Title of Study: Using data from a network of patients, families, clinicians, researchers and health care organizations to improve care and outcomes for children, adolescents and young adults with Inflammatory Bowel Disease

CCHMC IRB number: 2018-0129C

Principal Investigator: Peter Margolis (IRB of Record)

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LIST OF ABBREVIATIONS

ABP	American Board of Pediatrics
CCHMC	Cincinnati Children's Hospital Medical Center
CE	Comparative Effectiveness
CFR	Code of Federal Regulations
CRF	Case Report Form
EHR	Electronic Health Record
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IBD	Inflammatory Bowel Disease
ICN	ImproveCareNow
ICN2	ImproveCareNow Registry
NAM	National Academy of Medicine
IRB	Institutional Review Board
MRN	Medical Record Number
NIH	National Institutes of Health
ORCRA	Office of Research Compliance and Regulatory Affairs
PCDAI	Pediatric Crohn's Disease Activity Index
PHI	Personal Health Information
PIBDNet	Prior name for ImproveCareNow
PUCAI	Pediatric Ulcerative Colitis Activity Index
QI	Quality Improvement
UC	Ulcerative Colitis

PROTOCOL SUMMARY

Title:	Using data to improve the care and outcomes for children, adolescents and young adults with Inflammatory Bowel Disease
Precis:	The ImproveCareNow network has created a networked Learning Health System that uses data from clinical care, patient reported and generated data, quality improvement methods, and clinical research to accelerate learning, reduce unwanted variations in care, and spawn innovations in care delivery. This work has resulted in improved clinical care and outcomes for children with this condition.
Objectives:	The purpose of this project is to improve clinical care, redesign care delivery systems, and conduct clinical and health services, outcomes, and comparative effectiveness research to improve the health and well-being of children and youth with IBD.
Endpoint:	The registry will exist for an indefinite amount of time and data collection and analysis will be ongoing to identify gaps in outcomes and care that may impact the care and outcomes of patients with IBD, as well as to inform potential research studies that will address uncertainties in the management and care of patients with IBD.
Population:	All patients with a clinical diagnosis of IBD, regardless of age, gender, race or ethnicity will be recruited to participate in the study.
Number of Sites enrolling participants:	As of February 2021, 110 centers participate in the ImproveCareNow Network.
Description of study:	This is an observational cohort study in which patients with IBD are recruited to participate and followed over time
Study Duration:	Enrollment will continue indefinitely.
Keywords:	IBD, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Clinical Registry, Research Registry, Open Science, Quality Improvement, Health Services Research, Outcomes Research, Comparative Effectiveness Research, Patient Reported Outcomes.

1 ABSTRACT

Improving the health outcomes of children, adolescents and young adults with Crohn's disease, ulcerative colitis or indeterminate colitis, called Inflammatory Bowel Disease (IBD), is difficult without a system to design, develop and test new approaches to care delivery and conduct research so that learning is translated, reliably into actual patient care. The ImproveCareNow Network (ICN) was formed in 2006. The purpose of ICN is to transform the health, care and costs for all children and adolescents with Crohn's disease and ulcerative colitis by building a sustainable collaborative chronic care network, enabling patients, families, clinicians and researchers to work together in a Learning Health System to accelerate innovation, discovery and the application of new knowledge.

The Network has created a Learning Health System that uses data from routine care and patient generated data, data and knowledge sharing, quality improvement methods, and clinical research to accelerate learning, reduce unwanted variations in care, and spawn innovations in care delivery. This has resulted in improved clinical care and health outcomes for children with this condition. The purpose of this project is to further design, develop and test refinements to the ICN Learning Health System Network to improve clinical care, redesign care delivery systems, and to conduct clinical and health services, outcomes, and comparative effectiveness research resulting in improved health and well-being of children and youth with IBD. The protocol replaces the work covered in the original ImproveCareNow protocol. It expands the type of data that may be collected and used.

Keywords: IBD, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Clinical Registry, Research Registry, Open Science, Quality Improvement, Health Services Research, Outcomes Research, Comparative Effectiveness Research, Patient Reported Outcomes.

2 PURPOSE AND OBJECTIVES

Transforming the health, care and outcomes for children and adolescents with chronic health conditions is difficult within the current health system. There is great variation in care delivery, inadequate and slow application of existing evidence, and ineffective use of available data to generate new knowledge. To redesign the system, changes must take place at multiple levels, including the patient, clinician, the clinical practice, and the network. The purpose of this project is to design, develop, test and optimize a continuously improvement Learning Health System network focused on Inflammatory Bowel Disease (IBD), and to use data collected from routine clinical care, patient generated and contributed data to simultaneously improve clinical care, redesign care delivery systems, conduct quality improvement, and undertake clinical, health services, outcomes, and comparative effectiveness research.

The project will take advantage of recent advances in information technology, improvement and implementation science and a Learning Health Network (LHN) to develop and test methods to enable patients, families, clinicians, and scientists to work together to simultaneously improve care, create innovations in care delivery, generate and apply new knowledge. This type of research requires new levels of participation and cooperation among all participants in the network.

3 BACKGROUND AND SCIENTIFIC RATIONALE

New biomedical discoveries, advances in information technology and care offer the potential for immediate, continuous, and transformative improvement in health care, but not within our current health care system. As envisioned by the National Academy of Medicine (NAM), a Learning Health System (LHS) comprises a community of clinicians, patients, and scientists who view each clinical encounter as an opportunity to learn and apply learning to improve care, and ultimately patient outcomes [1]. Learning Health Systems rely on effective use of data and trustworthy data sharing to foster collaborative improvement, research, and innovation. Advanced LHSs are systems that integrate clinical care, improvement and research, as well as incorporating the efforts of all stakeholders (patients, families, clinicians, and scientists) to apply quality improvement methods and conduct research that improves patient health outcomes. We intend to continue to pursue the vision of an LHS. We will use data from the electronic health record (EHR), patient reported and generated data and other data sources. We will facilitate ongoing collaboration among clinicians, patients and researchers, and use of data for clinical care, quality improvement and research.

3.1 NETWORKS ARE “LABORATORIES” FOR QUALITY IMPROVEMENT AND RESEARCH

Most pediatric chronic conditions meet the NIH definition of a rare disease (fewer than 200,000 affected individuals in the US). Therefore, no single care center has a sufficient number of patients to produce generalizable knowledge, a barrier that, unless addressed by collaborative data sharing networks, will slow the pace of knowledge acquisition and outcomes improvement. Beginning in 2001, the American Board of Pediatrics (ABP) supported the establishment of sub-specialty improvement and research networks across all pediatric sub-specialties. Common themes drawn from collaborative pediatric research networks that have demonstrated marked improvement in the outcomes of children with chronic disease are an unrelenting commitment to collecting high quality data, continuously evaluating and proving their value to clinicians making in-the-trenches decisions, and the long-term engagement of the participants and their institutions to sustaining the network [2,3,4,5,6,7].

Disease and specialty-specific collaborative research and improvement networks are foundational to create research “laboratories” that can accelerate the production and application of knowledge. Creating total population registries within and across clinical care centers provides large and diverse study samples. By standardizing practice, variations in outcomes due to care delivery are reduced, thereby increasing statistical power. By linking research to care delivery and engaging patients, families,

clinicians and researchers directly, networks provide a forum for patient-centered outcomes research (PCOR). Not only are the end-users of research (patients and clinicians) in a unique position to identify critical health care knowledge gaps, clinicians and patients are the final common pathways for change at the point-of-care. Pediatric gastroenterologists formed ImproveCareNow as a sub-specialty research and improvement network to study and improve the care of children and youth with IBD.

3.2 HISTORY OF THE IMPROVECARENOW NETWORK

The ImproveCareNow Network was the pilot for the American Board of Pediatrics sub-specialty Maintenance of Certification network initiative, which now involves networks across virtually all pediatric sub-specialties. ImproveCareNow's practice-based improvement activities enable pediatric gastroenterologists to meet new competency requirements in systems thinking and performance in practice.

The National Academy of Medicine has described core concepts of the LHS including: a focus on continuously improving outcomes; learning as a partnership enterprise among patients, clinicians, and researchers; the point-of-care serves as the knowledge engine; advancing clinical data as a public utility; building research into practice; and, a governance model that promotes diverse leadership. The ICN Network has focused on developing 6 core process capabilities to realize these concepts including: leadership, governance and management, quality improvement, patient and family engagement, data and technology, and science.

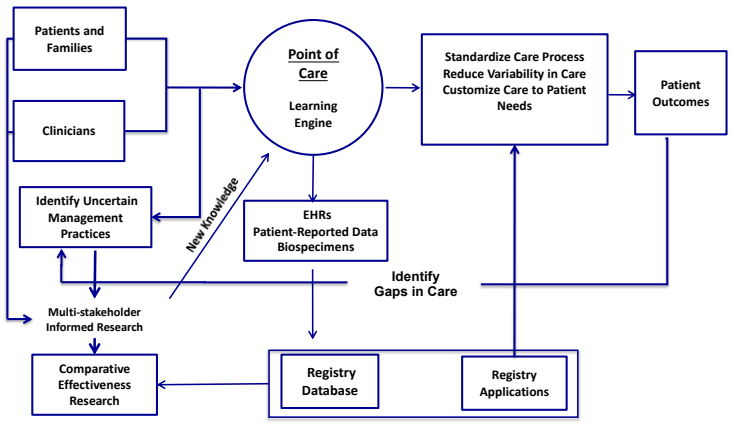
As of February 2021, ICN has grown to over 100 care centers located at universities, children's hospitals, multi-specialty clinics and private practices. The network includes both rural and urban settings within and outside the US. Multiple descriptions of the ICN Network have been published. These descriptions include the use of quality improvement methods, approaches to engaging stakeholders, the registry architecture, and the high level of data quality [8,9,10,11,12].

The project described in this protocol will continue and extend these successful efforts by expanding the ImproveCareNow network to enable deeper, more continuous engagement of all stakeholders in using and sharing data for clinical care, improvement and research.

4 RESEARCH DESIGN

The proposed study will use an observational cohort design to describe variability in outcomes, process and context of care at the level of individual patients and clinical care centers. The study will monitor and evaluate the relationship between individual patient and care center characteristics and the process and outcomes of care including its safety, effectiveness, efficiency, experience, cost and equity. Data will be drawn from routine clinical encounters and care processes, patient generated and reported data, and linkages with other data sources such as EHRs, devices and sensors, claims and pharmacy data. Data will be used as part of an ongoing process of continuous quality improvement and health system redesign and to conduct research including

Figure: Improving Outcomes with a Learning Health System



the comparative effectiveness of treatment strategies, cross sectional studies to assess the diagnostic accuracy of screening instruments, and interventional studies including randomized trials of health system interventions and drugs and devices. These processes form an iterative cycle (figure): data collected during routine care using EHRs and personal devices; standardized management practices to minimize variation across patients, clinicians and care centers; and new knowledge generated and evaluated through research.

4.1 Measures

Measures represent a number of domains of health and well-being including: 1) Measures of outcomes and processes of care (demographic characteristics, disease characteristics and locations, outcomes and adverse events, medications and treatments, laboratory tests, health care utilization including hospitalizations, ED visits, procedures and patient reported outcomes); 2) Measure of care processes (e.g., care center performance of pre-visit planning, population management and other clinical decision support activities that are part of chronic care management); 3) Measures of participation and engagement of patients and clinicians in the community (e.g., awareness of the network, frequency of knowledge sharing, and community interactions). Amendments to the protocol will be submitted as new data sources are added to the database.

4.2 DATA COLLECTION

Background: Evolution of the registry and EHR data collection. Under its two previous IRB protocols (CCHMC IRB #2008-0460 and CCHMC IRB#2011-2012), the Network established a registry that includes data about patient characteristics, disease characteristics, and the clinical care provided during each encounter (e.g., medication use). From 2007-2012 a registry was hosted by Clinipace Worldwide in Research Triangle, NC, via web-based data capture. Care centers participating in ImproveCareNow adapted their clinical encounter forms so they were structured to capture all required registry data elements in a way that made collection feasible within their practice setting. This method of data entry was a laborious process and did not take advantage of the potential to capture registry data directly in the EHR. The subsequent protocol evolved the network towards EHR-based data collection and the creation of an "enhanced registry",[13] where data are collected at the point of care during routine clinical workflows in a practice care center's EHR. The registry will transition to third party platform in July 2021.

Data collection via web-based case report forms or EHR data capture. Each center's data will be separated based upon the care center user's permissions and the site to which they are assigned. When a trained care-center user logs in to the system, they have the ability to see and modify the data from their own care center. Data are collected in two ways. First, care centers can enter data manually into the registry through electronic Case Report Forms (eCRF) via a secure web application. Second, clinicians and other care center team members can capture the majority of data elements directly in the EHR during routine care. These data are then transferred electronically to the registry. To ensure that the data are collected properly and that the same definitions are used, each care center is given an integration specification that contains all the fields, format, and integration details needed to collect the ImproveCareNow registry data elements in the health record (see Appendix A - ImproveCareNow Case Report Form). Each care center is also given a set of sample database reports that contain the logic necessary to pull the data elements out of the EHR. Both the EHR template and the reports can be customized to satisfy local care center conditions. Each care center creates a set of Excel or text-based reports (EHR extracts), which are then uploaded into the registry by study personnel.

The EHR extracts contain personal health information, like patient and visit identifiers, which are needed for linking patients to clinical care reports (see section on management of identifiers below). This allows care center clinicians to re-identify their patients so they can use clinical decision support/chronic care management reports such as pre-visit planning and population management reports, as well as other reports to customize clinical care to individual patients' conditions. Patient and visit identifiers are visible only to authorized users associated with the patient's care center. All patient and visit identifiers are segregated and replaced with study-specific identifiers before data are stored in a database for aggregate QI reports and research. This results in a limited dataset. This database is used to compute derived measures for clinical care reports, quality improvement reports and research. For quality improvement, authorized users care view care center-specific, care center comparison, and network-wide performance reports for quality improvement purposes. To generate network-wide reports, each care center's database will be queried and the results aggregated at the web user interface. Care centers have access to all of its patients' data, but will see only aggregate performance data from others care centers. Access to data for human subjects research will be subject to approval by the central IRB for network-wide studies or by the local IRB for investigator-initiated studies. All study proposals will be reviewed by the ICN Research Committee (see additional details in Section 9.2.3).

Additional Data Sources
Care center characteristics: Data will also be collected about the structural characteristics of the care centers and their teams (e.g., number of clinicians) and the context of care (e.g., support for QI, senior leadership). These data will be collected through routine interactions with care centers and via on-line surveys.

Patient reported outcomes: Data will also be collected for clinical care using mobile devices and web-application secure forms to capture standardized patient reported outcomes (e.g., using PROMIS measures) as well as data from apps and devices (e.g., activity). Data captured as part of routine clinical care will take place under this protocol. Data collected from mobile devices for research purposes only will take place following approval of a study-specific protocol

Claims and pharmacy data: Patients will be asked if they will consent to the use of health insurance claims data and pharmacy claims data that is linked to their clinical data using privacy preserving methods.

Biospecimen data: Patients will be asked if they consent to the use of biospecimen data that is linked to their clinical data.

4.3 LINKING PATIENTS AND VISITS TO STUDY ID

Data extracted from the medical record will include patient and visit identifiers. This information is needed: a) to link visit data that may change over time or be entered after the initial upload, and b) to provide ImproveCareNow clinicians with a way to re-identify patients in order to take clinical action. The patient and visit identifiers will be submitted to the linking/mapping module ("Pre-processing Consent/Patient Linkage database" in the figure) where they will be encrypted and stored in a "patient linkage" database table that separates identifiers from registry data. Patient identifiers in the linkage database include medical record number (MRN) as well as name and date of birth. The identifiers for each patient will be stored, along with a registry identifier code number (currently used by ImproveCareNow).

The purpose of this linkage database table is to serve as a map between patient identifiers and the patient-specific code used by the registry and to keep track of the consent and HIPAA authorization status for each patient. Patient-specific codes will be created as data is loaded into the database. These identifiers will be linked to the identifiers utilized by each care site in a table inaccessible to end-users. The registry identifiers will be utilized in all reporting except those provided to users at the patient's care center for clinical care. All data within the database (both identified and de-identified) are encrypted. Data are also encrypted as it is transmitted to the database and reported from the database.

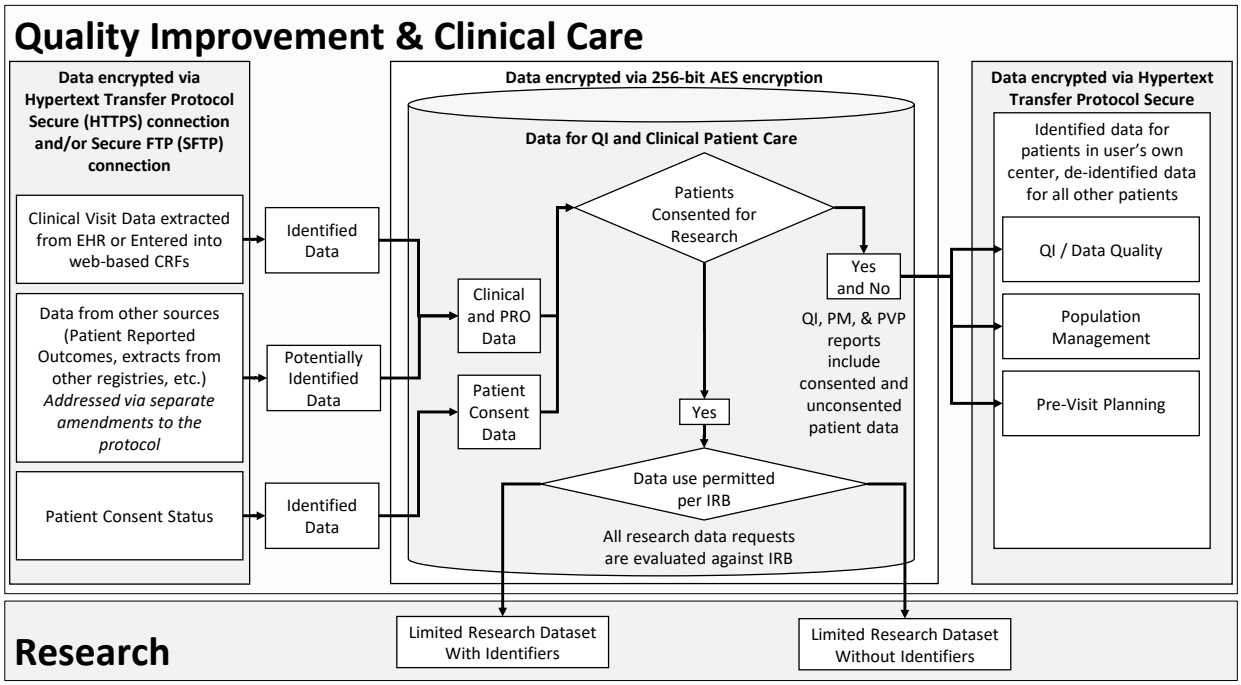


Figure 1: Workflow for registry data collection and generation of quality improvement (QI) and research datasets.

5 ANALYSIS

The unit of analysis will be at the level of care centers (e.g., to determine if changes to the system of delivery have been successfully implemented at individual centers as well as across all centers), and patients (e.g., to compare the effects of different treatment strategies on outcomes), depending on the study question being addressed. For example, the impact of care center changes in process will be analyzed using statistical process control methods that assess the relationship between changes in the proportion of patients receiving specific care processes, and changes in patient outcomes using measures that are reported monthly.

Analyses to support clinical care will also be available at all centers. Some examples of analyses for clinical care include: a population management tool that allows clinicians to automatically stratify patients on criteria such as *pre-specified outcome and process targets* (e.g., inadequate growth, inadequate medication dosage (such as out of range thiopurine or infliximab dose), sub-optimal drug levels, patients not seen in a pre-specified time interval; and patients needing preventive care or monitoring including (i.e., patients needing influenza vaccine or requiring blood test monitoring for adverse drug effects).

5.1 DATA QUALITY

We apply principles of quality and systems improvement to increase the quality of data collected during routine clinical care [13]. Reports will be provided from the Data Coordinating Center monthly to each care center on the quality of the data being uploaded into the registry from the EHR. These reports will include a list of missing data or data discrepancies) that care centers can resolve or use as a learning experience to avoid making similar mistakes in the future.

6 POTENTIAL RISKS AND BENEFITS

6.1 KNOWN POTENTIAL RISKS

There are no direct risks of physical harm from entry into the registry. The greatest risk would be from the inappropriate distribution of participant information to other parties. Steps to reduce risk to participants are detailed above.

To monitor the conduct of the registry, ImproveCareNow network, CCHMC, Hive and participation network care center staff will immediately report any patient contact related to research that lies outside the parameters set within this IRB application. In the event inappropriate distribution of participant information occurs at any study care center, the event will immediately be reported to the Central and Local IRB per institutional policy. Further, participants will be notified of the breach by the study staff via phone or mail, if deemed appropriate. Any adverse events resulting from the use of this registry will be reported to the Central and Local IRBs per institutional policy.

6.2 KNOWN POTENTIAL BENEFITS

The knowledge gained from the information collected may improve the outcomes for patients in the registry, as well as benefitting IBD patients beyond those participating in the registry. This project will build capacity to accelerate the uptake of evidence-based findings and tools for IBD care, and make continuous improvement a key part of the fabric of pediatric IBD care centers.

7 STUDY ENROLLMENT AND WITHDRAWAL

7.1 PARTICIPANT INCLUSION AND EXCLUSION CRITERIA

All patients with a clinical diagnosis of IBD, regardless of age, gender, race or ethnicity will be recruited to participate in the study. This includes children and/or adolescents (17 years of age or younger). This also includes recruitment of non-English speaking patients.

7.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patient recruitment will be conducted by the participating care centers. Care center physicians or trained staff included on the care center IRB protocol will be responsible for identifying and recruiting potential patient participants.

7.2.1 PAYMENT FOR STUDIES

Participants will not incur any costs associated with the registry. Patients will not be financially compensated for their participation, as the registry activities are part of their clinical care. For future research studies, participants may receive reimbursement and/or compensation, which will be addressed in future protocols.

7.2.2 MAXIMUM NUMBER OF SUBJECTS ENROLLED

There is no maximum number of subjects as this is intended to be a population registry. The total number of patients will continue to grow as more patients are entered. Enrollment will continue indefinitely, as will maintenance of data in the registry database. There is no maximum target enrollment number of subjects at each care center. All patients with an IBD diagnosis, who are receiving their IBD care primarily at the center, will be recruited and enrolled. Enrollment will continue indefinitely, as will maintenance of data in the registry database.

7.2.3 DURATION

The registry will exist for an indefinite amount of time and data collection and analysis will be on going to identify areas that may impact the care of patients with IBD, as well as additional potential research studies.

7.3 WITHDRAWALS

Patients will be able to withdraw consent for the use and disclosure of any of their PHI for this research study at any time, and their care will not be impacted by their decision to participate. Patient subjects may withdraw their consent, but must do so in writing to the ImproveCareNow Care Center Principal Investigator. If a patient, at any time, decides to withdraw consent for research, their data will still be retained for clinical, quality improvement and other activities that do not meet the regulatory definition of human subjects research. They will no longer be included in the registry for human subjects research purposes. No attempt will be made to retrieve data that has already been distributed for research purposes.

8 ETHICS/PROTECTION OF HUMAN SUBJECTS

8.1 INSTITUTIONAL REVIEW BOARD

We are proposing to use a Single IRB model to administer this project

8.2 INFORMED CONSENT PROCESS

8.2.1 CONSENT PROCEDURES AND DOCUMENTATION

All eligible IBD patients at each care center will be included in the registry for clinical care, quality improvement and other activities that do not meet the regulatory requirements of human subjects research. Use of data for these purposes is not considered to be a human subjects research activity, [2] and will be covered under a Business Associate Agreement executed between each institution and a Participation and Data Use Agreement between each center and ImproveCareNow, Inc.

In addition to the activities described above, this protocol is also focused on the use of the patient data for human subjects research purposes. Although the ImproveCareNow database will contain patient data on all IBD patients at participating care centers (per the terms of the Business Associate Agreement referenced above) all use of data for human subjects research (as defined by federal regulations) will be conducted under a separate IRB-approved protocol. The consenting requirements for that research will be followed per the IRB determinations for the project.

Patients may consent to this study using one of two methods: 1) in-person traditional paper consent, or 2) e-consent. Regardless of method, information on all eligible patients will be uploaded into a web-based consent application. It will be used to track whether a patient is participating in the research or not. The consent information to be uploaded includes patient first and last name, date of birth, medical record number and ImproveCareNow registry identifier code number, although the minimum required is date of birth, medical record number (or a proxy) and ImproveCareNow registry ID.

While the consent application and database will be used by all of the care centers in the network, care centers will be unable to see the information on the patients uploaded by other care centers. They will only be able to see the data on their own patients. The exceptions to this are the database and systems administrators who may need access to perform technical support, maintenance or quality assurance.

Under both the paper and e-consent methods, if a patient declines to participate, their records will be marked to denote their refusal and their data would not be used for human subjects research (as defined by applicable federal regulations). Similarly, if a patient elects to withdraw consent at a later date, their records would also be marked and their data would be excluded from all future human subjects research activities.

It is important to note that the consent is specific only to the human subjects research uses of the patient data. Therefore, if a patient chooses not to consent for research, their data would still be included for clinical, quality improvement and other activities that do not meet the regulatory requirements of human subjects research purposes. This separation allows all IBD patients at participating care centers to receive the benefits that result from any improvements in care achieved using the registry while still giving them the ability to choose whether they also want to be included in human subjects research.

8.2.1.1 Description of the assent process for participants ages 11-17 years

Paper method:
Parents and patients will review the consent form and be given a chance to ask questions. Patients will be given an opportunity to ask questions without their parents present. Once parent(s) and patient are comfortable that they understand the study, they will be asked to sign on the appropriate lines (parental permission line for parents and assent line for patients) of the consent form.

E-consent:
Parents will receive a flyer or e-mail with information about the study. Included in this document will be a link to the e-consent web site, along with an invitation code. Parents will log in to the consent application with their invitation code, where they will be presented with the consent form. Following confirmation of the individual's identify and after reading through the form, they will have an opportunity to document their agreement to provide their consent. There will also be a field for them to enter their name. If their child is between the ages of 11 and 17, the child will then be asked to read the consent form. After they are finished, the parent will be asked to check an attestation stating that their child understands the study and has no questions. There will be a field for them to type their name. Upon doing so, they will be able to submit the form. A copy will be e-mailed to the study staff of the center where the patient is seen. If the parent provides an e-mail address, they can have a copy e-mailed to them.

Included in the application will be an option for parents or patients to e-mail study staff if they have questions. Parents or patients can also provide a phone number if they wish to be called to discuss their

questions over the phone. If parents or patients have questions, they will be asked to come back to the application after those questions have been resolved.

Initially, e-consent will only be available to English-speaking participants. The application may eventually be expanded to other languages. An amendment to this protocol will be submitted before activating such functionality.

8.2.1.2 Description of the consent process for child participants on their 18th birthday

For patients who turn 18, but are lost to follow-up before turning 18, we are requesting a waiver of consent to continue to use their data for human subjects research. Their records will be flagged in the system such that if they ever have future contact with the participating ImproveCareNow care center they will be prompted to obtain an adult consent.

For patients who turn 18 and are still seen by a physician in ImproveCareNow, we propose a 12-month period to obtain the adult consent. This proposal is made to allow sufficient time to obtain a meaningful consent in conjunction with the patient's regular clinical visit schedule. IBD patients are typically seen by their IBD care provider on average 3 times per year, but may not be seen for 6 to 12 months. Study staff will be able to generate a report from the registry that provides a list of their patients who are turning 18. All attempts will be made to gain a patient's consent as soon as possible after they turn 18, including through clinic visits and the e-consent application.

If, after the 12-month period, the patient's consent has not been obtained (but has not been refused), their consent status will revert to "unconsented" in the database. The "unconsented" designation indicates that consent is neither valid nor refused and efforts may continue to secure the patient's consent as an adult. Patients who transition to an adult care center will no longer have data collected.

The actual consent process (paper or e-consent) will be similar to the original consenting process, but without the required parental interaction and with the patient signing on form on the consent line rather than the assent line.

8.2.3 WAIVER OF AUTHORIZATION

This protocol includes a partial waiver of authorization for recruitment purposes. The purpose of this waiver is to allow the ongoing review of PHI for the purpose of identifying patients who need to be approached to obtain consent/authorization for the research use of their clinical data as part of the ICN project. This review will include all patients who are currently having their clinical data shared with ICN as part of the clinical and quality improvement (i.e. non-human subjects research) activities of the consortium. For each of these patients, we will use the following information to identify the patient within the database: first name, last name, MRN, and date of birth. All four points of information are be used to ensure that we are identifying the correct person in the database in order to minimize the potential for mislabeling records and/or contacting the incorrect person. Additionally, for centers that wish to utilize a web-based e-consent module zip code and e-mail address will be included.

8.2.4 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

8.2.4.1 Description about the expectation of each center to incorporate their institution's HIPAA language into their consent process and document.

Each center will have the opportunity to either incorporate HIPAA language into the approved consent form or a separate form that will become part of the consent process. These revised forms will be

presented during the clinic visit and also loaded into the e-consent application where they will be presented to the patients of that particular center.

8.3 PARTICIPANT AND DATA CONFIDENTIALITY

The data in the registry are hosted by the ICN database. Care centers will access the registry via a web-browser. The connection is encrypted using SSL and is limited to authorized users, who have a unique username and password. The data from each care center will be stored in a care center-specific database which will be queried when creating reports (population management, pre-visit planning, data quality, monthly outcome reports, etc.). All database queries are tracked and audited and direct database access is limited to third party database staff, systems administrators and the ImproveCareNow data management team.

9 DATA HANDLING AND RECORD KEEPING

9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

9.1.1 SOURCE(S) OF DATA AND/OR SPECIMENS

Data will be collected during the course of clinical care and entered into the medical record. Please refer to Appendix A for the information accessed from the records or retrieved from the database.

9.1.2 MIGRATION OF DATA

All of the data previously collected in the ImproveCareNow registry under the original protocol (#2008-0460) will be migrated into the new registry and used for clinical care, quality improvement and other activities that do not meet the regulatory definition of human subjects research. The data for a given care center will be migrated as soon as that care center accepts the oversight/decision of the Single IRB or, if choosing Local Reliance, approves this protocol. If a patient chooses not to consent or withdraws consent, their data will no longer be used for human subjects research. If a patient was included in the registry but is no longer a patient at the center (moved to another city, lost to follow-up, transitioned to adult care, etc.), their data will still be migrated, no new data will be collected. The only data used for human subjects research will be from patients who have consented for research. Patients who refuse or withdraw consent will no longer have their data used for human subjects research.

The determination of whether a center's data can be migrated and used for human subjects research will be determined by the following process. For centers that were participating under the 2011-2012 protocol, when adopting the new protocol, a determination will be made regarding the status of the legacy patient consents and data. The status of the center will be evaluated against the categories listed in Section VI of Appendix C (ORCRA Guidance – ImproveCareNow). Depending on the determination of each center's IRB, a patient's legacy data and participation (consent) may be transferred to the registry and made available for research. This finding will be documented in an Amendment to this protocol.

9.1.3 USE OF PROSPECTIVE DATA

All patient data collected post IRB approval will be incorporated into the registry.

9.1.4 IDENTIFIERS ASSOCIATED WITH DATA/SPECIMENS

The ImproveCareNow registry data will be sent from the center EHR on a periodic basis. The EHR extracts will contain personal health information like patient and visit identifiers, which are needed for linking and quality assurance purposes and to allow the ImproveCareNow clinicians to re-identify their

site-specific patients so they can provide more targeted clinical care to their patients (discussed in detail earlier). These identifiers will be removed before any research is performed on the data, however. All patient and visit identifiers will be replaced with study-specific identifiers, leaving either a limited data set for quality improvement or a de-identified or limited data set for research.

The extracts with identifiers will be processed by a "linking mapping module" that replaces patient identifiers with study-specific identifiers. As indicated in Figure 1, the mapping itself is stored in an encrypted "Consent/Patient Linkage" database. The purpose of this module is to create and store a link, or a mapping, between the patient identifiers and the study-specific identifiers. As indicated in Figure 1, the linking module interfaces with the Patient Linkage Database, where identifiers can be encrypted. Certain identifiers (such as name and MRN) are necessary to implement population management and pre-visit planning at the level of the individual patient; **these identifiers are used only when clinicians use the data for individual patient care**. Clinicians will only be able to view these patient identifiers for patients enrolled at their care center. It will be shielded from clinicians at other care centers.

9.2 STUDY RECORDS RETENTION

9.2.1 DESCRIPTION OF IDENTIFIERS TO BE RETAINED

We will store and encrypt values for first and last name, visit number(s), MRN, date of birth, and visit dates, address, zip code and patient e-mail address. Other identifiers that may be needed in the future will be encrypted in a similar fashion.

9.2.2 DURATION AND JUSTIFICATION FOR RETENTION OF PERSONAL IDENTIFIERS

Personal identifiers will be retained indefinitely. Personal identifiers are needed for linking and to perform quality assurance of the data management systems, and to allow the ImproveCareNow clinicians to re-identify their site-specific patients so they can provide individualized clinical care to their patients. Name, MRN and birth date are necessary to implement population management and pre-visit planning at the level of the individual patient.

9.2.3 RETAINING DATA/SPECIMENS FOR USE IN FUTURE RESEARCH PROJECTS

Data will be used to support the analyses described here. Data without identifiers will be maintained for additional analyses that continue to advance the purpose of the study/study questions. Research involving human subjects that involves the collection of additional data or release of a limited data set, not covered by this protocol, will only be conducted with additional project specific IRB review and approval.

Data may be shared to expand the use of the data for research following IRB approval for each proposed study and a review process overseen by the ImproveCareNow Research Committee (described below). This includes research by qualified investigators from institutions that are members of the ImproveCareNow Network, as well as qualified investigators external to the network who are employed at, or affiliated with, institutions and organizations seeking to conduct clinical, health services, and patient-centered comparative effectiveness research. This includes research sponsored by for-profit entities for the purpose of FDA approval of medications and devices.

The review and data sharing process includes the following steps:

Categorizing the request: Data requests will be categorized based on the requester (network member or outside party) and the request type (data export or secure data environment) into four categories: 1)

Network member, secure data environment; 2) *Network member, data export*, 3) *Outside party, secure data environment*, 4) *Outside party, data export*. An outside party requesting to export of data or derivatives will require a review to ensure that data sharing is consistent with members' data use agreements, additional reviews from network stakeholders, the consent of the ImproveCareNow Board (which includes representation of network members), and contractual terms to ensure that the outside party does not unfairly benefit from the export.

Reviewing the request: The ImproveCareNow Network uses an established review processes to evaluate each data request, minimize risk, and ensure that a proposed use continues to support the values of the network. This includes review of each proposal by the ICN Research Committee for: 1) Scientific merit and feasibility of conducting the research using the ICN data; 2) Consent to ensure that the proposed use is covered by patient consents (if applicable); 3) Risk including ensuring IRB approval has been obtained and review for risks that may not be handled by the IRB such as group re-identification, consistency with network values, creation of derivatives such as algorithms, software or other material produced from the data, and steps to risk-minimize data requests where requested data is overly broad for the study question; 4) Appropriate data controls including ensuring that the data requester has sufficient controls to protect and secure network data. This will include signing an agreement that enables the network to prescribe specific security measures and controls, require regular security audits and penetration testing, and/or require compliance with industry or national cybersecurity standards, 5) Equity to reduce the risk of racial and socioeconomic biases from analyses that disproportionately focus on racial and demographic groups, to the exclusion of others. This will include reviewing research to identify potential racial and socioeconomic biases or limitations; 6) Open Access to encourage and ensure open access including requesting research sharing/openness plans from researchers as part of the review process. If the research is conducted in a secure data environment, ICN will facilitate open access if access to the data is needed to replicate the research: the research outputs, the tools to produce them, and the underlying data are already be in network custody. Requiring open access plans helps foster the positive feedback loops of research and sharing consistent with the values of the network.

Minimizing the risk by providing a de-identified data set when possible, minimizing PHI in the limited dataset to the minimum necessary to accomplish the intended research and narrowly tailoring variables to only those required to conduct the research. In all cases the ImproveCareNow Research Committee will ensure that any requests that constitute research involving human subjects according to the federal definition of human subjects research have received appropriate IRB review and approval prior to releasing data.

Community approval and oversight: For low-risk studies conducted by investigators at member institutions, this will take place via the processes established by the ICN Research Committee that include staff review of each proposal for the basic elements described above and review by the research committee for scientific merit, feasibility and additional risk. Higher risk studies will require additional community oversight including vetting the request with standing network committees, the ICN Board and in some cases, opting-in for data sharing by member institutions for uses not part of the existing DUA.

Contracting and agreements: To receive network data, requesters must sign a data use agreement, which governs how the requester can use network data and its derivatives. For investigators from participation network institutions, the ICN Network has incorporated data use policies into its participation agreements. Individual investigators are also required to sign an additional

data sharing agreement that includes the following terms: 1) the investigator cannot disclose PHI, or attempt to reidentify any patient, 2) the investigator must delete the data if access to the data is not necessary to support open access to enhance scientific reproducibility, 3) if additional identifiers are detected in the data, the investigator should notify the network data coordinating center, and identifiers should be deleted if possible, 4) no derivatives or secondary uses are allowed, other than uses explicitly permitted, 5) Data and derivatives should be open access and researchers must submit an open access plan, if available that adheres to the network's open access policy, 6) Derivatives and data outputs should be shared with the network. This includes hosting/ uploading results to network infrastructure, and granting access or license rights to network members, 7) the investigator cannot transfer, distribute or sell the data or derivatives, and 8) the investigator will submit to network monitoring and audit.

9.4 SAFETY MONITORING

There are no known risks or discomforts resulting from participating in this study. The project team will perform quarterly reviews to address unanticipated problems to the subjects or others. Results will be generated in a report and distributed to the CCHMC IRB committee, ImproveCareNow Network community, as well as the other performance centers in the network.

9.5 PUBLICATION

Manuscripts and abstracts developed from analyzing these data including research conducted under a separate IRB-approved protocol using data will be submitted for publication and presentation at national and international conferences. They will be made available to all network members and patients. Links to all manuscripts are included on the ImproveCareNow.org website so they can be easily shared and accessed by those interested in improving outcomes for children with IBD

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