize patient engagement strategies across GPC sites and ensure that the proposals selected for pilot funding employ best practices in this area.

In addition to GPC wide pilot projects, the GPC will facilitate projects conducted by two or more GPC sites and funded through institutional or external sources. Projects internally funded by health system leadership to address pressing management issues will be of particular interest. Central GPC support for such projects might include developing computable phenotypes, cohort characterizations, detailed assessments of data comparability across sites for specific data elements, use of the GPC shared IRB for project approval, assistance with the developing and implementing strategies for meaningful patient engagement, or support for collecting patient reported outcomes. The GPC will report the number of grants submitted that propose to use data from either PCORnet or GPC only sites in accordance with the Global Milestones.

**Communications Strategies:** The GPC employs a number of communications strategies, recognizing the challenges of facilitating communications across a geographically dispersed network of 12 large healthcare systems that encompasses a wide range of stakeholders. First, members of the Governance Council and the three Advisory Councils will play critical roles serving as liaisons to their organizations. Second, the GPC Project Management Office will provide communication resources at KUMC to coordinate GPC committees’ and councils’ meetings and activities. Third, the GPC website, listservs, and interactive wikis serve as a central repository for GPC and PCORnet meeting minutes and deliberations and are available to all GPC stakeholders. A “new opportunities” section of the website will have information on new studies being planned (from PCORnet or from individuals) so that interested persons (patients, clinicians, etc) may contact study organizers with their interest in participating. Fourth, each site will establish PCORnet Project Managers, who will be available by phone, email, or in person, to assist investigators and other stakeholders (patients, clinicians, etc) with accessing GPC resources, and who also provide information about research opportunities available through PCORI. Lastly, to ensure study findings are widely disseminated we will employ a number of dissemination strategies.

**Dissemination Strategies:** Dissemination is critical to ensuring that research results are implemented and improve patient outcomes. The challenges of effective dissemination and implementation, however, are widely chronicled. Moreover, dissemination and implementation strategies are highly contextual to the particular clinical condition, patient population, clinical setting, and delivery system. What may be an effective strategy for patients and clinicians involved in ALS may not be effective in impacting clinical practice or patient behaviors for obesity. Thus, dissemination strategies must be an integral part of the initial study design process, must be tailored to the specific clinicians, patients, and families involved, must reflect the expressed preferences of these stakeholders, and must be timely with regard to the completion of the study. Approaches that the GPC will use include developing: (1) succinct summaries of project findings (for both clinical and lay language) with a focus on the implications of the findings for clinical practice and/or patient
behaviors; (2) briefs for health system leaders on the potential impact of findings on health system operations, finances, and improvement efforts; (3) 2-3 minute YouTube videos highlighting key study findings and their implications for health care practices; and (4) targeted dissemination through PPRNs and other relevant disease advocacy groups with well-established dissemination pipelines. All of these strategies will be informed by active involvement of the patient, clinician, and health system leader collaborators on each study as they know best what will resonate with their groups. Separately, for any accepted publication by a GPC investigator, the GPC will submit notification to PCORI within 30 days.
Goal 2: Analysis-ready standardized data, use of the PCORnet Common Data Model, and preservation of strong privacy and data-security protections (Criterion 3)

**Analysis-Ready Standardized Data:** As described in the section on Phase 1 Goal 2, GPC sites maintain primary data repositories for network activities in i2b2 format, and then CDM tables are extracted at each site in order to maintain readiness for automated PopMedNet queries. However, GPC sites purposefully include in their repositories all patients and a much more extensive set of data elements as captured by the electronic health records of their corresponding medical centers and health systems. We believe this approach allows for a more robust contribution to the wide range of observational and interventional research studies contemplated across PCORnet and within the GPC. With sustainability as a critical goal of Phase 2, this approach can support fundable research for a wide range of partners and customers beyond that which can be accomplished through the CDM alone. The i2b2 model provides a ready platform for supplying additional elements to the CDM, and the GPC’s experience in expanding our i2b2 ontology over the course of Phase 1 positions us well to work closely with the Coordinating Center and the DSSNI team as expansions to the CDM are executed in Phase 2. The i2b2 model combined with the Babel terminology clearinghouse allows us to integrate novel data at the site level and expose ontological challenges early instead of committing to tables or bindings. For example, KUMC has recently extracted EHR alerts as facts into i2b2 that would be leveraged to monitor the effectiveness of recruitment and individual randomization alert interventions for prospective PCORnet trials (ontologies available on Babel service described below). While invaluable for PCORnet success, terminologies are not yet harmonized for clinical decision support and thus would not be expected to be incorporated into the CDM at this time. The i2b2 model also allows us to incorporate existing complex data sets such as tumor data in North American Association of Central Cancer Registries (NAACCR) format within the GPC and then later can evaluate harmonization of these data elements with CDM components.

Specific to CDM evolution, we will continue to conduct analysis of CDM V2.0 and V2.1 requirements against current EHR capabilities, e.g.: 1) a metadata build for RxNorm/NDC, 2) expanded GPC metadata –clinical LOINC for patient reported outcomes, 3) assistance for lab LOINC mapping and deployment across GPC; and, 4) expanded procedure metadata for Outpatient and Inpatient Medication Administration events. We will evaluate the extent of site access to outpatient dispensing claims data as well as prescription orders, and develop necessary data sharing agreements and ETL processes. We also will assess collaboration with Surescripts as an additional external approach.

As described in Phase 1 activities above, we are on track to fully populate and retain a physical instantiation of the CDM at all sites. Efforts to date have primarily focused on the approved version 1 CDM but we are currently extending our ETL to include the additional domains specified in version 2 and 2.1 as they are approved and tested with the Coordinating Center. We will initially target quarterly refreshes working towards monthly refreshes during Phase 2.

The programming code sites used to generate their CDMs is standardized and shared on the web under an open source license¹, linking CDM data quality across sites to the i2b2 data quality assurance activities already supported by the GPC Development group through their GPC analytics package work. A good portion of this quality work in Phase 1 has focused on the data elements that support the cohort characterization and survey process for the three GPC patient cohorts, and will continue into Phase 2 for both general and project specific data assessments. The weekly Development call and tracking process will continue to serve as a main point of communication about data contents and consistency across sites. However, the GPC will establish for Phase 2 a common maintenance cycle for the emerging data extract refresh and data quality evaluation process (quarterly initially; monthly as ongoing goal).

The GPC also will participate fully in the formal PCORnet data characterization and quality review process. We have two sites (Marshfield and Nebraska) that have volunteered to be among the first sites to tackle the data characterization process once the query scripts are written and rolled out by the Coordinating Center. Standard Operating Procedures established in Phase 1 will govern the regular i2b2 refresh and evaluation process and assure sites stay on a common maintenance cycle. Marshfield Clinic has nearly 6 years of experience working with the Harvard Coordinating Center staff as part of the Mini-Sentinel, both in the original development of the Mini-Sentinel CDM and the ongoing data characterization and quality review dialog process. In its role as GPC lead for PopMedNet activity, the Marshfield Clinic team will facilitate the process for the GPC sites.
**Record Linkage and Duplication Analysis:** One critical challenge for sharing patient information within a CDRN (beyond our sites being geographically dispersed) is that a patient may have received care in multiple settings. While unique identification numbers or personal identifying information (PII) such as surnames, given names, date of birth, and address would make record linkage straightforward, distribution of such information is restricted due to privacy concerns. Since patient’s trust is with their home health systems and academic medical centers, we will avoid transmitting PII through the GPC network infrastructure. To find records that represent the same individual without revealing the individual identity, researchers have developed several privacy-preserving record linkage protocols that vary in computational cost, security guarantees, and linkage accuracy. One of the latest approaches is based on Bloom filters to calculate similarity between two encrypted strings for probabilistic record linkage. In brief, data holders first convert an identifier string into a set of q-grams and store the q-grams in a Bloom filter of length \( L \) using \( k \) one-way hash functions. Each resulting Bloom filter is then assigned a randomly generated unique ID and replaces all other identifiers with this unique ID. The mappings between Bloom filters and randomly generated IDs will be sent to a trusted third party for approximate Bloom filter matching and the matched ID pairs will be transferred to the data recipient for final record linkage. A recent extension of the Bloom filter demonstrated that mixing multiple patient attributes (e.g., personal name and address) into a single encoding can sufficiently strengthen Bloom filter encoding against cryptanalysis. This protocol is secure because neither data holder has access to each other’s Bloom filters and the third party cannot reverse the encoding without knowing the agreed secret key.

Adopting a centralized method for generating global unique identifiers (GUIDs) to link records is another promising approach. Under the GUID protocol, a client application first transforms a set of PII into hash codes using one-way hash functions and transmits the codes in a secure manner to a server application. The server application then performs matching on subsets of hash codes against an internal database. If there is no match, the server application returns a randomly generated GUID to the client application; otherwise, it returns the associated GUID. Finally, for sharing patient records, all identifying information is replaced with the GUID. Each participating site maintains a table mapping local identifiers to the GUIDs. GUIDs can serve as a temporary bridge for data exchange in a point to point hashing with data partners such as Medicare and other payor representatives such as HealthCore and Patient Powered Research Networks. Having persistent GPC-level GUIDs would provide us valuable network level movement information of patients. However, permanent persistent GUIDs may be a privacy concern and subject to attack so we will work with the GPC Data Request Oversight Committee and its patients members to weigh these considerations as we coordinate with PCORnet. We will first deploy record linkage methods to understand the feasibility of different privacy-preserving record linkage protocols in terms of computational cost, security, and accuracy in two areas: (1) the CMS enclave pilot with Mid-South and the PCORnet coordinating center, so we can link CMS claims data with beneficiaries from each GPC site, and (2) KUMC is relicensing its Social Security Death Master file for PCORnet activities at GPC sites described below.

Linked data will be analysis ready by year 2 month 5. Additionally within the area of record linkage, the GPC will complete the secure transmission of currently held data sources such as the Social Security Death Index by month 10 of year 1. As a second milestone in this area, the GPC will demonstrate the secure transmission of additional source data (i.e. claims data) by month 10 of year 2.

**Data Requests and Governance:** In Phase 1 the GPC has established a PopMedNet implementation and operations team, comprised of each site’s main query analyst/honest broker and an interested investigator. In Phase 2, this team will continue its work under the leadership of Robert Greenlee, PhD, MPH and Laurel Verhagen, from Marshfield Clinic Research Foundation, a site with considerable experience in responding to PopMedNet queries through participation in the FDA Mini-Sentinel program and the NCI Cancer Research Network. The team will use its listserv to support regular communication internally, as well as communication in conjunction with the PCORnet DSSNI liaison assigned to the GPC. Each GPC site, with its CDM instance and PopMedNet datamart client, will be able to receive queries and respond directly to the Coordinating Center, based on the establishment of regulatory approval across the GPC in the form of an External Institution Collaborator Agreement. Once the External Institution Collaborator Agreement is signed on behalf of the coordinating center, we will work with the signing institution so that feasibility, data characterization, and quality assurance queries from the Coordinating Center (following well-described PCORnet SOPs) are approved in blanket fashion streamlining the governance to allow efficient, timely responses to the broadest set of PCORNet queries. Dr. Greenlee at Marshfield Clinic will serve as the GPC sponsoring investigator for these standardized queries, and will
assure the GPC Data Request Oversight Committee is informed periodically regarding the extent and nature of these feasibility and quality assurance activities as well as the various national proposals supported by the GPC.

The External Institution Collaborator Agreement will first be put in place to support the data characterization process in Phase 1. With this approval, GPC will provide the primary and backup capacity to respond in timely fashion to multiple Coordinating Center queries per week, up to 200 per year. For queries that fall outside of the broad regulatory approval, such as those requesting individual level data and requiring transmission of any personal health information, or to conduct actual human subjects research, which are expected to arrive less frequently and in smaller quantities, ad hoc regulatory approval will be sought from the patient-engaged GPC Data Request Oversight Committee (DROC), and individual GPC site authorities who will use timely on-line review and approval tools developed at KUMC. The GPC also will provide a CTSA aligned and honest broker mediated i2b2 query interface and data request process. During phase 2 we will evaluate implementing automated federated query technologies such as SHRINE for PCORnet and GPC use. This is being piloted in Wisconsin as the SNOW network. We also will continue developing advanced honest broker functionalities (i.e. automation, uniformity) and minimize the need to conduct adhoc queries not reproducible via CDM or i2b2. Over time in Phase 2, the GPC will streamline its PopMedNet Query communication architecture, making extensive use of the lead GPC Query SAS Analyst to be housed at Marshfield Clinic Research Foundation. While each GPC site will continue to generate and house its own formal instantiation of the CDM, the GPC will eventually support internal federated CDM query capabilities and provide a single point of 2-way query communication with the Coordinating Center.

**Complete Longitudinal Data Expansion:** As described in Phase 1 and previous reports, the GPC is able to combine data on an unselected population, estimated to exceed four million individuals, and to share access or datasets via our master data sharing agreement, currently only for noncommercial purposes. Some system partners in the GPC, due to geographic circumstances and health plan sponsorship, are able to achieve near complete and comprehensive data coverage on patients/members (e.g., Marshfield Clinic). Our efforts toward data completeness across all sites are broadly focused on enhancing our warehouses to define populations with near complete management by the tertiary Academic Medical Centers (AMCs) of the GPC. For example, critical to PCORnet’s support for rare disease populations are the AMCs that provide complete care or act as a hub of coordination for these patients (e.g., ALS, Duchenne). Additionally, major episodes requiring specialized care and coordination (e.g., breast cancer) often will be centralized at an AMC so that during this period the GPC sites may be considered the best foci for understanding these populations.

A continued focus for the GPC will be working with added data partners through the remainder of Phase 1 and into Phase 2 to enhance the longitudinal completeness of our data, such as supporting vulnerable patient populations that seek care at academic medical centers through Medicaid integration, and working through RESDAC or participating in the PCORnet led pilot with the GPC and Mid-South to secure an approach for data integration through CMS’ data enclave. In Phase 2 the GPC is excited to welcome the University of Indiana, a national leader in Health Information Exchanges to complement Dr. Jim McClay’s ongoing activities in Nebraska. The GPC will explore issues associated with record linking across geographic areas of the GPC when patients move between systems. Lessons learned from the Nebraska HIE experience will be shared across the GPC and with PCORnet to expand the national availability of EHR derived data for CER trials.

In Phase 2, the GPC also adds the University of Missouri (MU), which has a contract with the State of Missouri to store and manage Medicaid claims data that opens the possibility of linkage to valuable population-level data in de-identified format. In addition, MU has access to Medicare claims data on a cohort of 10,000 patients who are receiving primary care at MU Health Care as part of a CMS Health Care Innovation Award entitled, “Leveraging Information Technology to Guide Hi-Tech, Hi-Touch Care (LIGHT).” With appropriate agreements, these Medicaid and Medicare data sets could make important contributions to the GPC.

We also have reached out to HealthCore, a research subsidiary of Anthem (formerly Wellpoint) to establish a collaboration for developing and maintaining data linkages with private health insurance databases. HealthCore has extensive experience with the Mini-Sentinel CDM and Anthem and BCBS has high penetration within our region as an insurer or as a Medicaid managed care organization after Wellpoint’s acquisition of Amerigroup. We will establish a...
governance structure allowing bidirectional collaboration for enrolled patients. This can act as a model for subsequent collaboration with other insurer data partners (other Blue Cross Blue Shield plans have significant penetration in our regions: Wellmark, BCBS Kansas, BCBS Kansas City, BCBS Nebraska, Health Care Services Corporation). The GPC will submit plans for collaborations with health plans by month 5 of the first year of Phase 2. Additionally, the GPC will have a Commercial Collaboration Agreement ready for use by month 10 of the first year.

To test the processes of data linkage necessary to support work with these additional partners, the GPC will begin this summer distributing the KUMC licensed Social Security Death Index data with our sites in support of the ADAPTABLE and Bariatric obesity studies. While simple, we think it will test many of the use cases for the record linkage process mentioned in the previous section.

**Computable Phenotyping and Cohort Activities:** In Phase 2, the GPC will continue to leverage the existing and newly developed instantly transmissible computable phenotypes made possible using i2b2-based queries and the archive of i2b2 ontologies. All GPC sites have shared their i2b2 ontologies on our terminology clearinghouse: [https://babel.gpcnetwork.org](https://babel.gpcnetwork.org). This allows all PCORnet collaborators and other interested investigators to browse the types of data available within the GPC, build computable phenotypes as i2b2 queries, and copy the phenotype to individual repositories for execution. Examples posted in Babel’s shared folder include the ADAPTABLE trial eligibility, immune deficiency PPRN (diagnoses, lab tests and intravenous immunoglobulin), and our GPC three cohorts (obesity, ALS, and breast cancer). The GPC also has explored using PheKB.org, supported by the Mid-South CDRN, to assist investigators in intra and inter-CDRN computable phenotyping activities. Experience at Marshfield establishing computable phenotypes as part of the EMERGE Network and the Wisconsin Genomics Initiative will be incorporated into the GPCs growing phenotype library.

During Phase 2, the three GPC cohort working groups (Breast Cancer, ALS, and pediatric obesity/weight) will continue to provide support for tracking the patient cohorts established in Phase 1 and shift focus to supporting fundable research topics, providing further evidence of the desired sustainability of the GPC efforts. Below are examples of some of the plans of all three cohorts for activities in Phase 2. Beginning with the GPC Breast Cancer Group, this group will:

- Build a sustainable breast cancer research core (Criterion 7) by (1) supporting writing teams to prepare manuscripts beginning with the Phase 1 *Share Thoughts on Breast Cancer Study* results; (2) assist investigators with planning and implementing feasibility pilots preparatory to research; (3) collaborate with Comprehensive Cancer Centers on access to data resources and efficient trial recruitment; and (4) assist investigators with patient engagement for cancer research.
- Partner with patients as investigators and consumers regarding the analysis, interpretation, and publication of results of the Phase 1 *Share Thoughts on Breast Cancer Study* (Goal 1, Criterion 2)
- Expand collaboration with the ABOUT PPRN to expand diversity of membership in both networks (ABOUT and GPC); develop and validate a computable phenotype for HBOC; establish synergies in patient identification, recruitment, retention, and data completeness; determine research priorities, and plan research grants (Criteria 2,3,6)
- Continue to curate the GPC tumor registry data including standardized scripts and variable naming, quality assurance of data refreshes, and expert knowledge of coding rules (Criterion 3)
- Extensively develop and validate computable phenotypes for breast cancer diagnoses, treatments, and outcomes, including pathology data, EHR data, billing data, and gold standard tumor registry data (Criterion 3)
- Collaborate with PCORnet members and sponsors to develop and validate computable phenotypes for cancer research (Criterion 6)

The ALS working group will continue to develop comparative effectiveness research protocols in partnership with patient collaborators, such as the previously mentioned “Comparative Effectiveness Study of Treatment of Sialorrhea in Patient with Amyotrophic Lateral Sclerosis.” The community of neuromuscular researchers united around ALS also provides common connections and clinical collaborators for our planned activities with the DuchenneConnect PPRN. For example, Dr. Richard Barohn, leader of the ALS working group, has facilitated communications and helped identify collaborators for DuchenneConnect during Phase 1. Dr. Jonathan Katz, Director of Neuromuscular Research at the
Forbes Norris MDA/ALS Research and Treatment Center at California Pacific Medical Center and President of the ALS Research Group, has been advising this working group. Forbes Norris is working with Epic Corporation to develop standardized data instruments/forms for ALS clinics to understand how they can be made available to an even wider community. GPC sites (led by Minnesota who is beta testing the forms along with Massachusetts General Hospital) are evaluating adopting these forms to enhance collecting standardized data for the ALS patient population. As such, the ALS cohort working group will provide the GPC an opportunity to evaluate exploiting structured forms and phrases contained in modern EHR documentation tools, as well as computable phenotype methods reliant upon free text-based natural language processing techniques described below.

The obesity working group has focused, and is continuing to focus through Phase 1, on enhancing our ability to characterize pediatric obesity, notably incorporating body mass index percentiles directly into each site’s i2b2 data mart. The GPC will participate in both PCORnet-wide obesity observational studies and this work will be a major focus for the GPC in Phase 2. Our network level focus on pediatric obesity fits well with the “Long-Term Effects of Antibiotics on Childhood Growth” funding announcement. Dr. Dan Hale MD, leader of the current GPC obesity working group, will coordinate San Antonio’s role as the lead site for this study. San Antonio’s informatics team, under Dr. Alfredo Tirado-Ramos, has guided data analysis for the GPC pediatric obesity cohort. The GPC also is active in adult obesity research collaborations, which has been catalyzed by the recently funded PCORI study “Midwestern Collaborative for Treating Obesity in Rural Primary Care”\(^{11}\) (Christie Befort PI, KUMC). Dr. Jim McClay MD (GPC site PI, informatics director and emergency medicine physician) has coordinated with Nebraska collaborators in the rural obesity study (Drs. Cyrus Desouza and Ghada Soliman) and with the director of bariatric services in the department of surgery (Dr. Cori McBride) to act as the lead site for the “Short- and Long-Term Outcomes related to Bariatric Surgery” study. This creates a collaborative team of patient centered comparative effectiveness researchers actively contributing to prospective rural primary care weight loss treatment interventions and to evaluating tertiary bariatric surgery outcomes.

The GPC will submit progress reports of its ALS, Breast Cancer and Obesity cohorts at each scheduled interval (year 1 – months 5 and 10; year 2 – months 5 and 10; year 3 – months 5 and 10.

**Notes De-identification and Natural Language Processing (NLP):** To facilitate the capability to search and extract unstructured data (narrative text) from EHR data, the Medical College of Wisconsin and the Milwaukee School of Engineering are developing scalable, accurate, license free, and maintainable NLP and indexing pipelines for processing patient records to facilitate clinical research. The intention is to collaborate with our GPC partners (such as the current processes in place at the Marshfield Clinic and used for the EMERGE project and NIH funded research at the University of Minnesota) to integrate current state-of-the-art methods into scalable, maintainable, and open-source software engineered solutions that can be shared and continuously improved.

The initial effort toward this goal was to develop software to de-identify Protected Health Information (PHI) in EHR text as a foundation for NLP techniques. After careful review and evaluation, we found existing solutions were not accurate, not easily modified, or not scalable to the tens of millions of notes contained in the MCW EHR. Led by Dr. Jay Urbain, the group developed an open-source solution using current state-of-the-art NLP methods that is easily modifiable and highly scalable across multiple computing systems. The software was evaluated on a stratified sample of patient records (drawn from 48 care settings) and was demonstrated to be competitive with the current state-of-the-art systems. After a design review with GPC partners, modifications were made to incorporate patient record meta-data to further improve accuracy, and provide support for additional database platforms. The software has been released as open-source\(^{14}\) and has been used to de-identify 48M+ patient records at the Medical College of Wisconsin. It is now in the process of being deployed at the University of Kansas Medical Center.

In addition to i2b2’s integrated free text and structured search capabilities, MCW is currently developing the capability to integrate search of structured and unstructured data across our i2b2 instances. Using a natural language query we will provide the ability to search both discrete (structured) and textual (unstructured) data. By performing a complete natural language parse of each sentence during their indexing process, we are able to identify named entities (e.g., patients, doctors, relatives, drugs, diseases, etc.) from text and identify relations between such entities. We hope to leverage this capability to foster the development knowledge discovery tools that allow researchers to identify and relate concepts across structured and unstructured data.
Data Security and Auditing: As described above in the record linkage section, GPC central will avoid Personal information identifiers at the network level and keep the identifiers at the site or data partner level. The GPC’s robust regulatory governance structure for data sharing provides very streamlined access to fully de-identified data, as compared to the additional steps required for limited data sets. We expect this will encourage investigators to use de-identified data wherever possible, especially in preliminary studies. The size of our network also helps preserve the anonymity of our clinicians and health care systems where requested.

The GPC has a thorough Data Request Oversight Committee (DROC) process, as outlined in our Master Data Sharing agreement15 that has been implemented in Phase 1. Before any approval, the DROC, which includes patient representation, reviews the purpose of the request, verifies the identity of the requestor, and establishes their authority to request the type of data that they have requested. We also work through our GPC DROC and honest brokers to define the requirements, request management processes, and technical means to de-identify the systems and clinicians when desired or when necessary as a further step to protect confidentiality of the data.

Data are stored locally in secure frameworks, with primary use of fully de-identified repositories, where dates and other indirect identifiers are obfuscated. Repositories with identifiable information are only accessed as required.

The GPC is developing auditing standards and capabilities to support technical quality assurance of data extraction and reproducibility and for logging request characteristics and queries to support data transparency for the DROC and its patient representatives. Guided by the DROC, the site honest brokers working in conjunction with the informatics core will develop methods for logging both technical (i.e. log extra/intra-network data transfers) and organizational criteria (i.e. investigator team member usernames, research study topic, and time/date of data access). These activities will be aligned with methods and standard operating procedures to track queries and distributed analysis requests that come to the GPC through the Distributed Research Network (DRN) that is managed by the PCORnet Coordinating Center. Marshfield’s leadership in HMORN, Mini-Sentinel, and EMERGE also will facilitate sharing approaches and lessons to applying the Sentinel-based quality assurance methods (developed for claims data) and enhancing them for new EHR and registry data sources incorporated for PCORnet.

While GPC network level and site level information systems are managed and monitored in accordance with campus information security personnel for HIPAA compliance, in Phase 2 we will conduct independent penetration testing of GPC technical infrastructure both at the network level and at several sites. We will provide the results of this independent testing of the PopMedNet, PCORnet CDM/SAS environment, i2b2, and REDCap infrastructure with PCORI, the PCORnet Coordinating Center, and other interested CDRN and PPRN networks. We will update our standard operating procedures as different components and capabilities are implemented, tested, and monitored.

The GPC master data sharing agreement was signed after review and input by the general counsel offices of all 10 sites. The two newly added GPC sites have agreed to execute the agreement as well with no modifications. As evidence of its utility for Phase 2, the proper agreement appendices have been reviewed and agreed to by the legal counsel of investigators seeking to use the GPC for developing research proposals.

As emphasized above, a fundamental principle that reduces risk is general avoidance of transmitting identifiers across the network, except in the context of specific approved research projects that require such sharing for the successful completion of the work. For further protection, the GPC has developed and executed a reciprocal multisite master data sharing agreement that meets the legal and regulatory expectations of each of our member sites. Data breach practices are clearly outlined in this master data sharing agreement, including a 5 day maximum reporting window, inclusion of the privacy officers from both the administrative lead site and the site supplying the data, and willing cooperation in the ensuing investigation and any necessary reporting as required by HIPAA and applicable laws. We are further developing additional SOPs for Phase 2 to provide added process detail to the agreed upon principles.

As the GPC transitions into Phase 2 we are encouraged that our initial model for data and informatics infrastructure (original Phase 1 proposal figure provided as Figure 3 in the Appendix) has provided a solid framework. We now see our network evolving towards a more fully realized platform including data partner linkage, flexible data integration, analytics, and informatics infrastructure (shown as Figure 4 in the Appendix) to support the spectrum of comparative
effectiveness research envisioned by PCORnet and described further in Goal 3 below (and referenced in Figure 5 in the Appendix).
Goal 3: An infrastructure for supporting clinical trials embedded within network delivery systems (Criterion 4)

During Phase 1, the GPC established several critical infrastructure elements to support the fundamental expectation of PCORnet of seamlessly embedding research into clinical practice. As highlighted in Part A and depicted in Figure 1, the GPC adopted an inclusive governance model that brought together 10 geographically dispersed institutions, that represented the interests of patients, clinicians, health systems, investigators, and CTSA programs and that provided a framework for integrating new institutions during Phase 2 and for building partnerships with PPRNs, other CDRNs, health insurers, health information exchanges, and other organizations.

The GPC also established core informatics infrastructures and functions to standardize EHR data across sites, adopt PCORnet common data models, and query site data warehouses for cohort characterization. The GPC developed a unique tool (Babel) to share and compare the data elements captured in the individual GPC data warehouses. The addition of the University of Missouri in Phase 2 brings a unique private/public partnership with Cerner Corporation that is focused on innovating health care, connecting patients across Missouri, and empowering wellness. These efforts complement the GPC’s efforts during Phase 1 of developing common strategies for integrating data from Epic EHRs. The addition of Indiana University brings over 20 hospitals and affiliated health centers into the GPC that also use the Cerner EHR, as well as bringing in the world-renowned medical informatics capabilities of the Regenstrief Institute.

The GPC executed cross-institutional agreements to improve the efficiency of conducting multi-site research, including master data sharing agreements for internal and external users, a reliance IRB agreement, which is built around a “reciprocal deferral model” in which the lead IRB for individual research studies varies among individual sites based on the expertise of an institution. A number of GPC institutions were on the leading edge of the development and adoption of the Accelerated Clinical Trials Agreement (ACTA). In addition, the GPC developed and adopted 14 different SOPs (described in Part A) for conducting patient centered outcomes research studies, for minimizing variability across sites in research practices, and for enhancing compliance with recommended practices. During the remainder of Phase 1 and during Phase 2, we will develop additional SOPs to address issues that emerged as PCORnet matured and established new policies and approaches, and as we have begun to participate in initial PCORnet trials. These new SOPs will involve: (1) PPRN collaborations; (2) alignment of GPC data access and use with PCORnet governance processes; (3) adverse event detection and reporting for pragmatic trials and standard of care treatments; (4) “Good Clinical Practice” for pragmatic trials, building on the NIH/NCATS Good Clinical Practice initiative being co-led by Dr. Barohn; (5) use of EHR functions (e.g., alerts) in pragmatic trials; and (6) dissemination of results to clinicians, patient participants, and other stakeholders.

**Decision making processes for trial participation:** The GPC governance model supports a decision making process about whether to participate in trials that is based on the required levels of engagement. All trials are ultimately approved by the Governance Council, with input from the three GPC Advisory Councils representing patients, health systems, and translational science programs, respectively. Trials being considered are categorized into four levels of increasing complexity (see Figure 5 in the Appendix), with review processes commensurate with the level of complexity and type of engagement needed.

- **Level 1 trials** include observational studies that only use existing data. These trials may require well characterized data elements that already exist in the GPC data warehouses or may require extraction of new data from source EHR systems (e.g., data in provider flowsheets) or elements that are less well characterized or standardized. For such trials, the primary review is conducted by the GPC’s Data Review Oversight Committee (DROC) and site-level DROCs, with final approval by the GPC Governance Council. While our governance model allows sites to not participate in individual studies, ongoing membership in the GPC is predicated on sustained levels of participation. **Level 2 trials** include observational studies that require prospective cohort assembly and the collection of patient reported outcomes. While patients participate in Level 1 trial reviews through the DROC, Level 2 trials may require greater patient and clinician engagement. **Level 3 trials** involve prospective randomization at the cluster level (i.e., physician, clinic, health system) level and generally require informed consent. Such trials are ideally suited to test organizational or educational interventions. **Level 4 trials** involve patient level randomization and are best suited for comparative effectiveness trials of drugs, procedures, or diagnostic. Level 3 and particular Level 4 trials require significant patient and clinician engagement and buy-in from health systems due to their potential impacts on clinical workflows.
The decision making process for trial participation also considers other key factors, such as: (1) availability of adequate numbers of eligible patients and clinical champions within the GPC; and (2) potential burdens of the trial on GPC and health system informatics infrastructures and on clinical practices. As key strengths of the GPC are the diversity (e.g., ethnic and racial, urban and rural) of the patient populations across the 12 sites and the depth of clinician and investigator expertise, we do not anticipate availability of eligible patients and clinical champions will be limiting for us. For example, for the ADAPTABLE trial, the GPC easily identified a lead cardiologist and primary care provider at each site to serve as clinical champions. As requested in the RFA, a representative list of clinical champions who are interested in leading or participating in pragmatic trials is provided as Exhibit 2 in the Appendix.

**Approaches for facilitating multi-center randomized studies:** While the GPC does not yet have experience initiating and completing a practice-based pragmatic trial across the entire network, we have been active working with sites to enlist support for the initial PCORNet trials currently planned. For example, GPC investigators were active participants on the planning committee for the ADAPTABLE trial, and all GPC sites will be participating in ADAPTABLE (with the exception of Children’s Mercy Hospital as the trial involves adults). GPC sites also will participate in observational studies comparing the effectiveness of alternative bariatric surgery procedures and examining the impact of neonatal antibiotics on childhood weight and obesity. The 12 GPC sites bring tremendous experience conducting practice-based research and participating in new research networks to improve the quality and efficiency of multi-site research. For example, the Midwest Area Research Consortium for Health (MARCH), which was established in 2012, includes five GPC sites (Indiana, Wisconsin, MCW, Minnesota, and Marshfield) and provides an infrastructure for investigators and external sponsors to conduct collaborative clinical trials. MARCH implemented an IRB reliance agreement, a central administrative infrastructure for overseeing trials and negotiating with sponsors, a shared governance structure for approving trials, and numerous SOPs that are geared around conducting Phase I, II, and III clinical trials, patient and provider survey studies, and healthcare delivery interventions. The MARCH SOPs provided templates for many of the GPC SOPs.

A further example of GPC site experience is the involvement of most of our sites in NIH-funded multi-site studies of treatments for rare neurological diseases. Many of these studies were led by Drs. Richard Barohn (KUMC) and Michael Shy (University of Iowa). The existing clinical network for conducting these multi-site trials was a key factor in the GPC’s selection of ALS as its rare disease. Dr. Barohn also used GPC partners in his recently funded PCORI study to compare effectiveness of alternate therapeutics in peripheral neuropathies, and in his recent proposal to compare management approaches for patients with ALS. As another example, investigators at the University of Iowa have conducted numerous pragmatic studies of collaborative care models for managing hypertension that were conducted in academic and community settings (including affiliated rural practices) and that were funded by the NIH, AHRQ, and VA. One recent trial randomized 32 practices and enrolled 625 patients, more than half of whom were ethnic minorities. Lastly, GPC sites have been successful in obtaining funding for 17 different studies from PCORI as Exhibit 3 in the Appendix. These studies span a wide array of conditions, illustrate our collective success in patient engagement, and provide valuable experience in implementing studies that are embedded within different types of healthcare settings.

**Embedding trials in delivery systems:** Integrating research into practice is challenging, given demands for clinical productivity and the potential impact of research studies on clinical workflow. In addition to the activities described for Goal 1 to engage clinicians and test approaches (e.g., Research RVUs) to align economic incentives, GPC sites have experience testing approaches to improve participant recruitment and minimize workflow intrusions. For example, KUMC has a registry of more than 30,000 patients interested in participating in clinical studies and who agreed to be contacted regarding trial opportunities for which they may be eligible. Dr. Christian Simon and colleagues have tested an online platform for obtaining informed consent that was designed with substantial patient input and that was shown to improve participants’ comprehension of a study and satisfaction with the consent process. The platform, which is now being used to obtain consent for collecting biospecimens, substantially reduces the need for dedicated coordinators to obtain consent. All GPC sites have used the EHR to identify and contact patients for participation in clinical studies, and the GPC is working on standardizing IRB practices across sites with regard to the types of studies for which patients can be approached by investigative teams and not directly by the treating clinicians. All sites are exploring the use of EHR alerts to inform clinicians at the point of care that their patients are eligible for specific studies as a mechanism for improving patient enrollment. However, the use of alerts requires strategies to ensure that individual patients are not
Each GPC site also closely coordinates its informatics efforts with site IT functions to capitalize on EHR functions that can support PCOR studies. A number of GPC informatics team members serve on their site’s EHR implementation teams. An important focus in Phase 2 will be on using patient portals (e.g., Epic MyChart, Cerner Patient Portal) to inform patients about their eligibility for PCORnet trials, to collect patient-reported outcomes, and to disseminate the results of trials to participants. For example, several GPC sites will use MyChart to communicate potential eligibility for the ADAPTABLE trial. We also will broaden the use of EHR flowsheets for collecting patient data during clinical encounters. Flowsheets offer the promise of standardizing key data element capture by creating discrete fields, which can then be incorporated into sites’ i2b2 data warehouses. GPC efforts to broaden the use of flowsheets complement institutional efforts to enhance the capture of data elements are essential for quality measurement and reporting and for meeting Meaningful Use standards. Within the GPC, the UNMC team, which also supports EHR implementation for Nebraska Medicine, serves as an advisory group to the GPC. The University of Missouri “Tiger Institute” and the informatics team at Indiana University’s Regenstrief Institute bring additional expertise in embedding research into routine EHR processes.

To support the goal of embedding research into practice, the GPC developed effective centralized administrative functions. The Project Management Office uses Trac² software to maintain an ongoing log of outstanding issues, of strategies for resolving these issues, and of the responsible GPC site or investigator. Issues are summarized in a 1-page dashboard distributed weekly to site project managers and lead investigators. The informatics teams from each site also participate in weekly conference calls to review outstanding issues related to data standardization, ETL development and sharing across sites, adherence to the PCORnet Common Data Model, and maintenance of the PopMedNet node at each site. These activities ensure that PCORnet trial informatics needs are recognized and addressed.

**CTSA collaborations:** As described for Phase 1, PIs and co-investigators from the 8 CTSA programs in the GPC (Kansas, Iowa, Wisconsin, MCW, Minnesota, San Antonio, Southwestern, and Indiana) play key roles in GPC functions and are well represented by GPC’s Clinical and Translational Science Advisory Council. The commitments of our CTSA partners to synergize CTSA and GPC activities are clearly expressed in their letters of support. The increasing focus of the CTSA program (as expressed in the current RFA [RFA-TR-14-009]³) on research-practice integration and on improving the efficiency of multi-site clinical trials through central IRB mechanisms and novel patient recruitment approaches will further align CTSA and GPC functions. Indeed, GPC efforts to implement SOPs for conducting pragmatic trials is complementary to CTSA efforts to promote Good Clinical Practice principles and standardize the conduct of multi-site clinical trials.

**Biospecimen availability:** All GPC sites have well established programs for acquiring, storing, and archiving tissue, blood, and body fluids for future research studies. Two of our sites – Marshfield Clinic and UNMC – are recognized national leaders in biobanking with well-established protocols for linking a wide range of phenotypic information to individual specimens. Marshfield also participates in the NIH-funded eMERGE Network that has linked DNA biorepositories with EHR data at 14 sites nationally for large scale, high-throughput genetic research to support developing standardized phenotypes and implementing precision medicine. Collectively, GPC sites have more than 850,000 pathology tissue specimens, more than 100,000 stored blood specimens, and extracted DNA on nearly 80,000 patients. All GPC sites have registries for cataloguing and retrieving specimens using a variety of commercial and in-house systems. The GPC has already chosen to adopt the PCORnet Biospecimen Taskforce “Informed Consent Recommendations for Specimen Acquisition and Future Use.” During Phase 2, we will focus on approaches to standardize biospecimen management, while respecting institutional autonomy and each site’s current IRB policies. A key step will be linking biospecimens to each institution’s i2b2 data warehouses to enable rapid querying of available biospecimens for PCORnet study cohorts. Biospecimen linkage to computable phenotypes and other EHR characteristics was further described in Goal 2 above. A second step will be to build on our success developing an IRB reliance agreement and to standardize consent language for collection and future use of specimens. The GPC also will finalize protocols for a centralized biospecimen repository for storage and analysis for new PCORnet studies. At this time both Marshfield Clinic and UNMC have demonstrated capabilities and generated sample proposals to serve that central role based on the type of biospecimen. An estimated pricing structure for biospecimen management is shown in the Appendix as Exhibit 4.
Goal 4. An oversight framework that fosters public trust in research (Criterion 5)
The GPC built upon the existing infrastructure of Clinical and Translational Science Institutes (CTSI) across our region, leveraging investments already been made in informatics infrastructure and personnel. Building on these foundations, the GPC developed a nimble and diverse collaboration in which data, capabilities and responsibilities are shared in a distributed manner. We also collaborated with patients through existing community groups and community advisory boards. Some tangible results include:

- Each CTSI has active ongoing efforts to engage patients. Inputs from these CTSI-based community partners were used to select our common disease. The same channels are used to identify patients willing to engage in oversight and network development activities.
- The GPC continues to promote transparency and develop community partnerships through bi-weekly Global Call webinars that are open to all members of our community and potential collaborators outside the GPC.
- GPC investigators have populated PCORNet Task Forces including at leadership levels and have been key methodological experts in the development of the ADAPTABLE trial (Dr. Pollock and Dr. DeMets).
- Dr. John Lantos continues to work closely with the national leadership of PCORI (through the Clinical Trials Advisory Panel), PCORNet (through its Ethics and Regulatory Task Force), the Institute of Medicine (which held a meeting on Comparative Effectiveness Research in December, 2014) and with the NIH Collaboratory’s preparation of a special issue of Clinical Trials to develop recommendations for OHRP, HHS and FDA on the unique ethical and regulatory issues raised by pragmatic clinical trials. These efforts will be important as PCORNet launches the aspirin trial in 2015. Lantos is the first author of one paper in that special issue and a co-author on two others. He has also authored editorials on these issues in the New England Journal of Medicine and the Annals of Internal Medicine.

We also made progress streamlining the IRB review process across sites.

- The GPC draws strength from established relationships and common values of the CTSI programs and their leadership. Our leadership includes four CTSA PIs, seven Biomedical Informatics or Biostatistics/Epidemiology/Research Design section directors, and three Vice Chancellors or Deans for Research at GPC medical centers. This ensures clinical trials infrastructure and inter-institutional collaborations are aligned with processes at each medical center—catalyzing transformative agreements such as IRB reciprocity across our network.
- Within our network, multiple agreements are already in place among IRBs for a review process based on reciprocal deferral. Under these arrangements, the review of each multi-center study is assigned to a lead IRB. IRBs at other participating sites may choose to review each protocol or to defer to the decision of the lead IRB.
- For Phase 2 we will expand governance to also include key data partners and stakeholders in our regions to ensure network sustainability guided by our Clinical Translational Science and Health Systems Advisory Councils. We will continue engaging and integrating patients and community leaders into all levels of GPC activities, drawing on collaborations with other PPRNs and PCORNet.
- We also will review all national trials in which the GPC is participating using the GPC reciprocity process. All lead IRBs will be required to maintain AHRP or equivalent accreditation. Early participation in ADAPTABLE will help us further develop policies/agreements/processes.

While the Greater Plains IRB Consortium (GPIC) implemented several strategies to assist study teams and IRBs participating in multi-site research, for Phase II we propose an additional means of providing support to further improve regulatory review processes: an IRB Facilitator. The UW-Madison piloted using an IRB Facilitator for the Inner City Asthma Consortium¹ (ICAC), which is funded by the National Institute of Allergy and Infectious Disease (NIAID). The UW-Madison Health Sciences IRB and ICAC central administration, based at UW-Madison, collaborated on the creation and support of the IRB Facilitator position. Their IRB Facilitator plays a pivotal role in transitioning the ICAC to central IRB review. The IRB Facilitator helps institutions set up processes to work with this new IRB and helps study teams interact with the IRB, serving as a clearinghouse for issues and liaison between study teams, local IRB offices, the central IRB, the scientific center, and NIAID. The GPC IRB Facilitator will act as a guide for study teams and IRBs alike, assisting with troubleshooting problems that arise. This is a key position for Phase II, especially with the planned expansion to large-
scale studies. An IRB facilitator will effectively build trust in the GPIC in the many communities impacted by IRB review, the investigators, the participating institutions, patients, clinicians, and the public at large.

Another innovation planned for the GPIC, which anticipates the needs of PCORI studies, is forming a special IRB at GPIC sites focused on review of minimal risk research. Anticipating the implementation of the HIPAA Privacy Rule in 2003, UW-Madison formed a Minimal Risk IRB\(^2\). This Minimal Risk IRB became expert in medical-records based projects and research conducted in usual clinic settings, such as those that involve observation and/or evaluation of health care delivery or standard of care treatments. Many of the studies the UW Minimal Risk IRB reviews involve complicated determinations related to the HIPAA Privacy Rule, an in-depth understanding of hospital and clinic policies and procedures, knowledge about the content and capacity of the electronic medical record, and expertise in data security. Since the breadth and depth of this required knowledge for effectively evaluating studies that focus on health care operations and assessments of standard of care, especially across institutions, is unlikely to reside within a single person, the use of a Minimal Risk IRB composed of members with varied expertise is both necessary and efficient. Traditional expedited review, which allows the IRB chair or chair’s designate to review and approve a study for the full board can, for a variety of reasons, produce inconsistent reviews not completed in a timely manner. The UW Minimal Risk IRB meets on a biweekly basis, ensuring reviews are completed in a timely manner. Based on UW’s experience, we propose that the GPIC adopt the Minimal Risk IRB for the review of CER and other research based within or evaluating care within the clinical setting. The Minimal Risk IRB will include patients and positively impact investigators due to its efficiency and the trust built by all witnessing the specialized knowledge applied to and transparency of the IRB reviews.

- With the release of draft guidance on electronic consent (March 2015), the FDA is easing regulatory burdens and reluctance by institutions and IRBs to pursue the benefits to patients and researchers that can be realized through an electronic consent process. With the “endorsement” of the FDA, researchers can rapidly deploy electronic consents as new research questions come forward. Electronic consent provides a patient-friendly consent process that is convenient and efficient, allowing adequate time for patients to read and understand the nature of their involvement.

- Building upon our Phase I cohort surveys, during Phase II our CDRN will participate in the ADAPTABLE trial and other forthcoming studies that use an electronic process to efficiently enroll large samples to quickly answer new research questions.

- As we continue to deploy our electronic consent processes, we will pay careful attention to the important issue of authentication. Robust means of authentication serve the research community by ensuring informed consent is provided by the intended person or their legally authorized representative. Further, this authentication process is vital to fostering public trust regarding the security of their data collected through electronic means.

- Each of our partnering hospitals is taking steps to maximize uptake of the patient portal in the EHR in order to meet meaningful use guidelines for patient engagement. We will capitalize on these efforts to access an increasing number of patients who have already been authenticated in the patient portal for rapidly deploying electronic consents as new research questions come forward.

We developed an innovative research participant registry by which patients interested in participating in research are informed about the registry using web-based materials and are enrolled using electronic consent (see enrollment form at [https://www.pioneersresearch.org](https://www.pioneersresearch.org)). This program built on a prior registry that used face-to-face, paper-based enrollment to flag interest in research participation on the patient’s EHR. The original registry resulted from a data sharing agreement between the university, the hospital, and the physician practice plan at KUMC. KUMC’s HIPAA compliance officer reviewed and approved the enrollment process. While investigators have full access to de-identified EHR data to identify the number of individuals who meet specific study inclusion and exclusion criteria for research planning purposes, researchers with IRB approved studies may submit a request to the Pioneers Research Registry Request Committee (RRRC) for access to names and contact information of individuals for recruitment purposes whose EHR records indicate they meet inclusion and exclusion criteria for a specific study and are willing to be contacted. We also are developing innovative web-based consent procedures. Rebecca Ballard, Director of the Office for Research Integrity at Children’s Mercy Hospital, is building a library of videos and pictures for consenting messaging to be used on a RedCap platform. Susan Rahman (also of CMH) is researching images to explain consent concepts. Two videos are copyrighted and available commercially\(^2\) that cover two topics: “What is Informed Consent?” and “Research v.
Treatment” in English and Spanish. A third video on Privacy will be reviewed at this month’s meeting. Ballard led a workshop (“Putting the (E)asy in E-consent and the (I)nnovative in IC Documents”) at the Society of Research Administrators meeting in Kansas City in March, describing how we deliver e-consent to potential research participants, connect the e-consent to the EHR, and build study specific e-consent forms.

The GPC participates in the PCORnet Data Privacy Task Force and will comply with data security and privacy policies as they are finalized by PCORnet in a manner similar to the development of GPC’s support of the Common Data Model. The GPC’s use of REDCap and i2b2 implement logging and privacy preserving techniques (de-identification, obfuscation, de-identified access control), enhancing data transparency for patients and other stakeholders (see Phase 2 Goal 2.)

The GPIC looks forward to leading a fruitful integration of GPIC with the NCATS IRB Reliance Initiative (NIRI). NIRI was recently funded by the NCATS at NIH to create a reliance agreement among the 62 sites supported by NIH-CTSA grants. UW has contributed substantially to creating the reliance agreement for the CTSA sites, with Dr. Drezner serving on the NIRI Executive Committee, which provides overall direction for the project, and Dr. Cobb (UW IRB Director) serving on the Operations Committee, which drafted the IRB reliance agreement and the associated SOPs. As a result, the NIRI agreement and SOPs are based in large part on the GPIC reliance agreement and SOPs, similarities that will easily lead to cross-fertilization between NIRI and GPIC, and ultimately a merging of the agreements. Such interactions will favorably influence the growth of the GPC during Phase II funding.

As identified at the beginning of Goal 4, the GPC has benefited greatly from capitalizing on CTSA or CTSA-like organizational teams and structures at our sites. The overlap of GPC leadership with CTSA and CTSA-like structure leaders ensures continued mutually beneficial collaboration with local CTSA and the CTSA national consortium. It also will serve well to ensure that GPC activities are not conflicting or duplicative with those of CTSA.

In August, 2014, we held a “Learning Engagement Kick-off” (LEK) to engage stakeholders from around our network and brought together 75 patients, patient advocates, team members from all 10 GPC sites, and senior PCORI staff (J. Selby, M. Zirkle, and JB Smalley). A special session “boot camp” exclusively for patients was held the day before the meeting to prepare them to participate more fully in the group discussions. In addition to providing important face-to-face interaction, the LEK provided a forum for patients to contribute to developing our oversight framework by reviewing issues related to use of EHR data for advancing research to improve health, the critical role of patients for ensuring that studies address questions and concerns of relevance to them, and data sharing agreements and data governance. The LEK provided a first step toward positioning patients to be participants and reviewers of studies.

Patients and other stakeholders also serve on our Data Request Oversight Committee (DROC). The DROC establishes operating procedures to maximize data transparency and reviews internal and external investigator data requests and query permissions. Informed by our methods developed in Phase 1 and extended for record linkage described in Goal 2, we will work with the DROC patient representatives to develop an openly available “Date Use Statement” that explains de-identification methods, honest broker activities, data encryption and linkage, auditing, and the oversight process. We also are creating the Research Opportunity Assessment (ROA) process described in Goal 1. The ROA provides for patient oversight opportunities of both data requests and prospective research opportunities and ensures patients are engaged in identifying patient collaborators for research using the GPC. Figure 6 in the Appendix illustrates four scenarios for ways that the GPC positions patients to engage in research topics presented to the DROC and ROA, allowing differing levels of engagement at local, GPC, and external/national levels depending on the request. In 6a, we see a distributed query from PCORNet where patients on the GPC DROC will approve the responsible external investigator from the coordinating center to distribute queries across the GPC after review of the operating procedures and patient engagement process used by the coordinating center. For a PCORnet query it’s assumed the proper level of patient engagement would be in place at the national level. 6b illustrates a GPC investigator seeking to develop a CER proposal for PCORI funding that will use the GPC and is reviewed by the ROA. In addition to reviewing the requirements for patient and clinical collaborators at the site, the ROA will facilitate collaborator development across the GPC prior to submission to PCORI. In 6c, we see a fully de-identified data request from an external investigator sponsored by a GPC site faculty member. The DROC would review the request and offer patient collaborators for the investigative team. Finally, figure 6d illustrates the ROA activities to review and support an externally funded trial approaching the GPC for development and accrual. All of these approaches are designed to ensure patients are at the table at every stage.
Goal 5: A collaborative community that attracts a diverse set of researchers, funders, and other networks (Criterion 6)

As introduced in Goals 1 and 4, collaboration is a key focus for moving the GPC from ‘building’ to ‘operating’ a vibrant network that contributes fully to PCORnet’s vision. We have actively shared our governance processes and set the expectation for our network participants that our goal is to streamline collaboration processes, especially for the use of de-identified data requests or queries to sites’ Common Data Models via the PCORnet Distributed Research Network (DRN) and other use not requiring IRB approval. Early in our network’s development a majority of GPC sites executed the sub-award contract processes for the FDA Sentinel initiative led by the coordinating center; the vast majority of GPC sites supported the PCORnet ADAPTABLE trial; and we currently are mobilizing investigators for both the bariatric and pediatric antibiotic obesity studies—all evidence of our commitment to collaboration. We also have provided an active community of investigators for PCORnet; notably through David DeMets’ and Brad Pollock’s roles in developing the methodology for the ADAPTABLE trial. We fully anticipate continued interest across the GPC as willing data partners, collaborative investigators, or clinical sites for future PCORnet projects.

The GPC has been open in its methods and communications as much as possible: tracking progress on our wiki, using public worldwide readable listservs, holding open GoToMeeting events advertised on our listservs, wiki and Central Desktop, and using publically available bitbucket code repositories. All of these processes enhance opportunities for collaboration. We also enthusiastically support collaboration across PCORnet and will continue to welcome PCORI’s participation in our activities, much like what happened with our Learning Engagement Kickoff last year at which PCORI and PCORnet leadership attended and asked to bring their photographers. Following that successful event, we freely shared all of the materials from the graphics facilitator engaged by the GPC to summarize and document what happened for our needs and for PCORI to use for its communication needs1,2.

As shown in our letters of support, the GPC enjoys strong support from and collaboration with the CTSA and CTSI institutes at our academic medical centers. The majority of GPC site lead investigators are CTSA principal investigators, biomedical informatics core investigators, or senior deans or equivalent clinical research informatics leaders for their campuses. Just as institutional support provided the foundations for clinical and translational science, now the CTS infrastructure provides the engagement and informatics underpinnings for data interoperability and collaboration processes for broader national collaboration through PCORnet.

For Phase 2, we will extend and build a collaborator database, leveraging existing CTSA annual investigators reporting requirements with our current GPC request form3 that is modeled after the Mid-South CDRN’s process. As shown in Figure 7 in the Appendix, we will “seed” our collaborator database with the CTSA investigators and augment the areas of specialty required by the NIH with lay language equivalents (e.g. “oncology” translates to “cancer”) so that all collaborators (patients, investigators, clinicians, and health systems leaders) can sign up with their areas of interest identified. External collaborator requests also will specify areas of interest and keywords so that collaborator matching from our network with the needs of external collaborators may be made. Clearly aligning needs with local interests will support more effective engagement circles at the local, GPC, and national level. During Phase 2 we also will leverage the existing national library of medicine MyBibliography reference tool4 to provide richer description of investigators current activities, further strengthening PCORI and CTSA collaboration. Developing informatics capabilities for sharing GPC investigators’ PubMed scholarship with external investigators and vice versa also will streamline collaborator match making. Our hope is that external investigators will share their interests when GPC investigators seek external collaborators. The database, web portal, and methods we institute will be shared openly.

Current GPC collaboration capabilities already have resulted in successfully funded projects and protocols under development, including: “Midwestern Collaborative for Treating Obesity in Rural Primary Care (PCORI: Befort, KUMC; collaborations with Marshfield and Nebraska), “Identifying breast cancer patients receiving autologous fat grafting in the Greater Plains Collaborative” (Holden Cancer Center gift funds: Saftlas, ABOUT, and Chrischilles, Iowa), “Comparative Effectiveness Study of Treatment of Sialorrhea in Patient with Amyotrophic Lateral Sclerosis” (PCORI: Barohn, KUMC; Walk, UMN; Nations, UTSW; Jackson, UTHSCSA; Fernandes UNMC; Boeroe, Marshfield; Swenson, Iowa; Waclawik, UW; Barkhaus, MCW), “Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure” (Solomon and Vardeny, Harvard and Wisconsin), “A Pragmatic Clinical Trial of Nighttime Dosing of Anti-Hypertensive Medications” (Vander Weg, Iowa), “Finding Fractures and Osteoporosis Using Native Data from Computed Tomography” (Jarvik, Washington; GPC coordination by Dr. Joan Neuner at MCW), inter-CDRN collaboration on Sickle Cell Disease
latter collaboration builds on recent work CONNECT and for identifying infections related to the IgG levels of the patients to determine optimal therapy. This Dr. Kimminau (KUMC) and the ADVANCE CDRN, and with for patients around clinical trial participation. We also have been active with collaborations on research literacy led by collaborate with the DuchenneConnect, and the Multiple Sclerosis PPRNs during Phase 2. Through the GPC’s strong position to support rare disease PPRNs, and Dr. Barohn’s role on the rare disease task force, we have learned that all PPRNs desire common scalable approaches for transparent governance of data exchange and recruitment with CDRNs. We will leverage the privacy preserving record linkage protocols described in Phase 2 Goal 2 for GPC data partners for PPRNs. This work will be in collaboration with investigators from Mid-South, with whom we are piloting CMS connectivity, as well as with CAPRICORN and NYC CDRN investigators. The data core for ABOUT and Vasculitis is in South Florida and will help promote generalizability to other rare diseases. Our addition of the Multiple Sclerosis PPRN will provide experience also supporting a common disease PPRN.

As indicated in the letters of support, the GPC also will collaborate with the ABOUT, the Vasculitis, the PI-CONNECT, the DuchenneConnect, and the Multiple Sclerosis PPRNs during Phase 2. Through the GPC’s strong position to support rare disease PPRNs, and Dr. Barohn’s role on the rare disease task force, we have learned that all PPRNs desire common scalable approaches for transparent governance of data exchange and recruitment with CDRNs. We will leverage the privacy preserving record linkage protocols described in Phase 2 Goal 2 for GPC data partners for PPRNs. This work will be in collaboration with investigators from Mid-South, with whom we are piloting CMS connectivity, as well as with CAPRICORN and NYC CDRN investigators. The data core for ABOUT and Vasculitis is in South Florida and will help promote generalizability to other rare diseases. Our addition of the Multiple Sclerosis PPRN will provide experience also supporting a common disease PPRN.

Notably, the American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network (ABOUT) rare disease PPRN complements the GPC’s breast cancer efforts as our selected common disease cohort. Dr. Elizabeth Chrischilles (Iowa), and Dr. Sutphen and Dr. Friedman (ABOUT) have shared surveys, discussed the development of our cohort characterization, and explored further collaboration and recruitment between the GPC and ABOUT, which we plan to continue. We also have kept Dr. Peter Merkel informed of the GPC’s development and capabilities to support recruitment for the Vasculitis PPRN and have identified Dr. Jason Springer at KUMC as our leader for this GPC collaboration. Dr. Richard Barohn (ALS cohort and neuromuscular leader) recruited Dr. Kathy Mathews at Iowa to collaborate with the DuchenneConnect PPRN, regarding CER research development and to evaluate a decision aid tool for patients around clinical trial participation. We also have been active with collaborations on research literacy led by Dr. Kimminau (KUMC) and the ADVANCE CDRN, and with providing preliminary computable phenotype support for PI-CONNECT and for identifying infections related to the IgG levels of the patients to determine optimal therapy. This latter collaboration builds on recent work to standardize microbiology results, including drug sensitivities. In sum, the
GPC has been, and will continue to be, heavily involved in collaboration across our sites, with other CDRNs and PPRNs, on various PCORI projects, with CTSA programs, and with other external collaborations.
Goal 6. Research networks that are sustainable (Criterion 7)

Since its creation, the GPC has recognized the many challenges to creating a sustainable CDRN. In response, the GPC has proactively implemented a number of complementary strategies to ensure its long-term vitality. These strategies encompass both strategic and tactical elements and capitalize on a number of resources and programs within our institutions and on the unique missions and roles of our collaborating health systems.

At a strategic level, GPC leaders recognized that the sustainability of the GPC is predicated on our academic medical centers’ and health systems’ core values of advancing clinical and translational science as a catalyst for serving as leading learning health care systems for their regions. These core values are reflected in the investments that each of our institutions makes in the translational science enterprise. At a more granular level, each of our institutions recognizes that its success in an era of accountable care depends on the ability to harness the power of big healthcare data and develop the informatics and analytical infrastructures to support the delivery of high value healthcare. Our institutions further recognize the growing synergies between the data needs of investigators and health system leaders and the expertise that is needed to conduct patient centered outcomes research and to develop innovative delivery models. Thus, a fundamental strategy of the GPC has been to advance understanding among health system leaders of the value of PCORnet participation and of linking GPC capabilities and activities to health systems needs.

At a tactical level, the GPC will pursue a number of strategies to ensure sustainability. These include: (1) establishing a critical mass of committed participating sites; (2) collaboration with institutional translational science programs; (3) moving toward a service recharge model to support core infrastructure functions; and (4) use of low-cost open source technologies to decrease the shared cost of introducing innovative new tools and capabilities.

**Critical mass of committed participating sites:** PCORnet’s success depends on the ability to develop new research protocols for pragmatic studies and to rapidly respond to opportunities to participate in studies proposed by other groups. Thus the ability of the GPC to grow and establish a critical mass of institutions that share a common vision, that provide care to diverse populations, and that house research programs with a wide range of methodological expertise is essential. While Phase 1 brought ten institutions leveraging resources provided by PCORI, Phase 2 tests the generalizability of our network model by adding sites selected on the basis of 1) the regional reach of their healthcare systems, 2) their cutting edge work in EHR adoption, health services research and informatics, and 3) their innovative collaborations with Cerner Corporation, which complements the predominant use of the Epic EHR in the original GPC institutions. We believe that the twelve sites that will participate in Phase II position the GPC to participate in a wide range of PCORnet studies and in new initiatives that may emerge from the NIH Healthcare Systems Collaboratory, NIH institutes, and FDA, and to be of value to new partners, including the insurance, pharmaceutical and device industries.

**Collaborations with translational science programs:** As noted previously, the GPC has benefited from collaborations with CTSA programs and similar translational science programs at non-CTSA institutions, which enabled sites to significantly leverage resources provided by PCORI. The collaborations were particularly beneficial in developing data warehouses, REDCap and other informatics tools, shared IRB and contract models, and SOPs. During Phase II, these collaborations will expand to encompass a number of other areas that are also of vital importance to CTSA programs, including approaches to promote efficient patient recruitment, to engage a broader spectrum of stakeholders, to facilitate multi-site research networks, and to disseminate research findings to patients and practitioners. As described for Goal 1, a further area of collaboration will a new pilot grant program to support projects using GPC resources and developing innovative methods that could be employed in larger externally funded studies conducted through the GPC. Thus, with the decline in funding to individual GPC sites due to changes in PCORnet funding and expansion of the GPC, integration of GPC and translational science resources will be even more important during Phase II. Additionally, Dr. Brad Pollock, GPC methods core director and principal investigator of the National Cancer Institute funded Children’s Oncology Group, will assess opportunities at the intersection of the nation’s cancer research agenda and PCORNet.

**Service recharge model:** An important element in our plan for long-term sustainability is the implementation of a service recharge model in which much of the costs of maintaining central GPC and site-level infrastructures are supported by individual projects that utilize the GPC. The service recharge model will be governed by a Memorandum of Understanding (MOU) that will be based on the network finance model used by the MARCH. The MOU will also establish a recharge cost center, which will be administered by the KUMC Research Institute that currently holds the prime
PCORnet contract. Sites will invoice the cost center for services provided in support of individual projects. The funds generated from such invoices will be used to support a number of site-level infrastructure expenses (e.g. data standardization, data querying, enhancing shared IRB agreements, oversight of requests for data). In addition, the service recharge model will support a number of essential central functions that are described below.

1) **Supporting GPC honest broker functions that involve central analysis of data from individual GPC sites and/or the creation of de-identified or limited datasets to support external investigations.**

2) **Study feasibility queries (including projects that employ automated federated access approaches (e.g., SHRINE).**

3) **Developing REDCap projects to support the collection of patient reported outcomes for PCORnet studies.**

4) **Developing EHR tools (e.g., alerts) for interventional studies that can be installed at multiple sites.**

5) **Integration of payer and insurer data to capture out of system healthcare delivery and to create comprehensive longitudinal data warehouses for our captured populations.**

6) **Data integration (e.g. National Cardiology Disease Registry CathPCI) aligned with quality improvement initiatives.**

The success of the service recharge model for supporting essential core functions is dependent on the ability to create a steady stream of external funding through the development of new research proposals by GPC investigators and by attracting studies proposed by external investigators and building partnerships with industry and with health insurers. In the past year, the GPC supported proposal submissions by GPC investigators and external investigators (e.g., ADAPTABLE, FDA Sentinel, CDC Next-D proposal investigators at Northwestern). These proposals were based on our data sharing agreement for non-commercial use. Phase 2 will build upon our External Institution Collaborator Agreement for noncommercial use to transparently develop equivalent equitable agreements for collaboration with industry, guided by feedback from patients and other stakeholders, as outlined in Goal 4. GPC sustainability planning is supported by Dominique Pahud, former senior fellow in Research and Policy at the Ewing Marion Kauffman Foundation, and uses a Business Model Canvas. The Business Model Canvas provides a visual template for developing the GPC’s value proposition, infrastructure (activities, resources, and data partners), customers (customer segments, delivery channels, and customer relationships), and finances (cost structure and revenue streams).

**Low Cost Central Technologies and Processes:** By augmenting CTSA infrastructure and teams, we initially estimate the GPC can provide sites standardized PCORnet elements for on the order of $200,000 per year ($150,000 site expenses beyond CTSA; $50,000 site contribution to central technical and administrative functions). In turn this provides:

1) **Mapping i2b2 data to PCORnet specific common data models (CDMs) required for individual projects. The resulting standardization will provide additional research opportunities that leverage those standards (e.g., FDA Sentinel).**

2) **Replicating the data into the CDM and providing SAS environments for distributed analysis across GPC sites, as may be required for some projects. Costs contained through open source transform code and academic licenses.**

3) **Supporting PopMedNet distributed research queries from the PCORnet Coordinating Center. GPC will move to single coordinating site (Marshfield) that will have approval to access the CDMs at each GPC member site.**

Strategies for supporting these infrastructure components include: (1) offering network “memberships” to external organizations that would provide ongoing access to de-identified data for analyses that are consistent with the mission of the GPC; (2) garnering support from our collaborating health systems for value-added functions (e.g., creation of enhanced datasets to support population management, integration of institutional data with research registries, quality improvement benchmarking) that will position health systems to realize the potential envisioned at the Institute of Medicine roundtables last year; and (3) assessing GPC sites membership fees. Recharge activities and fee capture will be closely monitored during the first two years of Phase 2 funding. A key focus of this monitoring will be to determine if membership fees from GPC sites will be required during Year 3 to support central administrative and technical functions.

Our network’s vision brings together educated patients, clinicians, investigators, and health systems leaders as valued collaborators for national PCORnet initiatives and external investigators, promotes patient centered research and data exchange with PPRNs, and also develop topics from within the GPC that can be shared broadly. Our network is built on the foundations of our Clinical and Translational Institutes and committed to work with patients and all sectors of our
health care delivery system to equitably position the GPC in broad service to national health. The GPC will submit a sustainability plan to PCORI annually in accordance with the Global Milestone schedule.
C. Staffing and Organizational Requirements (Page limit: 4 pages) (Criterion 8)

The Greater Plains Collaborative will sustain the leadership, governance and communications approaches in Phase 2 that proved highly effective within Phase 1. These approaches are described in Part II - Section A of the GPC’s Technical Proposal for Phase 2 and are represented within Figure 1. We will continue to enhance and evolve these approaches based on our learnings from stakeholder feedback as well as our ongoing operational experience.

Russ Waitman, PhD, will continue as the primary Principal Investigator (PI) for the GPC within Phase 2. As required, Dr. Waitman is a full-time employee of the prime applicant (KUMC). For KUMC, Dr. Waitman directs the Division of Medical Informatics, is an Associate Professor in the Department of Internal Medicine and serves as Assistant Vice Chancellor for Enterprise Analytics. Within this phase, Dr. Waitman will be focused on: 1) overseeing the further build out of the GPC’s data infrastructure; 2) leading collaborations with the PCORnet Coordinating Center and other CDRNs; and 3) leading the planning and implementation of the GPC’s sustainability plan. He will also serve as Site PI for KUMC. His effort for Phase 2 is budgeted at 40%.

Gary Rosenthal, MD, will serve as Co-PI for Phase 2 while sustaining his role as the University of Iowa’s Site PI. Dr. Rosenthal is the Director of the University of Iowa Institute for Clinical and Translational Science (ICTS) and recently served as the Interim Chair of the Department of Internal Medicine. Though not formally designated as the Co-PI within Phase 1, Dr. Rosenthal has played a very active leadership role within the collaborative. To compliment Dr. Waitman’s biomedical informatics expertise, Dr. Rosenthal is as an accomplished investigator who has had a major impact on patient centered outcomes research and training. His own work has centered around three related themes: (1) interventions to improve health care quality and implementation of evidence-based practices; (2) measurement of quality of care and identification of variations in healthcare delivery and gaps in quality; and (3) practice-based pragmatic trials. For Phase 2, Dr. Rosenthal will lead the GPC’s Collaborator Engagement activities and will also lead the Research Question Prioritization and Research Opportunity Assessment functions. His effort for Phase II is budgeted at 25%.

In addition to Dr. Waitman (KUMC) and Dr. Rosenthal (Iowa), other Site PIs continuing from Phase 1 include:

- Laura Fitzmaurice, MD – Children’s Mercy Hospital and Clinics
- Marc Drezner, MD – University of Wisconsin - Madison (additionally overseeing the GPC’s IRB activities/function)
- Bradley Taylor – Medical College of Wisconsin
- Robert Greenlee, PhD - Marshfield Clinic Research Foundation
- Connie Delaney, PhD - University of Minnesota Academic Health Center
- James McClay, MD – University of Nebraska Medical Center (additionally overseeing the Interventional Informatics function)
- Alfred Tirado-Ramos, PhD – University of Texas Health Sciences Center – San Antonio
- Lindsay Cowell, PhD - University of Texas Southwestern Medical Center

Site PIs for the newly added sites in Phase 2 include Paul Dexter, MD (Indiana University/Regenstrief Institute) and Jerry Parker, PhD (University of Missouri). These two new sites have indicated a strong willingness to quickly integrate into the collaborative’s governance/organizational structure.

Steve Fennel, MHSA/MBA will continue as Administrative/Project Director. During Phase I, Mr. Fennel has coordinated our larger project management office in conjunction with John Steinmetz and Dan Connolly (who will continue as leader
of the GPC software development efforts). He has worked effectively in coordinating with all GPC sites during the course of Phase I and will continue to guide our project execution in an innovative and responsive manner. Mr. Fennel has had significant multi-site management and complex project/program management experience. He is budgeted at 50% for the three years of Phase 2.

Under the direction of Robert Greenlee (Site PI at the Marshfield Clinic), we have identified a lead SAS analyst for Mini-Sentinel/CDM coordination (Marshfield is a long standing HMORN and MiniSentinel data partner). Marshfield will also assume responsibility for Biospecimen support for the GPC on a fee-for-service basis. Separately, the GPC will have the support of a Lead NLP Analyst, Dr. Jay Urbain, from the Medical College of Wisconsin/Milwaukee School of Engineering under the direction of Brad Taylor, MCW Site PI.

The participating GPC sites are committed to adequate staffing to meet the Phase 2 objectives and key milestones. Each site is funded to support a common core staff infrastructure of a data warehouse/software development lead, an Honest Broker, a Project Manager and a Patient Engagement liaison. Site level budgets vary slightly in approach based on local needs and resource requirements. Additional site-level funding has also been provided dependent upon the leadership roles assumed for overall GPC activities. Specifically, the GPC is also engaging the following additional Key Personnel in Phase 2:

- Kim Kimminau, PhD (KUMC) – Patient Engagement Lead
- Ms. Cheryl Jernigan, - Patient Advisory Lead
- Elizabeth Chrischilles, PhD (Iowa) - Breast Cancer Cohort Lead; ABOUT PPRN collaboration
- Richard Barohn, MD (KUMC) – ALS Cohort Lead
- Dan Hale, MD (UTSHSCA) - Weight Cohort Lead
- Kathy Mathews, MD (Iowa) - DuchenneConnect PPRN collaboration
- Jason Springer, MD (KUMC) – Vasculitis PPRN collaboration
- James Campbell, MD (Nebraska) - Data Standards Lead
- Bradley Pollock, PhD (University of California – Davis)- Research Methods/Study Design Lead
- John Lantos, MD (Children’s Mercy) – Ethics Lead
- Mei Liu, PhD  (KUMC) – Data Security

In conjunction with the direction provided by the Principal Investigators, the GPC will continue to utilize a network Governance Council composed of the Site PIs site along with the lead patient representative, participating health system leaders and key functional leaders. As depicted in the governance structure/organizational diagram, GPC’s leadership will be advised by three councils: 1) the Health Systems Advisory Council; 2) the Clinical and Translational Science Advisory Council; and 3) the Patient Advisory Council.

As evidenced by the governance/organizational diagram, the GPC will operate with a well-defined organizational structure and with clear accountabilities as defined within subaward agreements that will be put in place to ensure that each partner site will support the delivery of the GPC’s contractual milestones. The overall Project Management Office will work with site level project management counterparts to monitor progress across all areas of commitment and to coordinate efforts across the collaborate. The majority of the site level project managers played this role within Phase 1 for their sites.

Many of the participating organizations have prior partnership and collaboration experience outside of Phase 1 and have the ability to leverage expertise and processes from CTSA infrastructure, inclusive of processes for administrative and fiscal management. It is anticipated that several overall GPC face-to-face meetings will occur during the course of the
contract period, with frequent virtual meetings to support the most efficient use of time and financial resources. Separately, there is strong organizational commitment across all institutions and health system partners as evidenced by the letters of support that are included with this application.

With twelve participating institutions, the GPC has broad access to leaders in the fields of medical informatics, comparative effectiveness research and pragmatic trials, epidemiology and research design methodologies, patient/stakeholder engagement, clinical research administration and project management. Throughout Phase 1, the GPC demonstrated the ability to engage the required expertise across all ten initial partner sites to support its efforts. Our two new partners bring supplemental expertise and both have indicated a strong willingness to actively engage in the network’s leadership, governance and research activities as well as are supportive of the GPC’s ongoing patient and clinician engagement activities.

As a model for a future operating structure, the GPC has looked to the successful formation and operation of the Midwest Area Research Consortium for Health (MARCH) which contains five (Wisconsin – Madison, Marshfield, MCW, Indiana and Minnesota) of the twelve GPC partners. The consortium and its jointly developed processes, governance and standardized methods provide the GPC with a framework for further moving the GPC towards a sustainable operating entity. Thus, as we approach Phase 2, the GPC anticipates executing a Memorandum of Understanding between the partner institutions to further define the governance, administrative and financial considerations in support of ongoing sustainability. Additionally, further work on enhancing and expanding standard operating procedures in support of the GPC’s governance will take place as needed.
D. Proposed Budget (Criterion 9)

This criterion is addressed by applicants in the Budget Template and justification. No additional response is required in this plan.
PROTECTION OF HUMAN SUBJECTS

For additional guidance, consult Section 5.0, “Human Subjects Research Policy,” from the Supplemental Grant Application Instructions for All Competing Applications and Progress Reports, from the U.S. Department of Health and Human Services. For detailed instructions, consult the application guidelines for your PFA. Do not exceed five pages.

Describe the protection of human subjects.

During Phase 1 of PCORnet, the institutions participating in the Greater Plains Collaborative (GPC) CDRN executed the GPC Institutional Review Board (IRB) Authorization Agreement. Through this agreement, each institution agreed to maintain a registered IRB and an Office for Human Research Protections (OHRP)-approved Federalwide Assurance (FWA) for human subjects research. Further, the signatory institutions agreed that they may rely on each other for review and continuing oversight of human subjects research under terms outlined within the agreement.

For Phase 2, we will capitalize on the alliances that have been formed in the process of creating the GPC IRB Consortium. Standard operating procedures for the consortium were finalized when the reliance agreement was adopted, and they will be used to guide and streamline our future collaborative efforts. The IRB consortium provides a mechanism for our institutions to efficiently communicate and reach consensus on a variety of regulatory topics. Further, the institutions have committed to an ongoing process of sharing and developing best practices for meeting regulatory standards and implementing the collaborative research.

For most research projects, plans to protect human subjects require researchers to categorize the research project as falling into one of six possible domains, as outlined in the six possible scenarios given in PHS 398. We anticipate research projects in the GPC going forward will fall into all six domains. Thus, we need to develop a plan to protect human subjects that is flexible enough to deal with any or all of the scenarios.

Some projects will not involve human subjects at all (Scenario A). That will occur when the data that we use are totally de-identified. According to OHRP, data are considered de-identified under the following criteria.

OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For example, OHRP does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:

1. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
   a. the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
   b. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
   c. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

1 Available at http://grants.nih.gov/grants/funding/424/SupplementalInstructions.pdf#5_4_IRB_Approval.
Other projects will fall under scenario C, exempt human subjects research. We anticipate that the most likely projects of this type will be those that meet the federal criteria outlines in 46.101(b)(4): *Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.*

However, we expect much of the research in the GPC will be non-exempt. For those that are prospective clinical trials, the GPC will develop individualized plans for the protection of human subjects, taking into consideration the following factors:

**Distinguishing when outcomes research or sharing of data/biological samples requires IRB oversight.**

1. Outcomes research is closely aligned with quality improvement (QI) and quality assurance (QA) activities. The GPC leadership recognizes that developing a consensus approach to distinguishing QI/QA activities, which do not require IRB oversight for human subjects research, is critical for efficient GPC operation.
2. Receiving/exchanging data or biological samples will be common in GPC studies. Regulatory oversight will vary, depending on whether data or samples are directly identifiable or coded and if data/sample recipients are collaborating with individuals who have access to the code. The GPC Greater Plains IRB Consortium (GPIC) will develop guidelines to address these issues. Whenever feasible, sharing of data or samples will be coded or de-identified to minimize risk to study participants, lessen regulatory burden for the institutions and reduce the time from conception to implementation.

**Regulation of subject identification and recruitment strategies.** To facilitate study subject identification across the consortium, GPC members will be familiar with the rules governing medical records access at collaborating institutions. Developing uniform standards regarding who can access medical records for research purposes, who can make first contact with potential subjects, and what constitutes the allowed content for recruitment materials is essential for efficient operation of the reciprocal deferral model. In addition, if data warehouses are used for recruiting research subjects, consensus regarding the need for IRB oversight of these activities is likewise critical. Thus, the GPIC will devote significant effort to characterize variation in these areas and develop best practices.

**Waivers and alterations of consent and authorization.** With certain limits, federal regulations provide flexibility for IRBs to grant a waiver of documentation of informed consent and authorization, a complete waiver of informed consent and authorization, or alteration to the consent or authorization process. For efficient GPIC operation we will develop guidelines regarding when this flexibility is appropriate and how it can be exercised, particularly in regard to use and extraction of data from medical records.

**Identifying and assessing research risks.** Given the close parallels between comparative effectiveness research and patient clinical care, developing standards for risk analysis of such research is essential for effective operation of the reciprocal deferral IRB model. The factors that an IRB considers in these analyses may significantly impact the regulatory determinations for a study, such as whether a waiver of informed consent can be granted, what should be included in a consent document, or if a formal data monitoring board is required. Thus, we will address these issues and develop practical and uniform guidance for the IRBs to use for risk analysis. To do so, we will use the following categories to categorize risks and to explain these to potential human subjects:

1. **Risks associated with the standard of care.** All patients, when receiving the standard of care, encounter risks both due to the underlying disease processes and of iatrogenic harm. Patients in research studies must be informed about undesired events or outcomes that are likely to occur commonly or that would be severe.
2. **Risks (and benefits) of intervention A as compared with intervention B.** The need for comparative effectiveness research (CER) studies arises when, within the range of the standard of care, more than one intervention is in common use for the same therapeutic purpose and experts disagree about which of the interventions is superior. In such situations, the relative risks associated with interventions A and B may be unknown, or one intervention may be known to be riskier or most costly but potentially offers compensatory benefits. CER measures the difference in the marginal risks and benefits of A and B relative to each other.

3. **Risks due to randomization.** In Randomized Clinical Trials (RCTs), randomization dictates which intervention a participant will receive. If common treatments A and B were identical, the associated risk would be zero. In RCTs of two different interventions, when the differential risks of A as compared with B are unknown — hovering in a state of so-called clinical equipoise — the risks posed by assigning patients to one of the two interventions either by randomization or by uncertain clinician preference are not marginally different. Nevertheless randomization is not always well-understood by patient populations. Thus, any patient who is to be enrolled in a study that entails randomization will be informed of the need for randomization and their consent will be sought.

4. **Risks due to experimental assignment versus practice variation.** Patients receive care at particular sites. At each site, physicians may have their own preferences for one treatment over another. Thus, from the patient’s perspective, enrollment in a trial usually entails a describable alteration in the likelihood of receiving either intervention A or intervention B. If the patient is at a site that has mostly used intervention A, then entering the study entails an increased likelihood of exposure to B, and vice versa. Participants at a specific site should be given this site-specific information, when possible, in order to evaluate how their treatment in the study differs from what they would have received outside the study.

5. **Risks due to masking of “standard” interventions.** Blinding of participants and investigators to treatment allocation and assignment reduces outcome-measurement bias but introduces risk. In attempting to mask standard interventions, researchers must consider how masking may affect the overall care of the participant as a patient. Research participants and health care professionals must be made fully aware that they will not be allowed to either choose or know the treatment assignment.

6. **Risks due to protocol fidelity.** In standard clinical care, disease- or condition-specific pathways or protocols are often suspended or altered when a patient is not doing well. Deviations from routinized care are common practice, even though they may or may not benefit the patient. Comparative Effectiveness Research (CER) RCTs need to identify when a particular intervention or treatment protocol should be altered, suspended, or stopped according to standard-of-care practices and evaluate and minimize the risk associated with delays in such alterations of standard medical care. Prospective participants need to understand the investigator’s obligation to ensure fidelity to the protocol, the protocol-specified limits to that obligation, and their right to withdraw from the study.

7. **Risks of being assigned to the study group that receives less benefit.** In CER RCTs, neither treatment option is universally accepted as the default or control. This symmetry has implications for informing subjects about both risks and benefits. Since both interventions are simultaneously presumed to be effective (albeit to a different yet unknown degree), participants may perceive the risks as low. One treatment may, however, yield greater benefit. The participants assigned to the other group may perceive their lower benefit as an actual harm. Potential participants should be informed of this possibility.

8. **Risks due to acknowledgement of uncertainty.** In obtaining informed consent, investigators must clarify the existing uncertainty regarding the interventions. This clarification may cause psychological discomfort in patients who find uncertainty disconcerting. Though concealing uncertainty may appear warranted in order
to avert this discomfort, doing so would constitute a failure to respect persons. Patients need facts in order to make informed decisions. These psychological risks are, therefore, unavoidable in the ethical conduct of randomized trials. But it is crucial to recognize that informed consent for standard-of-care interventions requires similar disclosure of uncertainty about treatment alternatives with similar psychological risks. Thus, this is only a risk of research if informed consent for standard of care interventions is inadequate.

9. **Risks associated with being in the trial as compared with not being in it.** Overall, if participation in clinical trials posed risks to participants, then participants in clinical trials would be observed to experience more harm or poorer outcomes than those receiving care outside clinical trials. There is no evidence that they do. Instead, participants in clinical trials have outcomes equivalent to those among similar patients not enrolled in studies who receive the same treatments. Unless specific reasons dictate otherwise, participants in CER RCTs should be informed that their outcomes will most likely be the same, but could be better or worse, whether or not they participate in the trial.

For each proposed study, the GPC IRB Consortium will evaluate the overall risks and benefits in each of these domains separately and then integrate them into an assessment of the risks and benefits of the study as a whole. This approach will require judgments when comparing one sort of risk to another. Communication of this complex risk/benefit information requires a balancing act. Detailed explanation of each separate risk may be overwhelming and confusing. Summaries of the risks may oversimplify or underemphasize particular risks. Evaluation of the acceptability of studies and of the adequacy of consent forms must reflect consideration and communication about these potential risks and benefits both separately and as a whole.

**Inclusion of Women and Minorities**
Our network will include 5-10 million individuals. Any particular study will include a subset of these individuals. Our IRB Consortium will continue to evaluate each project to insure that women and minorities are included.

**Vulnerable populations**
Studies that include vulnerable populations will be evaluated in accordance with HHS policies.

**Data Safety and Monitoring Board (DSMB)**
There will be no overarching DSMB for this project. Individual research studies may require DSMBs. This will be determined by the GPC on a study-by-study basis.
CONSORTIUM CONTRACTUAL ARRANGEMENTS
For detailed instructions, consult the application guidelines for your PFA.

Describe the proposed activities that will be performed by subcontracted organizations. Explain the strengths that these partners bring to the overall project.

The Greater Plains Collaborative (GPC) operated within Phase 1 of PCORnet as a partnership of ten medical centers located across seven states, the formation of which was driven by the initial PCORI vision of an integrated national data infrastructure to support practice-based outcomes and comparative effectiveness research. For Phase 2, the GPC will expand to include two additional institutions, bringing the total sites to twelve and the states covered to eight. The GPC will separately subcontract with the University of California – Davis for the continued engagement of Dr. Brad Pollock as the lead for the GPC’s Innovative Research Methodology Core.

The primary applicant organization (KUMC) and its eleven subcontracting institutions each have well-established research programs as well as significant operational experience with both commercial EHR systems and informatics/data warehouse infrastructures. Additionally, the partners bring strong working relationships at both the localized level (between investigators and informatics/information technology organizations) as well as at the broader cross-institutional level. The subcontracting institutions within the collaborative each bring unique strengths and complimentary areas of expertise. The majority of sites are also CTSA sites or are participants in a CTSA consortium.

As was the case in Phase 1, there will be standard expectations for each partner site in terms of the delivery of key milestones. The scope of work to be performed by each participant in the GPC CDRN will include the supporting activities necessary to allow the consortium to successfully complete all requirements over the three year period of Phase II. The associated work requirements for each partner focus on further building out each site’s data infrastructure to support efficient and complex clinical research trials and to begin addressing increasing volumes of research queries. Additionally, the network sites will work together on establishing the GPC as a self-sustainable resource for standardized, accessible data for patient-centered clinical trials.

Each GPC partner has completed and submitted to KUMC the Commitment Form to Establish a Subaward Agreement. Similar to the approach executed in Phase 1, KUMC will establish formal subaward agreements with each institution participating in Phase 2.

The following briefly describes each subcontract site, their associated key personnel and their expected contribution to the consortium.

The Children’s Mercy Hospital and Clinics, Kansas City, Missouri
The Children’s Mercy Hospital and Clinic (CMH) provides advanced pediatric care to patients and families throughout the Midwest. Affiliated with the University of Missouri – Kansas City School of Medicine, CMH has a medical staff of 68 primary care physicians as well as 757 pediatric specialists practicing in more than 40 pediatric specialties. For the GPC partnership, CMH represents 2 hospitals, 36 clinic sites and 227,120 active patients with data in their EMR. The site lead, Laura Fitzmaurice, MD and CMH CMIO, will provide continued insight from a CMIO perspective regarding aligning the research network with the various health systems’ electronic health records. Additionally, John Lantos, MD, the site’s Co-Investigator, is a bioethicist and researcher on the risk and benefits of Comparative Effectiveness Research. Dr. Lantos, who has been Co-Chair of the PCORnet Ethics and Regulatory Task Force, will continue to bring this important perspective to the GPC’s centralized governance processes.

University of Iowa Healthcare, Iowa City, Iowa
University of Iowa Healthcare provides tertiary and quaternary-level patient care to the state of Iowa and the surrounding region as well as is a national leader in biomedical research. For the GPC partnership, University of Iowa
Healthcare represents 1 hospital site, 12 clinic sites and 519,915 active patients with data in their EMR. The institution has a medical staff of 161 primary care providers and 1,047 specialty providers. The University of Iowa is both a CTSA site and is a NCI Designated Cancer Center. Gary Rosenthal, MD, is the Director of the University of Iowa Institute for Clinical and Translational Science (ICTS) and will be Co-Principal Investigator for the GPC in Phase II. Dr. Rosenthal will continue to lead the GPC efforts around healthcare system and clinician engagement. Additionally, he will also contribute to the development of novel approaches for conducting pragmatic trials. Further, Elizabeth Chrischilles, PhD, will direct further development of the GPC’s breast cancer cohort as well as lead the GPC’s collaboration with the ABOUT PPRN. Dr. Chrischilles is a Professor in the Department of Epidemiology and the Director of the Health Effectiveness Research Center in the College of Public Health, and Associate Director for Population Sciences in the Holden Comprehensive Cancer Center. Further, Dr. Kathy Mathews will be engaging in GPC activities in Phase II and will focus on the GPC’s collaborative efforts with the DuchenneConnect PPRN.

University of Wisconsin, Madison, Wisconsin

The University of Wisconsin – Madison and its affiliated University of Wisconsin Hospital and Clinics represent 1 hospital and 43 clinic sites for the partnership. The medical staff consists of 691 primary care providers and 743 specialty providers. Further, the University of has 416,106 active patients with data in their EMR. The University of Wisconsin – Madison has is both a CTSA site and a NCI Designated Cancer Center. Umberto Tachinardi, MD, Associate Dean for Biomedical Informatics, will serve as the local Co-Investigator for the University of Wisconsin – Madison and will support the delivery of the standard partnership obligations. Additionally, Marc Drezner, MD, will lead the establishment of the network governance and centralized IRB processes for the GPC, specifically overseeing an Ethics, Regulatory and Contractual Processes committee. Dr. Drezner is Senior Associate Dean in the School of Medicine and Public Health and Executive Director of the NIH/CTSA-funded Institute for Clinical and Translational Research (ICTR) at the University of Wisconsin – Madison.

Medical College of Wisconsin (MCW), Milwaukee, Wisconsin

MCW is a private, freestanding medical school and graduate school of sciences located in Milwaukee, Wisconsin. For the partnership, MCW represents 4 hospitals and 189 clinics and brings 490,178 active patients with data in their EMR. The associated medical staff of MCW includes 406 primary care physicians and 2,293 specialty care providers. MCW is a CTSA site.  MCW will assume the standard responsibilities as a member of the GPC under the leadership of Bradley Taylor, Chief Research Informatics Officer. Mr. Taylor will contribute his expertise from over twenty years of experience in enterprise software solutions and engineering systems for whole genome sequencing. MCW will provide GPC-wide expertise for the unstructured notes de-identification pipeline and Natural Language Processing (NLP). Further, MCW will participate in developing the sustainability model for the GPC.

Marshfield Clinic, Marshfield, Wisconsin

Marshfield Clinic is a health care system operating in northern, central and western Wisconsin with 2 hospitals and 61 clinics. Its medical staff consists of 285 primary care providers and 724 specialty care providers and represents 169,961 active patients with data in their EMR. Marshfield Clinic Research Foundation (MCRF), a division of Marshfield Clinic, is the largest private medical research institute in Wisconsin, with 25 Ph.D. and M.D. scientists and 160 other staff. In addition, approximately 150 physicians and other healthcare professionals throughout the Marshfield Clinic system are engaged in medical research. Marshfield also has 44 dentists, 4 oral surgeons and 44 hygienists as a part of their staff. From an infrastructure perspective, Marshfield’s internally developed EHR system (CattailsMD) will allow the demonstration of the extensibility of the data sharing approach used by the GPC to a variety of electronic medical record systems, including non-commercial ones. Additionally, dental data is maintained within i2b2. Further, as an integrated care system, Marshfield has a health insurance branch that will become engaged within the effort for piloting administrative/payer data integration. Robert Greenlee, PhD, Research Scientist, Epidemiology Research Center at the Marshfield Clinic Research Foundation, is the Site Lead. Marshfield will also provide support to the GPC on PCORnet CDM through a Lead CDM Analyst.

University of Minnesota Academic Health Center, Minneapolis, Minnesota
The University of Minnesota (UMN) Academic Health Center (AHC) has partnered with one of the largest large care provider organizations in the state, Fairview Health Services, to create a secure link to data to support health research. Fairview Health Services, one of the largest healthcare providers in Minnesota, has 9 hospitals and 153 clinics and over 2.2 million patients with data in their EMR. The medical staff consists of 1,311 primary care providers and 2,814 specialty providers. The University of Minnesota is both a CTSA site and a NCI-Designated Cancer Center. The GPC partnership will benefit from the participation of the site leader, Connie Delaney, PhD, RN. Dr. Delaney is the Dean of the School of Nursing and also serves as the CTSA Biomedical and Health Informatics (BMHI) Director and as the Acting Director for the Institute for Health Informatics (IHI). Additionally, Dr. Delaney an inaugural member of the Health Information Technology (HIT) Policy Committee of the U.S. Department of Health and Human Services and has conducted research and published extensively in the area of nursing data standards, nursing outcomes, their integration and alignment with other medical terminologies, and ultimate integration electronic health records and personal health records.

University of Nebraska Medical Center (UNMC), Omaha, Nebraska
The University of Nebraska Medical Center is Nebraska’s only public academic health sciences center. With its associated Clinical Enterprise, Nebraska Medicine, it represents 2 hospitals and 28 clinic sites and brings 267,799 active patients within their EMR. Its medical staff consists of 240 primary care providers and 1,066 specialty providers. UNMC is both a COBRE IDEa award site and a NCI-Designated Cancer Center. In addition to standard partnership responsibilities, Dr. James McClay, the enterprise physician informaticist for UNMC, will also play a key role in the GPC. Dr. McClay will provide informatics support to CER design and contribute to standards deployment across the GPC. Additionally, UNMC’s Dr. James Campbell, CMIO, will guide the management of terminology and the design of informatics methods and data collection instruments so that the GPC network can act as a feedback mechanism to measure Meaningful Use Stage 2 alignment at each site’s healthcare systems.

University of Texas Health Sciences Center at San Antonio (UTHSCSA), San Antonio, Texas
UTHSCSA is the largest health sciences university in south Texas, serving both the San Antonio metropolitan area as well as the broader central and south regions of Texas. There are 36 affiliated clinics with 172,929 active patients in their EMR. Its medical staff includes 70 primary care providers and 339 specialty providers. UTHSCSA is both a CTSA site as well as a NCI-Designated Cancer Center. Alfredo Tirado-Ramos, PhD, Chief of the Clinical Informatics Research Division of the Department of Epidemiology and Biostatistics, will continue to have site leadership responsibility. Additionally, Daniel Hale, MD, will lead the GPC’s work in support of the Weight Cohort. Dr. Hale is the Chief of the Division of Pediatric Endocrinology at UTHSCSA and has been a leader on the Consortium Child Health Oversight Committee (CC-CHOC) for the national CTSA Consortium. He is an expert on child and adolescent obesity as well as on the design of clinical research investigations, both interventional and observational.

University of Texas – Southwestern Medical Center, Dallas, Texas
The University of Texas Southwestern Medical Center represents 2 hospitals and 51 clinic sites that serve the Dallas area. These hospitals and clinics bring 833,059 active patients with data in their EMR. The medical staff includes 180 primary care providers and 981 specialty providers. The institution is both a CTSA site as well as a NCI-Designated Cancer Center. UT Southwestern will assume the standard partnership responsibilities as a member of the GPC under the leadership of Lindsay Cowell, PhD. Dr. Cowell brings expertise in the development of data standards and ontologies as well as experience in developing novel methods for representing and computing with biomedical knowledge, including in the context of EMR. Working with Dr. Cowell are members of the Academic Information Systems group which has extensive experience working with i2b2, REDCap, and other open source software. The group is also responsible for the development and maintenance of our clinical data warehouse and has participated in our GPC Phase I efforts. In aggregate, the collective partnership has considerable strengths in both informatics and clinical research. It represents a broad geography with a highly diverse patient population.

Indiana University (Regenstrief Institute, IU Health and Eskenazi Health), Indianapolis, Indiana
Indiana University School of Medicine has developed from a small teaching hospital into one of the nation’s largest medicine centers. Now on the campus of Indiana University Purdue University at Indianapolis (IUPUI), it encompasses
five hospitals: Eskenazi Health, Roudebush VA Medical Center, IU Riley Hospital for Children, IU University Hospital and IU Methodist Hospital. In addition to staffing these hospitals with over 800 faculty, the IU School of Medicine conducts a broad range of basic, translational, and clinical research. A supporting organization, The Regenstrief Institute, is an internationally-recognized informatics and healthcare research organization. The Institute has been a leader in the development, implementation, and evaluation of health information technology and standards for over three decades. Investigators at Regenstrief created the Indianapolis Network for Patient Care (INPC) in 1995 with the goal of providing clinical information at the point of care for the treatment of patients. INPC now includes data from 94 hospitals, 110 clinics, surgery centers and other healthcare organizations, and reaches 25,000 physicians. The two largest contributors, Eskenazi and Indiana University Health account for approximately 4.5 million unique patients alone. Paul Dexter, MD, Associate Professor of Clinical Medicine and Associate Professor -Knowledge Informatics & Translation, will be the Site Lead. Additionally, Dr. Dexter is the Chief Medical Information Officer (CMIO) of Eskenazi Health.

**University of Missouri, Columbia, Missouri**
The University of Missouri (MU) School of Medicine in conjunction with the University of Missouri Health Care represents 5 hospitals and a network of more than 50 primary and specialty clinics located throughout mid-Missouri. MU’s inclusion within the collaborative contributes 455,246 active patients with data in their EMR. The school is nationally ranked in such areas as family and community medicine, primary care, pharmacology and physiology, and health management and informatics. The school also includes University Physicians, the multispecialty practice plan of approximately 500 physicians affiliated with University of Missouri Health Care. Further, The University of Missouri is home to an AHRQ Patient-Centered Outcomes Research (PCOR) Capacity-building award, so we are developing a strong nucleus of faculty who have both strong interests and well-developed expertise in the area of patient-centered outcomes research. MU also is home to a CMS Health Care Innovation Award. This award has provided a strong foundation for the enhancement of the institution’s clinical and research informatics infrastructure. Dr. Jerry Parker, Site Lead for MU, is associate dean for research and a professor of physical medicine and rehabilitation at the MU School of Medicine.

**University of California – Davis** (Non-data partner)
Brad Pollock, PhD, will continue to chair the Innovative Research Methodology Committee within the GPC and will also provide biostatistical and epidemiologic expertise on an ongoing basis to the collaborative. Additionally, Dr. Pollock was engaged as a co-chair of the PCORnet Clinical Trials Task Force during Phase 1. In Phase 2 his added role as Co-PI of the UC-Davis CTSA and its membership in the pSCANNER CDRN facilitates inter-CDRN communication.
REFERENCES CITED
For detailed instructions, consult the application guidelines for your PFA. Do not exceed 10 pages.

Following scholarly citation practice, list the source material cited in this research plan.

Executive Summary

Phase 1 (RC1)

Phase 2, Goal 1 (RC2)

Phase 2, Goal 2 (RC3)

Phase 2, Goal 3 (RC4)
Phase 2, Goal 4 (RC5)
1. NIAID Programs on Asthma in the Inner City.  
   http://www.niaid.nih.gov/topics/asthma/research/Pages/innerCity.aspx; last accessed April 5, 2015.

Phase 2, Goal 5 (RC6)
2. Greater Plains Collaborative Learning Engagement Kickoff PCORnet photos.  
5. Greater Plains Collaborative Learning Engagement Kickoff.  
6. 2014 HERON Fishing Trip and 2013 HERON Fishing Trip.  
7. Preventive Medicine Independent Study course on Medical Informatics Driven Clinical Research.  
8. The Next Generation of Neurologic Treatments.  
9. HMO Research Network.  
    https://www.amia.org/jointsummits2015/cr- posters-1

Phase 2, Goal 6 (RC7)
1. American College of Cardiology National Cardiovascular Disease Registry Hospital Registries.  
APPENDIX (Optional)
For detailed instructions, consult the application guidelines for your PFA. Do not exceed 25 pages (does not count towards page limit for Technical Proposal).

Figure 2. GPC Patient Engagement Circles

GPC Patient/Community Engagement Circles

At the local level, patient partners and community groups work to increase bidirectional information sharing, assist in registry recruitment to engage the community and provide local connectivity to community efforts that compliment GPC projects.

Once projects are selected and begin, cohort groups who have informed the process will continue to contribute to advance project aims by helping with issues such as PROs, recruitment, participant remuneration, survey design and administration, etc.

Patient partner participation on GPC function committees ensures that patient voice infuses governance and decision making.

Each GPC site has a patient partner representative on the Patient Advisory Council. Two patients serve on the GPC Governance Council. Patient engagement officers and GPC leaders encourage and facilitate patient partners to communicate and collaborate across sites to address patient concerns and to provide timely patient partner input.

GPC patient leaders continue to share their perspectives, attend meetings and serve on PCORnet national committees.
Exhibit 1: Greater Plains Collaborator External Institution Collaborator Agreement (Key Terms)

This Greater Plains Collaborative Cooperative External Institution Collaborator Agreement (the “Agreement”), effective as of the day of______, 201_ (the “Effective Date”), is entered into by____ (“External Institution”) and the following entities (individually a “GPC party” and collectively the “GPC Parties”):

i. University of Kansas, an agency of the State of Kansas, on behalf of its University of Kansas Medical Center, whose principal office is at 3901 Rainbow Boulevard, Mail Stop 2013, Kansas City, KS 66160;

ii. The Children’s Mercy Hospital, a Missouri non-profit corporation whose principal office is at 2401 Gillham Road, Kansas City, MO 64108;

iii. Marshfield Clinic Research Foundation, a division of Marshfield Clinic, Inc. whose principal office is at 1000 North Oak Avenue, Marshfield, WI 54449;

iv. The Medical College of Wisconsin, Inc., a Wisconsin corporation whose principal office is at 8701 Watertown Plank Road, Milwaukee, WI 53226;

v. University of Iowa, whose principal office is at Division of Sponsored Programs, 2 Gilmore Hall, Iowa City, IA 52242;

vi. The Regents of the University of Minnesota, whose principal office is at 200 Oak Street S.E., 450 McNamara Alumni Center, Minneapolis, MN 55455-2070;

vii. Board of Regents of the University of Nebraska, d/b/a the University of Nebraska Medical Center, an agency of the State of Nebraska whose principal office is at 987835 Nebraska Medical Center, Omaha, NE 68198-7835;

viii. University of Texas Health Science Center at San Antonio, an institution of the University of Texas System and agency of the State of Texas, whose principal office is at 7703 Floyd Curl Drive, MSC 7828, San Antonio, TX 78229-3900;

ix. University of Texas Southwestern Medical Center, an institution of the University of Texas System and agency of the State of Texas, whose principal office is at 5323 Harry Hines Boulevard, BL9.100, Dallas, TX 75390-9105; and

x. Board of Regents of the University of Wisconsin System on behalf of the University of Wisconsin – Madison, School of Medicine and Public Health, whose principal office is at Office of Research and Sponsored Programs, 21 North Park Street, Suite 6401, Madison, WI 53714.

RECITALS

WHEREAS, The GPC Parties desire to lead the way in biomedical informatics data sharing and network infrastructure through the formation of the Greater Plains Collaborative (“GPC”) and the sharing of biomedical data with appropriate privacy and security protections to facilitate information sharing, strengthen outreach and research capabilities, facilitate translational research and enable the deployment of increasingly sophisticated techniques to optimize care, and have executed a cooperative medical informatics data sharing and network infrastructure agreement to that end (“GPC Data Sharing Agreement”); and

WHEREAS, External Institution desires to enter into this Agreement so that its Affiliate Investigators may have access to GPC Data for Patient Count Queries, Feasibility Queries, and Proposed Research Projects under the obligations set forth below.
NOW, THEREFORE, in consideration of the mutual representations, warranties and covenants herein contained, and on the terms and subject to the conditions herein set forth, the External Institution and the GPC Parties hereby covenant and agree as follows:

ARTICLE I.
DEFINITIONS AND KEY TERMS

In addition to the defined terms that appear throughout the Agreement, the following terms, when capitalized, have the following meanings:

1.1 Affiliate Investigator. The term “Affiliate Investigator” means a researcher who is authorized by and affiliated with the External Institution to submit Patient Count Queries, Feasibility Queries, and Proposed Research Projects.

1.2 Aggregate Response. The term “Aggregate Response” means the compiled information (in the form of either De-Identified Information or a Limited Data Set) of all the accepting GPC Parties which is disclosed to the Affiliate Investigator.

1.3 Agreement. The term “Agreement” means this Greater Plains Collaborative External Institution Collaborator Agreement, as amended from time to time.

1.4 Data Request Oversight Committee (DROC). The term “Data Request Oversight Committee” or “DROC” means the GPC Committee charged with reviewing and approving Proposed Feasibility Queries and Proposed Research Projects.

1.5 De-identified Information. The term “De-identified Information” means information that has been de-identified in accordance with the requirements for de-identification of Protected Health Information under 45 CFR §164.514(b).

1.6 Feasibility Query. The term “Feasibility Query” means a query, submitted to the DROC pursuant to Section 2.04 below, for preliminary De-identified Information from one or more GPC Parties which is necessary for an Affiliate Investigator to generate a hypothesis and/or determine if a Proposed Research Project is feasible within the GPC, which may include not only patient counts but also other descriptive statistics, lab results, etc.

1.7 GPC Administrative Site. The term “GPC Administrative Site” means the site which is responsible for the administrative duties associated with the GPC. The GPC Administrative Site is currently the University of Kansas Medical Center. Any changes to the GPC Administrative Site will be posted on the GPC website.

1.8 GPC Data. The term “GPC Data” means any data within each GPC Parties’ Research Repository which may, as contemplated by this Agreement, be provided or is provided to an External Institution or Affiliate Investigator in response to a Patient Count Query, Feasibility Query, and/or Research Project.

1.9 Honest Broker. The term “Honest Broker” means an individual identified and authorized by a GPC Party to conduct queries on behalf of an Affiliate Investigator for approved Feasibility Queries and approved Research Projects, and to extract Information (in the form of either De-Identified Information or a Limited Data Set) from each GPC Party’s Research Repository.

1.10 GPC Governing Council. The GPC will have a “GPC Governing Council” comprised of representatives of each GPC Party, which oversees the infrastructure and software development of Research Repositories and authorizes
the GPC Honest Broker to create Aggregate Responses.

1.11 **GPC Honest Broker.** The term GPC Honest Broker means an individual identified and authorized by the GPC Governing Council to create the Aggregate Response to provide to an Affiliate Investigator.

1.12 **Individual,** The term “Individual” has the same meaning as the term “individual” in 45 CFR § 160.103 and includes a person who qualifies as a personal representative in accordance with 45 CFR § 164.502(g).

1.13 **Limited Data Set.** The term “Limited Data Set” has the same meaning as the term “limited data set” in 45 CFR §164.514(e).

1.14 **Patient Count Query.** The term “Patient Count Query” means a direct query of the Research Repositories of one or more GPC Parties for De-identified Information in the form of patient counts necessary for an Affiliate Investigator to generate a hypothesis and/or determine if a Proposed Research Project is feasible within the GPC.

1.15 **PCORI.** The term “PCORI” means the Patient Centered Outcomes Research Institute, a District of Columbia non-profit organization whose principal office is at 1828 L Street, NW, Suite 900, Washington, DC 20036 and which is an independent, non-Federal, non-profit research organization created pursuant to the Patient Protection and Affordable Care Act, 42 U.S.C. § 118001.

1.16 **Privacy Rule.** The term “Privacy Rule” means the Standards for Privacy of Individually Identifiable Information at 45 CFR Part 160 and Part 164, Subparts A and E, as amended from time to time.

1.17 **Protected Health Information (PHI).** The term “Protected Health Information” or “PHI” has the same meaning as the term “protected health information” in 45 CFR § 160.103.

1.18 **Research Project.** The term “Research Project” means a research protocol which contemplates the use of an Aggregate Response.

1.19 **Research Repository.** The term “Research Repository” means a database containing information maintained by each GPC Party that utilizes and supports the software used to conduct Patient Count Queries, Feasibility Queries, and create Aggregate Responses.


**ARTICLE II.**

**SYSTEM ACCESS SCOPE AND HANDLING REQUESTS FOR INFORMATION**

2.1 **Scope of Agreement.** The following Proposed Research Projects and/or information are beyond the scope of this Agreement:

(a) Any request for the use or disclosure of information which does not constitute either a fully de-identified data set as defined by 164.514(b), or a limited data set as defined by 45 CFR 164.514(e). Any such requests must be directly proposed to, and approved and contracted for by, each GPC Party individually and must be approved by such GPC Party’s institutional review board in accordance with its policies and procedures.

(b) Any Proposal requesting the use or disclosure of information which consists of alcohol and drug abuse patient records, or data derived from such records, that are maintained in connection with the performance of any federally assisted alcohol and drug abuse program which are protected from disclosure by 42 C.F.R. Part 2,
psychotherapy notes as defined by 45 C.F.R. § 164.501, or where otherwise protected by state or Federal law.

2.2 Data Request. The Affiliate Investigator will complete and submit the required form/agreements to the GPC Administrative Site as specified in Sections 2.04, 2.05, and 2.06.

2.3 External Institution Requirements. The External Institution will verify that the Affiliate Investigator is authorized to submit Patient Count Queries, Feasibility Queries, and Proposed Research Projects and has completed any and all human subjects research training, and/or received IRB approval, as may be necessary for the Patient Count Query, Proposed Feasibility Query or Proposed Research Project. The External Institution will provide, or will require the Affiliate Investigator to provide, proof of such qualification, training and IRB approval to the GPC, and the Proposed Research Projects will be archived in accordance with, processes to be outlined in standard operating procedures approved by the GPC Governing Council. The External Institution will notify the GPC Administrative Site in writing immediately if an Affiliate Investigator is no longer authorized to submit Patient Count Queries, Feasibility Queries, and Proposed Research Projects.

(a) Compliance with Applicable Laws. In performance of this Agreement, the External Institution will comply and will ensure that its Affiliate Investigators comply with all applicable laws, rules and regulations, including the Privacy Rule and Security Rule. The External Institution and its Affiliate Investigators agree to use appropriate physical, technical, and administrative safeguards to prevent use or disclosure of the GPC Data other than as provided for by this Agreement.

(b) Reporting; Breach. The External Institution agrees to report, within five (5) calendar days of discovery, any use or disclosure of GPC Data not provided for by this Agreement and any corresponding Data Use Agreement using the form attached as Exhibit D, of which it becomes aware, to the Privacy Officer of the GPC Administrative Site. The External Institution agrees to cooperate in the handling and mitigation of any unauthorized use, disclosure or breach of GPC Data in accordance with the requirements of the Health Insurance Portability and Accountability Act of 1996 (“HIPAA”), the Health Information Technology for Economic and Clinical Health Act (“HITECH”) and their implementing regulations, and any other applicable laws.

(c) Agents; Subcontractors. The External Institution may not provide any GPC Data to any agent or subcontractor. Any agent or subcontractor, or the employer of such agent or subcontractor if the agent or subcontractor is an individual, must enter into the appropriate agreement with the GPC Parties.

2.4 Feasibility Queries.

(a) The Affiliate Investigator will submit to the GPC Administrative Site a fully-executed GPC System Access Agreement, a template of which is attached as Exhibit C, which will prohibit the downloading, printing, or retaining of the Aggregate Response obtained as a result of the Feasibility Query, prohibit use of the Aggregate Response for any purpose other than determining the feasibility of a potential Research Project, and require the conduct of the cohort identification in a responsible manner and in compliance with applicable laws.

(b) Upon the GPC Administrative Site’s receipt and processing of the GPC System Access Agreement, the Affiliate Investigator may submit a Proposed Feasibility Query, via a request management system to the DROC for review. The Proposed Feasibility Query will include a list of requested GPC Parties. DROC representatives will first review the Proposed Feasibility Query for alignment with the goals of, and suitability for, the GPC generally. If the Feasibility Query is approved, then each GPC Party (following its own internal approval process) will determine if it wishes to accept the request. GPC Parties may only Accept Feasibility Queries which are Approved by the DROC. Any GPC Party may refuse to Accept any Feasibility Query in which it does not want to participate.

(c) Upon completion of the review process described in the previous paragraph, the Honest Broker for
each accepting GPC Party will query its Research Repository and submit the requested information (in the form of De-Identified Information) to the designated GPC Honest Broker. The GPC Honest Broker will create the Aggregate Response for use in accordance with the GPC System Access Agreement. The Aggregate Response will be stored on GPC Hosted Services, and will be available on a REDCap data base with attached files for retrieval by the Affiliate Investigator.

(d) The Affiliate Investigator will submit a valid user name and password to gain access to the GPC Hosted Services hosting the Aggregate Response.

(e) To prevent inadvertent identification of patients, information for sample sizes of fewer than ten (10) patients will not be provided.

2.5 Patient Count Queries.

If the GPC Parties decide to allow Affiliate Investigators of External Institutions to perform automated Patient Count Queries, the Affiliate Investigator will be required to follow GPC policies and procedures, the External Institution must agree to be responsible for its Affiliate Investigators, and the External Institution must agree to execute any supplemental agreements that may be necessary to allow automated Patient Count Queries. Each GPC Party may decline to allow such automated Patient Count Queries.

2.6 Research Projects.

(a) The Affiliate Investigator may submit a Proposed Research Project via the GPC request management system to the DROC for review. The Proposed Research Project will include, at a minimum: a list of requested GPC Parties; a detailed protocol; documentation of IRB approval and waiver, if necessary, if the protocol design so requires (IRB approval will not be required for Research Projects requesting only De-identified Information); and the identity of any other entities supporting the Research Project, whether by funding, study drug support, or otherwise and the amount of such support.

(b) The DROC will first review the Proposed Research Project for alignment with the goals of, and suitability for, the GPC generally. DROC representatives may request additional information from the Affiliate Investigator, at any time to aid in its review. If the Proposed Research Project is approved, a DROC representative from each requested GPC Party will then review it pursuant to its own internal approval process, to determine if it wishes to accept the request. GPC Parties may not Accept any Research Project which is not approved by the DROC. Any GPC Party may refuse to Accept any Research Project in which it does not want to participate.

(c) The GPC Administrative Site will notify the Affiliate Investigator upon Approval of the Proposed Research Project and provide a list of accepting GPC Parties. If the Affiliate Investigator wishes to proceed, regardless of whether the GPC Data requested is De-identified GPC Data or a Limited Data Set, the Affiliate Investigator will be required to submit to the GPC Administrative Site an executed GPC Data Use Agreement (see Exhibit D) prior to being permitted to access the Aggregate Response.

(d) Upon completion of the review and contracting processes described in the preceding paragraphs, and the collection of prospective data if applicable, each Honest Broker for each accepting GPC Party will query its Research Repository as directed by the Approved Research Project and submit the information in the agreed upon format to the GPC Honest Broker.

(e) The GPC Honest Broker will create the Aggregate Response for use in accordance with the Data Use Agreement and any other agreements which may apply to the Approved Research Project. The Aggregate Response will be stored on the GPC Hosted Services, and will be available on a REDCap data base with attached files
for retrieval by the Affiliate Investigator.

(f) The Affiliate Investigator of the Approved Research Project will submit a valid user name and password to gain access to the GPC Hosted Services hosting the Aggregate Response.

(g) To prevent inadvertent identification of patients, De-Identified Information for sample sizes of fewer than ten (10) patients will not be provided to an Affiliate Investigator.

ARTICLE III.
TERM AND TERMINATION

3.1 Term. This Agreement will commence on the Effective Date and will expire on ______ ("Initial Term"). Thereafter, this Agreement will automatically renew for successive one (1) year terms (each a “Renewal Term”). The “Term” of this Agreement includes the Initial Term and all Renewal Terms.

3.2 Not for Cause Termination. The External Institution may terminate this Agreement upon sixty (60) days written notice to the GPC Administrative Site. Any GPC Party may withdraw from this Agreement upon sixty (60) days written notice to the GPC Administrative Site. The GPC Parties may terminate this Agreement upon thirty (30) days written notice after a majority vote to terminate this Agreement by the GPC Parties to this Agreement.

3.3 For Cause Termination. This Agreement may be terminated immediately upon notice to the External Institution if the External Institution or one of its Affiliate Investigators:

(a) Reidentifies or attempts to reidentify GPC Data;
(b) Is involved in research misconduct involving GPC Data or utilizing GPC Data;
(c) Uses GPC Data for commercial purposes without prior written approval; or
(d) Fails to obtain IRB approval when required for a study utilizing GPC Data.

3.4 Effect of Termination. The withdrawal or termination of less than all of the GPC Parties will not be considered a termination of this Agreement and the remaining Parties will continue to operate under the terms of the Agreement, as amended. The External Institution and its Affiliate Investigators will continue to be bound by the terms of any agreement(s) governing any ongoing Approved Research Project(s) or possession of Aggregate Response(s) from a completed Patient Count Query, Feasibility Query, or Approved Research Project.

3.5 Use and Disclosure of GPC Data after Withdrawal or Termination. Unless this Agreement is terminated for cause, upon a termination of this Agreement or a GPC Party’s withdrawal from this Agreement, the External Institution will return to each withdrawing or terminating Party, or if such return is not feasible destroy (and provide any documentation requested confirming such destruction), all of each withdrawing or terminating GPC Party’s GPC Data residing in its electronic files other than Aggregate Responses which have already been created for Affiliate Investigators and archived prior to the date of withdrawal or termination, which may continue to be used and disclosed in accordance with the terms of this Agreement, solely for purposes of ongoing Research Projects initiated prior to the effective date of the Party’s withdrawal or termination and for purposes of any regulatory or oversight requirements pertaining to such Research Projects. If this Agreement is terminated for cause, then the External Institution will immediately return or destroy any and all GPC Data to the applicable GPC Party and provide any documentation requested by the GPC Party confirming that all GPC Data has been returned or destroyed.

Destruction of GPC Data as described above will be done with the use of technology or methodology that renders PHI
unusable, unreadable, or undecipherable to unauthorized individuals as specified by the U.S. Department of Health and Human Services (“HHS”). If the External Institution believes that the return or destruction of the GPC Data as described above is not feasible, it will provide written notification to the relevant GPC Party of the conditions that make return or destruction infeasible. The External Institution will cause the protections of this Section 3.05 of the Agreement to be extended to the GPC Data received from the GPC Parties, and will limit further uses and disclosures of such GPC Data, for so long as the External Institution or Affiliate Investigator maintains the GPC Data.

ARTICLE IV.
MISCELLANEOUS

4.1 Intellectual Property Rights of External Institution or Affiliate Investigators. External Institution and its Affiliate Investigators will not have intellectual property rights associated with the activities of the GPC and GPC Parties under this Agreement.

4.2 Additional GPC Parties. If additional GPC Parties are added to the GPC after the effective date of this Agreement, then the new GPC Party and the External Institution may complete Exhibit B attached hereto and incorporated herein. Each completed Exhibit B will be attached hereto and will be incorporated into this Agreement. The new GPC Party will become a party to this Agreement and all of the GPC Parties will receive a copy of the completed Exhibit B.

4.3 Disclaimer of Liability. Neither the GPC nor any GPC Party makes any warranties, expressed or implied, as to any matter whatsoever, including, without limitation, the GPC Data, condition of the research or any invention(s) or product(s), whether tangible or intangible, conceived, described or developed under this Agreement, or the ownership, merchantability, or fitness for a particular purpose of the GPC Data, research or any such invention or product. In no event will the GPC nor any GPC Party be liable for any indirect, special, consequential, incidental, punitive or non-contractual damages or lost profit or income arising out of or related to this Agreement, even if the GPC or a GPC Party has been advised of the possibility thereof. Neither the GPC nor any GPC Party will be responsible for claims, expenses, damages or liabilities arising out of the negligence or wrongful act or omission of the External Institution, its Affiliate Investigators, or their respective agents, servants or employees in connection with this Agreement.

4.4 Restrictions on Use. The External Institution will not, and will ensure that its Affiliate Investigators do not, use any GPC Data, regardless of the context or format in which the information is received, for its competitive institutional or individual advantage, including but not limited to, patient recruitment or marketing purposes. Patient recruitment purposes do not include using data for preparatory to research purposes for instance to determine whether there are sufficient numbers to conduct the study. The External Institution will not, and will ensure that its Affiliate Investigators do not, under any circumstance, sell or permit the sale of any GPC Data for any purpose.

4.5 Indemnification. The External Institution agrees to be responsible for the negligence, of any of its Affiliate Investigators, and for assuring the Affiliate Investigator’s compliance with the agreement(s) governing the Affiliate Investigator’s receipt or use of GPC Data. Subject to and without waiving any immunities provided under applicable law (including constitutional provisions, statutes and case law) regarding the status, powers and authority of the External Institution, External Institution agrees to indemnify, defend, and hold each GPC Party and each GPC Party’s regents, directors, officers, employees, agents, and volunteers (“Indemnitees”) harmless with respect to any and all third-party claims, losses, damages, liabilities, judgments, or settlements incurred by any Indemnitee arising from, in connection with or resulting from any willful or negligent act or omission of the External Institution, Affiliate Investigators, or any of its or their directors, officers, employees, investigators, agents, contractors, subcontractors, or affiliates (“Indemnitors”), any breach of this Agreement by any Indemnitor, or any failure to comply with applicable laws. State institutions will not approve any Affiliate Investigator that is not covered by either liability coverage sufficient to cover any claims bought or the applicable federal or state tort claims act.
4.6 **Binding Effect.** This Agreement will inure to the benefit of, and will be binding upon, the parties hereto and their respective successors and assigns.

4.7 **No Third-Party Beneficiaries.** This Agreement will not confer any benefit or rights upon any person other than the parties hereto and no other third party will be entitled to enforce any obligation, responsibility or claim of any party to this Agreement.

4.8 **Non-Assignment.** This Agreement may not be assigned, nor any duty or obligation delegated, by any party hereto without the express written consent of all the other parties.

4.9 **Modification and Amendment.** Except for the addition of a GPC Party, which may be added by the External Institution and new GPC Party completing and executing Exhibit B as described in Section 4.02 above, this Agreement may be modified or amended only by a writing mutually authorized and executed by all of the Parties. Any amendment purporting to allow transmission of PHI other than in the form of a Limited Data Set (accompanied by a valid Data Use Agreement) will be null and void.

4.10 **Severability.** If any provision of this Agreement is, or is adjudged as, unlawful or contrary to public policy, then that provision will be deemed null and void and severable from the remaining provisions of this Agreement, and in no way will affect the validity of this Agreement.

4.11 ** Entire Agreement.** This Agreement constitutes the entire understanding among the Parties hereto regarding the subject matter of this Agreement. Any prior agreements, promises, negotiations, oral or written, not expressly set forth herein which relate to the subject matter of this Agreement are of no force or effect, except for any and all existing agreements between GPC Parties.

4.12 **Confidentiality.** Except as otherwise permitted herein, no party hereto will disclose any privileged or confidential information obtained or learned from any other party as a result of this Agreement, except as may be required by applicable law, regulation or order of a court with jurisdiction or as set forth below.

4.13 **Subpoenas and Other Compelled Disclosure.** If any party or any of its agents are required in any legal or governmental proceeding, or otherwise required by law, to disclose any confidential information or GPC Data, such party will: (i) immediately notify the other parties in writing of the existence, terms and circumstances surrounding such event, and (ii) consult and cooperate with the other parties so that the other parties may seek an appropriate protective order and/or waive compliance with the confidentiality provisions of this Agreement. If, in the absence of a protective order or the receipt of a waiver hereunder, such party or any of its agents are nonetheless legally required to disclose the information or else stand liable for contempt or suffer other censure or penalty, such party or its agents, as the case may be, may disclose the information to the minimum extent so required without liability hereunder.

4.14 **Notices.** Unless otherwise provided in this Agreement, all notices, certificates, or other communications will be sent in writing, will be deemed given at the time received, and may be sent by personal delivery, overnight express, next-day delivery service, courier, or registered or certified mail, postage prepaid, return receipt requested, addressed as outlined in Exhibit A attached hereto and incorporated herein. Any party may, by notice as provided in this Section 4.14, designate any further or different addresses to which subsequent notices, certificates or other communications will be sent.

4.15 **Counterparts.** This Agreement may be executed in any number of counterparts, each of which will be treated as an original, but all of which collectively constitutes a single agreement; facsimile and/or portable document format (PDF) to be accepted as original and legally binding.

4.16 **Adoption of Agreement.** Each party to this Agreement represents to the other parties to this Agreement that the person signing for such party has full authority to bind the party he/she represents and to sign on
4.17 **Waiver of Breach.** No waiver of a breach of any provision of this Agreement will be construed to be a waiver of any breach of any other provision of this Agreement or of any succeeding breach of the same provision. No delay in acting with regard to any breach of any provision of this Agreement will be construed to be a waiver of such breach.

4.18 **Electronic Signature.** The electronic signatures below constitute acceptance and agreement to the terms of this Agreement with the same validity and meaning as handwritten signatures which will be considered “in writing” and “wet signed.” External Institution will not, at a later date, repudiate the meaning of the electronic signature or claim that electronic signatures are not legally binding. A printed copy of this electronically signed Agreement will be deemed an original.
Figure 3: GPC Phase 1 Architecture and Technical Governance

GPC PCORI Network Components and Levels of Governance

- Site Governance: (ex: KUMC IRB, HERON Exec/DROC, KUH/UKP EMR Steering)
  - CER Trial Component in EHR (CTMS integration?)
  - LDS 'ideally' data extractor
  - IRB & DROC oversight

- Cross site CER trial configuration
  - Cross site PROM configuration
  - Cross site CER Trial Evaluation

- Shared concept paths -> content standardization
  - Aggregated De-identified data
  - Cross site Cohort characterization
  - Cross site Specimen Request coordination

Legend:
- Black items are current site processes/systems
- Green items are data sources which might be piloted at each site, but not deployed across the network
- Red items are new components deployed at each site across the network
- Blue items are components deployed centrally
- Purple lines show the feedback processes to configure sites for PROM, CER, and coordinating amongst biospecimen repositories

Each site through their CTSA and HealthSystem has current approaches to governance and oversight. This typically involves:
A) IRB protocol and oversight of the honest broker protocol governing the data repository
B) IRB oversight for identified data requests
C) IRB oversight for prospective trials
D) HealthSystem oversight for data requests (de-identified)
E) CTSA oversight for contacting prospective trial patients (concerns of overlap)
P) HealthSystem CMIO/CO oversight of EMR modifications and components

Author: Russ Waitman
August 18, 2013
Figure 4: GPC Phase 2 Architecture, Data Partner Linkage, and Technical Governance
Figure 5: GPC Comparative Effectiveness Research Data and Intervention Methods

**Observational**
- Level 1

**Observational with Patient Reported Outcomes**
- Level 2

**Cluster Randomized**
- Level 3

**Individually Randomized**
- Level 4

**Note:** Randomized trial designs naturally exploit data collection methods employed by observational studies.

**Pragmatic EHR alerts for recruitment; extracting EHR alert effectiveness**

**Patient Reported Outcome Measures from EHR Portal: Health System Engagement**

**Patient Reported Outcome Measures from REDCap Survey**

**Supplemental Abstraction via Case Report Forms (REDCap)**

**Pragmatic dynamic EHR (flowsheets, NLP note concepts, medication history), registry, and novel data collection**

**Pragmatic core EHR (diagnoses, labs, medical dispensing) billing/claims data collection**

**GPC and PCORnet Data Analysis and Delivery Mechanisms Shown Below**

**Aggregated Limited Data Sets from sites**
- REDCap & SQLite Limited Data Set
- i2b2 with GPC compliant ontologies
- PCORnet CDM

**Aggregated De-identified Data Set from sites**
- REDCap & SQLite De-identified Data Set
- SAS Environment
- Simple Queries via PopMedNet
- i2b2 queries

**SAS Analysis against the CDM**
- Feasibility Query Using DRN and CDM
- i2b2 query and descriptive statistics

**Informatics Interventions Require Heightened Clinician and Health System Engagement**

**Trial Designs and Accompanying Informatics Interventions and Data Collection Methods**

**IRB Oversight: Required for Limited Data Sets and Identified Data Collection or Analysis**

- Lower Barrier to Research; IRB review not required
- Scalable to support a multitude of investigators; especially self service queries
Exhibit 2: Greater Plains Collaborative CDRN – Clinical Trials Champions

<table>
<thead>
<tr>
<th>University of Kansas Medical Center</th>
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<tbody>
<tr>
<td>Richard Barohn, M.D.</td>
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<tr>
<td>Vice-Chancellor for Research</td>
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<tr>
<td>Chair – Department of Neurology</td>
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<tr>
<td>Adult Neurology, Amyotrophic Lateral Sclerosis (ALS), Muscular Dystrophy, Myasthenia Gravis</td>
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<tr>
<td>PCORI funded investigator</td>
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<tr>
<td>Edward F. Ellerbeck, M.D., MPH</td>
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<tr>
<td>Chair – Preventive Medicine and Public Health</td>
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<tr>
<td>Director, Cancer Control and Population Health, KU Cancer Center</td>
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<tr>
<td>Director, Clinical and Translational Research Education Center</td>
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<tr>
<td>Primary care delivery; Delivery of preventive services with a particular focus on tobacco control,</td>
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<td>cancer screening, diabetes management, and cardiovascular health</td>
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<tr>
<td>PCORI funded investigator</td>
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<tr>
<td>Christie Befort, Ph.D.</td>
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<tr>
<td>Associate Professor</td>
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<tr>
<td>Co-Director, Breast Cancer Survivorship Center</td>
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<td>Behavioral and psychosocial factors associated with obesity and its treatment outcomes and developing</td>
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<td>effective behavioral weight control interventions particularly among women disproportionately</td>
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<td>impacted by obesity</td>
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<tr>
<td>PCORI funded investigator</td>
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<tr>
<td>John Chen, M.D., Ph.D., MPH</td>
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<tr>
<td>Director – Health Services Research, Department of Internal Medicine</td>
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<tr>
<td>Quality improvement, mobile-based care delivery, outcomes and health services research, and</td>
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<td>economic evaluation in medicine</td>
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<tr>
<td>Joseph LeMaster, M.D., MPH</td>
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<tr>
<td>Associate Professor – Family Medicine Research Division</td>
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<tr>
<td>Improving care for the underserved. Promotion of physical activity and management of type 2 diabetes</td>
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<td>and its complications</td>
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<th>Children’s Mercy Hospital</th>
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<tr>
<td>Ann Davis PhD, MPH, Director, Center for Children’s Healthy Lifestyles and Nutrition</td>
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<tr>
<td>Sarah Hampl M.D. Pediatrician, Center for Children’s Healthy Lifestyles and Nutrition</td>
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<td>Pediatric Obesity</td>
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<td>Mark Clements, M.D., Ph.D. Director, Pediatric Clinical Research Unit</td>
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<td>Pediatric Endocrinology</td>
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<td>Brad Warady M.D., Pediatric Nephrologist</td>
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<td>Reversing kidney failure</td>
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<th>University of Iowa</th>
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<tr>
<td>Saket Girotra, MD, MPH</td>
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<tr>
<td>Assistant Professor of Internal Medicine</td>
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<td>Division of Cardiovascular Medicine</td>
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<td>Variations in delivery of cardiovascular care</td>
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<td>Measurement of hospital quality and performance</td>
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<td>Eli Perencevich, MD, MS</td>
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<td>Professor of Internal Medicine</td>
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<td>Division of General Internal Medicine</td>
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<td>Director, Center for Access and Delivery Research and Evaluation</td>
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<td>Prevention of healthcare associated infections</td>
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<td>Organizational interventions to improve healthcare delivery</td>
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<td>Mathematical modeling of complex disease prevention strategies</td>
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<td><strong>Susan Schultz, MD</strong></td>
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<td><strong>Bradley Erickson, MD</strong></td>
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<td><strong>Catherine Bradley, MD, MSCE</strong></td>
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<td><strong>Howard Bailey, MD</strong></td>
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<td><strong>Mellissa Meredith, MD</strong></td>
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<td><strong>Neil Binkley, MD</strong></td>
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<td><strong>Maureen Smith, MD, MPH</strong></td>
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<td><strong>Alexandra Adams</strong></td>
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<td><strong>Julie A. Panepinto, MD, MSPH</strong></td>
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<td><strong>Joan Neuner MD, MPH</strong></td>
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<td><strong>Paul E. Barkhaus, MD, FAAN, FAANEM</strong></td>
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<td>John Meurer, MD, MBA</td>
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<td>Robert W. Hurley MD, PhD</td>
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<td>Paul Knudson, MD</td>
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<td>Marshfield Clinic</td>
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<td>Brian Chow, M.D., Pediatric Infectious Disease Specialist</td>
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<td>Ram Pathak, M.D., Endocrinologist</td>
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<td>University of Minnesota</td>
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<td>Jeffrey S. Miller, M.D., Professor of Medicine, Deputy Director Masonic Comprehensive Cancer Center (MCC), Deputy Director Academic Health Center’s Clinical and Translational Sciences Institute (CTSI)</td>
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<td>James D. Neaton, PhD, Professor Biostatistics</td>
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<tr>
<td>Jakub Tolar, MD, PhD, Associate Professor of Pediatrics, Director of the University of Minnesota Stem Cell Institute</td>
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<tr>
<td>Dorothy K. Hatsukami, PhD, Professor Psychiatry, Forster Family Chair in Cancer Prevention</td>
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<tr>
<td>Russell V. Luepker, MD, Professor, Epidemiology &amp; Community Health</td>
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<tr>
<td>Principal Investigator</td>
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<td>Timothy Schacker, M.D.</td>
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### University of Nebraska Medical Center

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<tr>
<th>Name</th>
<th>Title</th>
<th>Research Area</th>
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<tbody>
<tr>
<td>Cyrus Desouza, MBBS</td>
<td>Professor and Chief Internal Medicine Division of Diabetes, Endocrine and Metabolism Director Endocrinology Fellowship Program</td>
<td>Diabetes, Obesity, Metabolic Syndrome PCORI funded investigator</td>
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<tr>
<td>Rob Schwab, MD</td>
<td>Assistant Professor Director, Turner Park Medical Home Project Internal Medicine Division of General Medicine</td>
<td>Primary Care Practice Based Research Network</td>
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<tr>
<td>Americo Fernandes, M.D.</td>
<td>Associate Professor Director - ALS Program and Multidisciplinary Clinic Department of Neurological Sciences</td>
<td>ALS PCORI funded investigator</td>
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<tr>
<td>Pariwat Thaisetthawatkul, M.D.</td>
<td>Associate Professor Director – Peripheral Nerve Program Department of Neurological Sciences</td>
<td>Neuropathies PCORI funded investigator</td>
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<tr>
<td>Corrigan McBride, M.D.</td>
<td>Professor, Department of Surgery Director of UNMC Bariatric Surgery</td>
<td>Bariatric Surgery</td>
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### University of Texas Health Sciences Center – San Antonio

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<tr>
<th>Name</th>
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<tr>
<td>KoKo Aung, MD, MPH, FACP</td>
<td>Chief, Division of General Internal Medicine O. Roger Hollan Professorship in Internal Medicine Director, Office of Educational Programs, Department of Medicine</td>
<td>Evidence synthesis, comparative and effectiveness research and health outcome research</td>
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<tr>
<td>Ismail Jatoi, M.D., PhD, FACS</td>
<td>Dale H. Dorn Chair in Surgery Professor and Chief, Division of Surgical Oncology</td>
<td>Surgical Oncology, Breast Cancer</td>
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<tr>
<td>Ian M. Thompson, M.D.</td>
<td>Director, Cancer Therapy and Research Center</td>
<td>Urology, Oncology</td>
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<tr>
<td>Carlayne E. Jackson, MD, FAAN</td>
<td>Professor of Neurology and Otolaryngology Assistant Dean for Ambulatory Services Chief Medical Officer/UT Medicine</td>
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<td>Principal Investigator</td>
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<td>Steven R Bailey M.D., MSCAI, FACC,FACP</td>
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<td>Chair, Division of Cardiology</td>
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<td>Janey Briscoe Distinguished Chair</td>
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<td>Daniel E. Hale, M.D.</td>
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<td>Gail E. Tomlinson, M.D.,Ph.D.</td>
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<td>Greehey Distinguished Chair in Genetics and Cancer</td>
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<td>Chief, Division of Hematology and Oncology</td>
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<td>Deputy Director of Simmons Comprehensive Cancer Center</td>
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<td>Andrea L. Simmons Distinguished Chair in Cancer Research</td>
<td></td>
<td></td>
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<tr>
<td>Lung Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethan Halm, MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chief, Division of General Internal Medicine</td>
<td></td>
<td></td>
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<tr>
<td>Head, Primary Care Clinics</td>
<td></td>
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<tr>
<td>Walter Family Distinguished Chair in Internal Medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer Screening, Chronic Disease Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indiana University</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaz A. Boustani</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Center Scientist, Indiana University Center for Aging Research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chief Operating Officer of the Center for Innovation and Implementation Science at Indiana University</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator, Regenstrief Institute, Inc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chief Research Officer, Indianapolis Discovery Network for Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research Director, Healthy Aging Brain Center</td>
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<td></td>
</tr>
<tr>
<td>Interventions to improve the care of patients with cognitive impairment in general, and those with dementia in particular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brad N. Doebbeling, M.D., M.Sc., FACP, FNAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chair, Department of BioHealth Informatics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor of Health Informatics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor of Medicine, IU School of Medicine; Professor of Biomedical Engineering</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informatics, healthcare systems engineering and implementation science</td>
<td></td>
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<tr>
<td>University of Missouri</td>
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<td>--------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Dean P. Hainsworth, M.D.</td>
<td>Battens disease, diabetic macular edema, retinopathy, uveitis, sustained release drug devices</td>
<td></td>
</tr>
<tr>
<td>Professor of Ophthalmology, Retina/Vitreous, MU School of Medicine, Ophthalmology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Director for Clinical Research, MU School of Medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greg Flaker, M.D.</td>
<td>Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation; Apixaban vs Aspirin in atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Professor of Medicine, Wes and Simone Sorenson Chair in Cardiovascular Research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MU School of Medicine/Medicine/Cardiovascular Medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Director of Research, Division of Cardiovascular Medicine; Director, Electrophysiology Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Daniel Kingsley, M.D., F.A.C.P.</td>
<td>CLL, Lymphoma, Lung Cancer, Breast Cancer, Colorectal Cancer, Melanoma, Brain Cancer, Testicular Cancer, Bladder Cancer</td>
<td></td>
</tr>
<tr>
<td>Associate Professor of Clinical Medicine, Director, Clinical Trials Office, Hematology/Medical Oncology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MU School of Medicine/Medicine/Hematology and Oncology</td>
<td></td>
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</tr>
</tbody>
</table>
### Exhibit 3: PCORI Grants at Participating Institutions

<table>
<thead>
<tr>
<th>Institution</th>
<th>Grant Title</th>
<th>Principal Investigator</th>
<th>Year Funded</th>
<th>Funding Amount</th>
<th>Summary Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Iowa</td>
<td>Evaluation of Parent-Based Interventions to Support Children after Traumatic Injury</td>
<td>Marizen Ramirez, MPH, PhD</td>
<td>2013-2016</td>
<td>$1,751,367</td>
<td>This project will compare two approaches that parents use in helping children recover emotionally and socially from injuries. Our goal is to give health care professionals more tools to help parents promote their children’s full emotional recovery from injury.</td>
</tr>
<tr>
<td>University of Iowa</td>
<td>Methodologies to Adjust for Respondent Status Effects on Health Outcomes</td>
<td>Fredric D. Wolinsky, PhD, MA, BA</td>
<td>2012-2015</td>
<td>$637,901</td>
<td>This study will develop a strategic plan for re-engineering surveys and survey items to maximize their accuracy for use in comparative effectiveness studies to determine the relative value of different treatment methods so that patients, their families, and their physicians can make the most informed health care choices.</td>
</tr>
<tr>
<td>University of Kansas Medical Center Research</td>
<td>Extension Connection: Advancing Dementia Care for Rural and Hispanic Populations</td>
<td>Ryan Michael Carnahan, PharmD, MS</td>
<td>2012-2015</td>
<td>$1,612,680</td>
<td>This collaboration proposes to test a new outreach and education strategy to improve dementia care for rural older adults and develop new dementia care training and resources for Hispanic and Latino care providers and patient families.</td>
</tr>
<tr>
<td>University of Kansas Medical Center Research</td>
<td>Midwestern Collaborative for Treating Obesity in Rural Primary Care</td>
<td>Christie Befort, PhD</td>
<td>2014-2019</td>
<td>$10,017,143</td>
<td>This study will compare PCMH and DM to the traditional fee-for-service model for treating obesity in rural primary care practices in the midwestern United States.</td>
</tr>
<tr>
<td>University of Kansas Medical Center Research</td>
<td>Informing Tobacco-Treatment Guidelines for African American Non-Daily Smokers</td>
<td>Nikki Nollen, PhD</td>
<td>2014-2017</td>
<td>$2,015,632</td>
<td>This study will examine whether standard quit-smoking medications are an effective treatment option for African American nondaily smokers.</td>
</tr>
<tr>
<td>University of Kansas Medical Center Research</td>
<td>Smoking Cessation Versus Long-Term Nicotine Replacement among High-Risk Smokers</td>
<td>Edward Ellerbeck, MD, MPH</td>
<td>2013-2016</td>
<td>$2,085,870</td>
<td>The purpose of this study is to see if guided maintenance therapy (GMT), using long-term nicotine replacement therapy (NRT) might prove to be a reasonable alternative to the standard approach of asking patients to quit smoking immediately.</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Project Title</td>
<td>Principal Investigator</td>
<td>Year Range</td>
<td>Funding</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------</td>
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<tr>
<td>Richard J. Barohn, MD</td>
<td>Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTROLS)</td>
<td>Richard J. Barohn, MD</td>
<td>2013-2016</td>
<td>$1,676,275</td>
<td>We are proposing a study to look at four different drugs in patients with cryptogenic sensory polyneuropathy (CSPN) and plan to determine which drug is most effective: nortriptyline, duloxetine, pregabalin, or mexiletine.</td>
</tr>
<tr>
<td>KM Islam, MBBS, PhD</td>
<td>University of Nebraska: Patient-Defined Treatment Success and Preferences in Stage IV Lung Cancer Patients</td>
<td>KM Islam, MBBS, PhD</td>
<td>2013-2016</td>
<td>$1,787,153</td>
<td>This study is aimed at facilitating treatment choices for patients with advanced lung cancer and their physicians. We will compare treatment preferences among different patient groups when available drugs offer the same survival but different side effects. We will then communicate patients’ preferences to physicians to assess changes in clinical practice.</td>
</tr>
<tr>
<td>Elizabeth A. Jacobs, MD</td>
<td>University of Wisconsin: The Effectiveness of Peer-to-Peer Community Support to Promote Aging in Place</td>
<td>Elizabeth A. Jacobs, MD</td>
<td>2014-2017</td>
<td>$1,906,141</td>
<td>Our overall objective is to investigate the comparative effectiveness of peer-to-peer support programs in preventing acute emergency department visits and hospitalizations and nursing home placement in older adult populations at risk for needing these services; we will also investigate how they promote health and wellness in this population.</td>
</tr>
<tr>
<td>Elizabeth D. Cox, MD, PhD</td>
<td>Family-Centered Tailoring of Pediatric Diabetes Self-Management Resources</td>
<td>Elizabeth D. Cox, MD, PhD</td>
<td>2013-2016</td>
<td>$2,100,386</td>
<td>This study will examine whether families who use PRISM to select resources to improve diabetes management will have better blood sugar control and child/parent QOL than families receiving usual care.</td>
</tr>
<tr>
<td>Peter H. Schwartz, MD, PhD</td>
<td>Indiana University: Describing the Comparative Effectiveness of Colorectal Cancer Screening Tests: The Impact of Quantitative Information</td>
<td>Peter H. Schwartz, MD, PhD</td>
<td>2014-2017</td>
<td>$1,507,162</td>
<td>Our long-term goal is to determine how decision aids can ethically and effectively support patients making decisions.</td>
</tr>
<tr>
<td>University of Texas Southwestern Medical Center/Dallas</td>
<td>Collaborative Assessment of Pediatric Transverse Myelitis: Understand, Reveal, Educate (CAPTURE) Study</td>
<td>Benjamin Morris Greenberg, MD, MS</td>
<td>2013-2017</td>
<td>$1,458,488</td>
<td>This study will assess the current state of Pediatric TM in terms of diagnosis, treatment and outcomes. Ultimately, it will lead to an improved understanding of the current status of care for individuals afflicted with TM, and reveal what are the current best practices.</td>
</tr>
<tr>
<td>University of Texas Health Science Center at San Antonio</td>
<td>Improving Transitional Care Experience for Individuals with Serious Mental Illness</td>
<td>Dawn I. Velligan, PhD</td>
<td>2013-2016</td>
<td>$1,310,383</td>
<td>This is a randomized treatment outcome study comparing two transitional service packages within our TCC: a Standard Care package versus an Engagement-Focused package that features a novel intake procedure and a Shared Decision-Making intervention.</td>
</tr>
<tr>
<td>Evaluating Methods to Engage Minority Patients and Caregivers as Stakeholders</td>
<td>Barbara J. Turner, MD, MED, MA</td>
<td>2013-2016</td>
<td>$715,539</td>
<td>Based on this work, we will develop a guide that will allow patients to advise how PCOR can best meet their own and their community’s needs with a final goal of improving their health.</td>
<td></td>
</tr>
</tbody>
</table>
Exhibit 4: Biospecimen Management Pricing Structure

<table>
<thead>
<tr>
<th>Biobanking Costs</th>
<th>Start up costs of $20,000/per study; plus as listed below for DNA from blood samples:</th>
<th>$10,000 per study, plus costs below for DNA from Blood</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lab Activities</th>
<th>Staff Effort</th>
<th>Estimated cost based on $50/hour salary + fringe</th>
<th>Materials Costs</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extractions (new and replacement)</td>
<td>30 mins/sample</td>
<td>$</td>
<td>$20.00</td>
<td>N= is variable</td>
</tr>
<tr>
<td>Quantification</td>
<td>15 mins/sample</td>
<td>$</td>
<td>$12.50</td>
<td>$3.50</td>
</tr>
<tr>
<td>Creating working aliquots</td>
<td>15 mins/sample</td>
<td>$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily QC (temperature logs)</td>
<td>30 min/day</td>
<td>$</td>
<td>$25.00</td>
<td></td>
</tr>
<tr>
<td>Weekly QC</td>
<td>1 hour/week</td>
<td>$</td>
<td>$50.00</td>
<td></td>
</tr>
<tr>
<td>Monthly QC</td>
<td>2 hours/month</td>
<td>$</td>
<td>$100.00</td>
<td></td>
</tr>
<tr>
<td>Sample Data Management</td>
<td>15 mins/sample</td>
<td>$</td>
<td>$12.50</td>
<td></td>
</tr>
<tr>
<td>Annual QC (pipet calibration n=10)</td>
<td>30 min/pipette</td>
<td>$</td>
<td>$500.00</td>
<td></td>
</tr>
<tr>
<td>LIMS support (Nautilus)</td>
<td>200 hours/year</td>
<td>$</td>
<td>$10,000.00</td>
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<table>
<thead>
<tr>
<th>Indirect Costs</th>
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<tbody>
<tr>
<td>Freezer space</td>
<td></td>
<td>$7,000/study of 1,000 samples or less</td>
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<tr>
<td>Service agreements (equipment)</td>
<td></td>
<td>$1500/study of 1,000 samples or less</td>
</tr>
<tr>
<td>LIMS licensing agreements</td>
<td></td>
<td>$1500/study of 1,000 samples or less</td>
</tr>
</tbody>
</table>
Figure 6: GPC Engagement Circles for Data Request Oversight and Research Opportunity Assessment

a. DRN simple query from PCORnet
   - Coord Cen (CC) signs EICA
   - Transparent Recipient
   - Defined SOPs
   - Patient centered

GPC Site
   - EAI approval aligned w/GPC
   - Patient collab? na
   - review data transparency

GPC DROC
   - Seek annual EAI approval for CC
   - Patient collab? na
   - Audit usage, data transparency

PCORnet

b. GPC site developed trial seeking PCORI funding
   - Trial proposal
   - computable phenotype
   - GPC feasibility optional
   - budget
   - other GPC collaborators
   - patient collaborator
   - Proposal Review and Approval
   - Patient/Clinician Collaborators
   - Informatics, Study Design
   - Budget
   - IRB Reciprocity

GPC Research Opportunity Assessment
   - Normal LOI and full proposal processes

GPCSite
   - GPC Faculty Found
   - Proposal (no IRB)
   - Budget
   - External Investigator

GPC Site
   - Feasibility
   - Fiscal
   - Clinical Collaborator
   - Patient Collaborator
   - IRB

GPC Research Opportunity Assessment
   - Collaborators
   - Feasibility
   - Budget Approval
   - Trial Go/No Go Decision

External Requestor
   - Reviews request
   - Patient Collaborator Offer
   - Review query interoperability
   - Broker merges data post approval

GPC DROC & Honest Broker
   - Reviews/approves
   - Broker executes queries to generate data
   - Broker uploads to GPC

Site Review and Honest Broker

GPC Site
Figure 7: Collaborator Database Components and Methods

- **External or Internal Investigator**
  - CTSA Investigators
    - Curated by Sites’ CTSA
    - required Annual Report
    - Area of Specialty: “Oncology”
    - “ERACommons”
    - MyBibliography link
  - GPC Research Opportunity Request Form
    - Contact info, “ERACommons”
    - Proposal, funding status
    - Areas of Collaboration needed
  - REDCap
    - Data Collection and Database
    - Request and Retrieve Matching Investigators and GPC Collaborators
  - NIH NCBI Services
    - PubMed citations
    - Manuscript Submissions
    - Awards
  - Research Opportunity Assessment Team
    - Oversee concierge activities
    - Monitor Investigators and GPC Collaborators matches
    - Evaluate Opportunities for network.

- **Patient/Family Member**
  - Patient Collaborator Sign Up Form
    - Area of Interest: “Cancer”
    - email address
    - not a “subject”

- **Health System Contacts**
  - Curated by Sites
  - Service Line Administrators
  - Clinicians’ Services and Divisions