Enhanced Infrastructure for Optimizing the Design and Execution of Clinical Trials and Longitudinal Cohort Studies in the Era of Precision Medicine

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In 2006, the National Institutes of Health (NIH) launched the Clinical and Translational Science Awards (CTSA) program in order to support an accelerated pace of translational science (from bench to bedside and community, and back), both within and among academic centers. The CTSA program was also developed with an aim of training the next generation of clinical and translational scientists. The CTSA program replaced the previous General Clinical Research Centers program, for which the utilization of resources and infrastructure toward industry-sponsored trials was restrictive and had led to maintenance of both the General Clinical Research Centers and the Clinical Trial Office as dual and often redundant1 organizations for centralized research support and review processes for NIH-funded vs industry-sponsored studies. CTSA-funded institutions have centralized both laboratory cores for research-based analytics and staff resources for regulatory (Food and Drug Administration [FDA]- and Institutional Review Board [IRB]-related) expertise and process improvement. In addition, the CTSA cooperative group and colleagues have developed informatics approaches to enhance recruitment in research studies and facilitated broad adoption of a free electronic data capture system developed previously via NIH funds (REDCap).2

In its evaluation of the CTSA program, the Institute of Medicine identified as one of its 7 major recommendations the need to “strengthen clinical and translational science relevant to child health.”3 Yet, institution-based infrastructures and resources can no longer rely mainly upon extramural funding for sustainability; federal research dollars are strained, pediatric-specific resources are limited,4 and many pediatric academic health centers (AHCs) lack CTSA funding. In order to meet these challenges, children’s AHCs must develop and implement a best model for research operations and administration that provides enhanced infrastructure for the design and execution of clinical trials and longitudinal cohort studies with capacity for parallel biobanking, which are central to the vision of “precision medicine.”5 In addition, pediatric AHCs must commit at the executive leadership level to ongoing institutional investment in this research infrastructure amid often competing priorities and actively monitor efficiency and quality of the model, as well as academic productivity and compliance, as key metrics for return-on-investment.

There is variability among pediatric AHCs throughout the US with regard to clinical and translational research infrastructure. Our objective in this article is to present a recently established institution-based model of research infrastructure to meet the need for expert design and experienced, efficient execution of investigator-initiated clinical trails and longitudinal cohort studies with parallel biobanking. This children’s Clinical and Translational Research Organization (CTRO) model exists in total or in large part at both All Children’s Hospital Johns Hopkins Medicine (St. Petersburg, Florida) and Children’s Hospital Colorado (Aurora, Colorado), and entails a more robust infrastructure for clinical and translational research than existed previously in many pediatric AHCs.

At All Children’s Hospital Johns Hopkins Medicine, the opportunity was envisioned and actualized (2012–2013), to build what was perceived to be the optimal centralized model for efficiency and subspecialized expertise in clinical and translational research support, given that (apart from a department of research administration [eg, contracting and

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1. Academic health center
2. Clinical Research Coordinator
3. Clinical and Translational Research Organization
4. Clinical and Translational Science Awards
5. Clinical Unit-Based Research Nurse
6. Data Specialist Research Assistant
7. Electronic Health Record
8. Food and Drug Administration
9. Good Clinical Practice
10. Investigational Device Exemption
11. Institutional Review Board
12. Information technology
13. National Institutes of Health
14. Principal investigator
15. Quality assurance
16. Regulatory Specialist Research Assistant
17. Standard Operating Procedure
18. 2-dimensional

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financial functions] and a long-standing independent pediatric IRB) such an infrastructure did not exist at All Children’s Hospital prior to its integration with Johns Hopkins Medicine. In the case of Children’s Hospital Colorado, when child health research infrastructure was being re-evaluated in 2011, a CTSA infrastructure existed in parallel with a Clinical Trials Office, and it had been more than a decade since the Children’s Hospital prior to its integration with Johns Hopkins Medicine. It had been more than a decade since the Children’s Hospital Clinical Trials Office was described.6 The establishment of an enhanced model of Children’s hospital-based research infrastructure in Colorado required new core structure and functions as well as enhanced coordination among existing cores from the CTSA and former Clinical Trials Office.

In the sections that follow, we discuss in detail the composition and functions of the cores of the Children’s CTR, as well as briefly describe the informatics systems and financial strategies that have enabled these institutions and their investigators to leverage CTR capabilities toward the successful design and conduct of clinical trials and longitudinal cohort studies with capacity for parallel biospecimen banking, in a financially sustainable fashion. The execution of such studies is logistically challenging, yet is a vital component in improving children’s health. The Children’s CTR model presented here is not uniquely advantageous to child health research; however, given that rare or low-prevalence disease is often the “norm,” requiring a multicenter approach, the need to optimize institution-based centralized infrastructures for clinical and translational research is particularly critical in pediatrics.

Cores

A flow diagram of the processes for study proposal/design, review and approvals, and implementation using the CTR Cores is provided in Figure 1 (available at www.jpeds.com), for internal investigator-initiated trials under an Investigational New Drug (IND)/Investigational Device Exemption (IDE) application with the US FDA. The schema can be modified to suit the needs of non-IND/IDE internal investigator-initiated studies as well as externally-sponsored (ie, pharmaceutical industry-driven; external investigator-initiated) studies.

Research Administration

A Research Administration Core provides contracting services on behalf of investigators, as well as pre- and postaward (or postcontracting) financial and administrative support for grants and contracts. The Core also plays a key role in financial management, analysis and reporting. It is critical that the Core collaboratively establish, and then capture and report, metrics on budget development and negotiation, contracting, and grant presubmission review time frames. Contracting services include rapid and efficient execution (and development, in the case of studies initiated by an institutional investigator) of confidentiality/nondisclosure agreements, master agreements, primary contracts, and any pertinent subcontracts. For efficiency, the Core works closely with attorneys responsible for research affairs within the institution’s Legal Department, and may have some designated roles and responsibilities by the latter Department. Budget development for contracting or during the pre-award process for grant submissions is performed by a team approach that engages the Research Operations Core and other relevant Cores, in order for the budget to be well-aligned with estimated personnel efforts of key support staff within the Cores, and in accordance with the study protocol, schedule of assessments, and specific assessments required (eg, history, physical examination, drug dispensing, research-based testing and biospecimen collection, and outcome assessments). Optimally, budget development can be initiated by a Grants/Contracts Finance Assistant within the Research Operations Core, for review and approval by the Research Administration Core.

Additional pre-award functions include grant submission support, with particular emphasis on review of presubmission materials against the sponsor- and mechanism-specific requirements for content and format. The Research Administration Core also collaborates with research leadership (eg, division/department chief, institute director, or chief research officer) to assemble and conduct mock grant review committee sessions (at minimum, on behalf of junior investigators for federal award mechanisms) prior to grant refinement by the faculty member and final grant submission by the academic institution’s Office of Grants and Contracts. The Core functions as a direct liaison to the Office of Grants and Contracts and ideally serves some designated roles and responsibilities of that Office.

Postaward support services provided by the Research Administration Core include account set-up, verification of charge delineation for research vs routine clinical care (billing compliance with federal and state guidelines, performed in direct liaison with the institution’s Office of Compliance and Risk Management), invoicing, other accounting functions, verification of faculty effort reporting compliance as per institutional and sponsor (eg, NIH) requirements, and project-specific research account close-out. A number of these processes require that the Core also serve as a direct liaison to the health system’s Office of Finance. A recent additional postaward function served by the Research Administration Core is to collaborate with Research Operations staff in supporting investigators to fulfill their obligations for trial registration and updating (including timely reporting of study findings) on www.clinicaltrials.gov.

Research Operations

A Research Operations Core provides key services critical to the implementation and conduct of clinical research studies, with protocols and procedures performed under the delegated authority of principal investigators (PIs). The Core also plays a lead role in study feasibility assessment, with guidance from CTR leadership. The Core is comprised of Regulatory Specialist Research Assistants (RSRAs), Clinical Research Coordinators (CRCs), Data Specialist Research Assistants (DSRAs), and Clinical Unit-Based Research Nurses.
Era of Precision Medicine

Enhanced Infrastructure for Optimizing the Design and Execution of Clinical Trials and Longitudinal Cohort Studies in the Research Coordinator Taskforce, this subspecialized and co-compliance, and staff professional development and retention of data and biospecimen collection, regulatory participant recruitment and retention, protocol adherence, with clearly defined roles/responsibilities is able to optimize RSRAs, CRCs, DSRAs, and CUBRNs working collaboratively with clearly defined roles/responsibilities is able to optimize participant recruitment and retention, protocol adherence, completion of data and biospecimen collection, regulatory compliance, and staff professional development and retention. In fulfillment of the recommendations of the CTSA Research Coordinator Taskforce, this subspecialized and coordinated Research Operations organizational model is also crucial in facilitating a more manageable set of PI-delegated responsibilities for each role/position, fostering efficiencies, and enhanced compliance.

RSRAs provide direct support to CRCs (and hence to PIs) for IRB submissions and regulatory document collection and filing. CRCs (who may have clinical training or a nonclinical background in the health sciences) have responsibilities in overall study coordination and project management, outpatient recruitment, coordination of research encounter scheduling, data collection, and collaboration with RSRAs on study-specific submissions to the IRB. CRCs achieve and maintain certification through the Society of Clinical Research Associates or Association of Clinical Research Professionals, and are typically subspecialized within a given discipline or disciplines (hence, specific groups of therapeutic areas), which facilitates growth in clinical expertise and long-term relationships with a group of PIs. The centralization of a group of CRCs with diverse therapeutic area expertise facilitates the ability to quickly respond to external grantors as well as internally funded studies, and reduce lag-time during timesensitive start-up periods of grants and contracts, relative to a de novo CRC hire. For investigator-initiated multicenter studies led by the institution and its faculty, CRCs who have multicenter project management experience also provide core project management functions of a Clinical Coordinating Center on behalf of the overall PI, including investigator meeting coordination, site initiation visits/videoconferences for participating centers, site project management and protocol/procedure support, collection of essential documents from participating centers for maintenance in the overall trial regulatory file, query generation and resolution with site staff, and coordination of close-out at participating centers.

DSRAs are typically nonregistered nurse-degreed individuals who assist with data entry, allowing for optimal utilization of the more advanced skill level of the CRC. If appropriately trained and experienced in pediatric phlebotomy, they may also assist with specimen collection. CUBRNs are responsible for research oversight and facilitation of all studies (irrespective of primary division/subspecialty affiliation of the PI) conducted within a given hospital unit (eg, intensive care units, inpatient wards, perioperative setting, emergency center), and typically have past clinical experience in that particular clinical setting. Hence, for existing and potential research participants receiving clinical care within a specific hospital unit, the CUBRN plays a key role in recruitment, coordinates study procedures and their timing with the primary CRC for a given study, administers investigational drugs dispensed by the investigational pharmacist, and performs a critical function of adverse event surveillance and alerting to the CRC and PI. The CUBRN also provides protocol-specific and generalized basic clinical research education to bedside nurses within the unit, to promote awareness of studies and their requirements, and to build and strengthen a culture of engagement in the child health research mission. The CUBRN role can be extended to outpatient settings involving multiple subspecialties, wherein the registered nurse training may not be required depending on clinical procedural expectations on research subjects, but wherein the overall roles and responsibilities of the position mirror that of the inpatient CUBRN. Like CRCs, CUBRNs achieve and maintain Society of Clinical Research Associates or Association of Clinical Research Professionals certification. The Grants/Contracts Finance Assistant (described above) is not only responsible for collaborative budget development, but also partners with the CUBRNs to monitor unit-specific financial metrics across all projects.

Study Design and Analysis

A Study Design and Analysis Core provides consultation, services, and collaboration on study design and statistical analysis, including publication/presentation support pertaining thereto. In lieu of a Children’s CTRO-based core, a structured relationship between the Department of Pediatrics and a Department of Biostatistics may achieve the same functions. Nevertheless, the Study Design and Analysis Core collaborates closely with the Database Design and Data Management Core to provide integrated and comprehensive data analytic support for clinical and translational research. The epidemiologists and biostatisticians leading the Core assist and/or help to train investigators in refining a research concept or question in order to yield a strong, testable hypothesis, and selecting an optimal study design, appropriate to the current state of knowledge and level of evidence on the research topic and question. In addition, the Core’s epidemiologist and biostatisticians support the PI by performing the following key functions: (1) determining the appropriate sample size in order to have sufficient power to test the hypotheses and to detect clinically important differences (as appropriate); (2) developing a statistical analysis plan, including the descriptive and inferential statistical methodologies designed to address all primary, secondary, and exploratory hypotheses; (3) independently generating, validating, and executing randomization schemes, for investigator-initiated randomized clinical trials; (4) performing data quality assurance (QA) checks after closure of the database, including identifying outliers and questionable observations not already addressed via query generation and resolution during Database Design and Data Management Core operations; (5) executing the a priori statistical analysis plan on the clean and final dataset, and performing any well-described post-hoc analyses in order to generate future hypotheses;
and (6) supporting publications and presentations of study findings by co-authoring the descriptions of statistical methods employed and by generating or validating data tables and figures.

Based on this deeply embedded role and critical expertise provided toward a successful study, institutional leadership and CTRO must effectively communicate the value of investigators engaging the Study Design and Analysis Core early and closely throughout the study life-cycle, and that a bona fide coinvestigative role for the epidemiologist/biostatistician is strongly encouraged for present and future success.

**Database Design and Data Management**

A Database Design and Data Management Core provides collaboration, consultation, and services on database design and data management. The Core works collaboratively with the PI and designees on the study team in the design of the overall database, case report forms, individual data fields, data range and logic (eg, edit/dependency) checks, secondary verification sign-offs of data where applicable, and standing report templates on missing data, query generation, and query resolution, in accordance with standards and best practices. The Core also verifies that the data fields requested by the PI correspond to those data elements that were specified in the application for which IRB approval was granted. After facilitating training on database access and use, followed by beta-testing, database revisions as needed, and subsequent launch, the Core then provides ongoing database and data management assistance throughout the life of the study. This includes user-restricted access to the database for data entry, data editing, or read-only, as per the specific user role.

The Database Design and Data Management Core works closely with the Study Design and Analysis Core to provide integrated and comprehensive support for clinical research. Specifically, the two Cores collaborate to ensure that the case report forms are designed to capture the key variables of interest upon which the a priori statistical analysis plan relies, as well to assure maximum data quality through prioritization of data checks on the most susceptible and most critical variables. The Database Design and Data Management Core also works closely with the Study Design and Analysis Core in database close and lock procedures following resolution of all outstanding data queries, and prior to transfer of the clean and final dataset for statistical analyses. Optimally, the research electronic data capture systems and Standard Operating Procedures (SOPs) employed by the two Cores enable them to also serve an integrated and compliant (eg, FDA 21CFR part 11) role as a Data Coordinating Center for multicenter studies.

**Biorepository**

A Biorepository Core provides centralized processing, cryopreservation, and storage options for a variety of biospecimens including sera, plasma, viable peripheral blood mononuclear cells, DNA, RNA, saliva, cerebrospinal fluid, urine, stool (eg, microbiome applications), and solid tissues (eg, tumor). Specifically, a pediatric Biorepository Core provides capability for secure, Protected Health Information (PHI)-free, short-term and long-term storage of cryovials of viable cells requiring liquid nitrogen vapor phase temperatures (≤−160°C), as well as pediatric-appropriate (including neonate) low-volume samples of plasma, DNA, RNA, and other biospecimens types and purified molecular species at ultra-low (−80°C) temperatures. Sample tracking and sample-to-clinical-data relation is provided via an informatics system, as described below in the section on Informatics Systems. Supporting technology may include 2-dimensional (2D)-barcoding of long-term storage microvials, as well as automated specimen retrieval systems utilizing the 2D-barcoding system and interfaced with the biospecimen informatics system. The Biorepository Core also coordinates its efforts on a study-specific basis with the Molecular Determinants Core Laboratory, in order to assure seamless biospecimen transfer and tracking thereof, in support of the laboratory-based analyses.

The Biorepository Core and its biospecimen tracking system are fundamental to supporting the biomarker and other molecular determinant discovery and validation work across the institution. Thus, paramount concerns (also tracked among the Core’s metrics for operational efficiency and quality) include the achievement of a high volume of episodes of specimen collection, processing and storage, as well as specimen processing protocol adherence and sample integrity/QA monitoring—with annotation of samples for each, as applicable. Systems QA measures in the Core include continuous electronic monitoring and data capture of temperatures and dry contacts on all freezers and equipment, with an associated alarm system. These QA features, along with those of the informatics system and policies and procedures that govern their use, are greatly emphasized in the biorepository accreditation process by the College of American Pathologists—accreditation which should be sought in order to meet the growing expectations of investigators, research grant funding agencies, and research participants.

In addition to meeting the needs of the local investigator engaged in single-center pediatric research, the Biorepository Core must also support the PI who leads multicenter studies, in which the investigator’s institution serves as the coordinating center for the study. Hence, the Core must be equipped to serve a central biorepository role, particularly when the central laboratory for the study resides at the same institution as the Core. The multicenter study “central biorepository” capabilities include specimen collection kit development, quality control, shipment and tracking; support to participating sites, regarding local biospecimen processing, storage, and shipment needs as per the study’s laboratory manual of procedures; biospecimen receipt, logging, and storage; and biospecimen transfer to the PI and/or designated central laboratory for analyses.

As an example, the Johns Hopkins Pediatric Biorepository at All Children’s Hospital is a state-of-the-art, College of American Pathologists biorepository-accredited facility that was established in 2013, and now holds over 3000 2D-barcoded aliquots of plasma, purified DNA, RNA, and
other biological specimens and derivatives collected on institution-based prospective cohort studies, and a similar number of such specimens collected in pediatric multicenter studies for which the facility serves as central biorepository. The biorepository facility and operations (including personnel), and their staged growth, are funded via core academic investments, philanthropy, and study-specific grants and contracts. Oversight for the biorepository is provided via an Executive Committee that reports into the All Children’s Hospital/Johns Hopkins Medicine Research Council, and governance of its biobanks is achieved through a Specimen Access and Use Committee and associated Hopkins policies/procedures.

**Molecular Determinants Laboratory**
A Molecular Determinants Core Laboratory provides analytic and bioinformatics services and expertise for “omics”-based early diagnostic and prognostic biomarker discovery and validation studies using clinically well-annotated biospecimens. This omics work may include genomics, transcriptomics, proteomics and peptidomics, metabolomics, and/or lipidomics. The integration of omics-based discovery with clinical research electronic data capture and biospecimen banking in clinical trials and multiple prospective cohort studies across a broad spectrum of pediatric patient groups and institution-based populations is a key step in the pathway toward leadership in clinical and molecular determinants of outcome in children’s health and disease.

**Investigational Drug Services**
An Investigational Drug Services Core provides investigational drug study set-up, storage (with appropriate temperature controls and monitoring thereof, ideally using a continuous electronic monitoring and logging system), dispensing, and complete chain-of-custody drug accountability. Compounding of pediatric-appropriate formulations of investigational drugs under an investigator-held Investigational New Drug Core registration and stringent pharmacy procedures and controls is also a highly valuable function. The Core also performs FDA regulation-compliant documentation of investigational drug shipment receipt from Sponsors and of the return of residual investigational drug supply to Sponsors at end of study, or its destruction, as appropriate.

In addition to responding to the needs of the local investigator engaged in single-center pediatric clinical trials or as a participating site in a multicenter trial run elsewhere, the Investigational Drug Services Core must also support the PI who leads a multicenter trial (including trials under an FDA-regulated investigator- or institutionally held IND), in which the investigator’s institution serves as the clinical coordinating center. The Core must, therefore, be equipped (and have corresponding SOPs) to serve “central investigational pharmacy” roles, including drug shipment to investigational pharmacies at participating centers in the trial (following central receipt of investigational drug supply from a Sponsor), oversight of drug accountability across the multicenter trial (including reconciliation of locally dispensed vs destroyed/returned supply), and centralized return to sponsor (or destruction, as appropriate) of residual supply for the overall trial.

**IND/IDE Support**
The IND/IDE Support Core assists investigators in requesting and participating in pre-IND/IDE meetings with FDA, and in preparation and submission of IND/IDE new applications, annual reports, modification/update submissions, and closure/withdrawal submissions. The Core also provides SOP-related training for investigators holding INDs/IDEs on unique responsibilities of the sponsor-investigator under an IND/IDE. The establishment of such a core affords both broad-based (eg, seminar series) and one-on-one training to PIs on the responsibilities of the sponsor-Investigator, recently identified as a key aspect in research training at AHCs, but which requires committed institutional investment—particularly when paired effectively with routine internal monitoring of sponsor-investigator activities.

**Research Regulatory Affairs and QA**
A Research Regulatory Affairs and QA Core is responsible for conducting study-specific, risk-based internal monitoring (or assuring that appropriate external monitoring is in place) of compliance with guidelines for Good Clinical Practice (GCP) in research, federal regulations, and institutional policies and SOPs. Study-specific internal monitoring includes assessment of Investigator Site Files/Trial Master Files; Informed Consent Forms and Informed Consent process documentation; serious adverse event and protocol deviation reporting; selected primary source data (eg, risk-based source document verification of eligibility criteria and primary endpoint; biorepository procedural compliance and correspondence of biospecimen inventory to permissions given in signed Informed Consent Forms; investigational drug procedural compliance and chain-of-custody, as well as correspondence of investigational drug administration timing vs timing of signatures on Informed Consent Forms). The Core also plays a lead role, in partnership with research leadership, in the development of (as well as conduct of investigator and research staff training on) a comprehensive cadre of user-friendly and auditable SOPs designed to facilitate adherence to GCP, federal regulations, and institutional policies. The investigator and research team member education and training roles served by the Core in regard to SOPs, policies, and guidelines is augmented by the conduct of regular GCP refresher training seminars, as well as quarterly Research Regulatory Affairs and QA “rounds” in which real examples of common noncompliance themes (eg, FDA warning and debarment letters to investigators, posted on www.fda.gov) are highlighted, and institutional SOP components that directly address these themes/examples are reviewed. This model embraces the lessons learned from other training paradigms that competence and compliance are achieved most successfully via frequent reinforcement and application.

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Informatics Systems

A detailed discussion of the functionalities and types of research informatics systems is beyond the scope of this article. However, the infrastructure and functioning of the modern-day Children’s CTRO cannot be appreciated without a familiarity of the informatics systems upon which investigators and its Cores rely, in order to successfully execute studies and optimize efficiency and compliance at both the individual study and organizational levels. Systems must adhere to rigorous information technology (IT) standards for server security and back-up, password protection, and role-based restrictions. These research informatics systems include: (1) a research Electronic Data Capture System for clinical research data, using electronic signature and audit trail functionalities; (2) a Clinical Trials Management system that interfaces with the institution’s IRB informatics system, affording (on a study-specific level) stream-lined annual reporting to IRB (eg, auto-populated enrollment table for annual continuing review submissions) and automated invoice development toward milestone payments specified in a contract with the sponsor, and generating (on a system-wide level) programmed reports on study start-up times as well as enrollment, recruitment, and retention metrics; (3) a clinical trials module within the Electronic Health Record (EHR) that flags research participants, provides links to appropriate study-level summary information (including investigator’s brochure, signed informed consent document, and contact information for study personnel) accessible to treating physicians, generates real-time notifications to the PI and other research team members (eg, email, EHR user inbox) when emergency department visits and hospital admissions occur in research participants (facilitating surveillance and reporting efforts for serious adverse events), and allows restricted (ie, patient- and time-specific) read-only access by study monitors; (4) an EHR-derived Clinical Research Data Warehouse with end-user query tool, enabling deidentiﬁed queries of clinical data for cohort-ﬁnding or pre-research, with capability to execute cross-queries against the biospecimen tracking system; (5) a biospecimen tracking system serving as a relational database of research specimens, their derivatives, sample QA/pre-analytic variables, and links to informed consent documents pertaining to storage of genetic material and use in future research; (6) a Molecular Determinants Core Laboratory database for storage of large complex sets of data on molecular determinants (eg, omics) separately from (but capable of exporting, and then merging with) clinical research data from the Electronic Data Capture system; and (7) an effort/time-tracking system to track CTRO staff effort by project/study, position, and task, in order to determine available capacity by position, inform strategic hiring with best match of tasks to skills and salary costs, enable transparent reporting to PI (affording opportunity for real-time adjustments in position-related efforts as per project needs), and facilitate data-driven budgeting of personnel efforts by study type, therapeutic area, and Sponsor.

The optimal utilization of these systems for CTRO functions and processes requires the engagement of a research-based systems administrator and data analyst as part of the CTRO team. This position may reside within the pediatric AHC’s IT department (and trained on systems administration with supervision via IT), but derives salary support via the CTRO budget, with direct accountability to the CTRO Director and designees (Director of Research Operations, Director of Research Administration).

Financial Sustainability

Although an in-depth discussion of financial sustainability is similarly beyond the scope of this report, a few concepts warrant emphasis: (1) assuring return-on-investment requires establishing key metrics for the CTRO and investigators/studies using its resources (eg, publications; grants; salary-offset for pre-specified CTRO staff positions—such as CRCs, DSRAs, and CUBRN through grants and contracts; participant recruitment and retention; data and biospecimen QA; compliance; survey scores from PI and CTRO staff; CTRO staff retention and professional development); (2) appropriate governance structures and processes (Figure 2; available at www.jpeds.com) must be established for both scientific peer-review and strategic prioritization of research studies in alignment with the institution’s Research Strategic Plan, to facilitate resourcing of high-merit, high-priority studies for which a funding gap exists; (3) systems-based approaches are critical to optimizing revenue-to expense ratios on a per-study basis as well as CTRO-wide; and (4) active monitoring of actual vs budgeted revenues and expenses on a per-project basis is essential, to identify and address overspending. This process engages researcher faculty, CTRO leadership, and institutional finance leaders in a shared responsibility and accountability for conducting research in a financially sustainable manner.

In addition, institution-based capacity for the participation in, and leadership of, multicenter trials in pediatric rare/low-prevalence disease warrants enhanced support from FDA and the pharmaceutical industry.9

Conclusions

In an era of precision medicine, the child health research mission requires the capacity for expert design and efficient, high-quality execution of clinical trials and longitudinal cohort studies with parallel biobanking, which is a capacity achieved through a more robust model of institutional research infrastructure than previously described. The Children’s CTRO model presented here is not uniquely advantageous to child health research; however, given that rare or low-prevalence disease is often the “norm,” requiring a multicenter approach, the need to optimize institution-based centralized infrastructures for clinical and translational research is particularly critical in pediatrics. At pediatric AHCs where CTSA funding helps to support research infrastructure (albeit limited), or where proximity to university/medical school-wide research cores permits ease of access,
leadership should develop an integrated institutional vision to resource and implement this enhanced model. Although local institutional environments and needs may require additional or alternative cores, systems, and processes, the present description of cores and processes provides a paradigm for successful and sustainable facilitation of high-yield investigator-initiated studies, which must continue to evolve to meet future needs in child health research.

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References


Figure 1. Flow diagram for application of Children’s CTRO support services for investigator-initiated trials under and IND/IDE (ie, sponsor-investigator). CDA/NDA, Confidentiality/Non-Disclosure Agreement.
Figure 2. Flow diagram for processes to identify funding gaps in research studies and facilitate scientific peer-review, strategic prioritization, and subsequent funding determinations.