HIMSS

Using Technology to Transform Recruitment Strategies in Clinical Research

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Executive Summary

Research is the lifeblood of healthcare, and core to Cleveland Clinic's mission of "Caring for life, researching for health and educating those who serve." Recruiting participants in clinical research is key, but is often the Achilles heel in the research process. Identifying eligible participants and requesting their participation is a challenge made more acute by COVID-19 and virtual care. Cleveland Clinic has used technology and the electronic health record (EHR) to innovate efficient and effective electronic recruitment strategies. Examples include:

- Creating an enterprise-level Epic-based digital infrastructure for subject identification, electronic consenting and automated phenotyping for the Cleveland Clinic BioRepository (CC-BioR) accelerated recruitment 20-fold while reducing cost five-fold. From the Heart, Vascular and Thoracic Institute alone, CC-BioR enrolled 1,172 subjects and collected 3,565 blood and cardiac tissue samples in 2021 for translational research with significant cost savings over traditional methods.

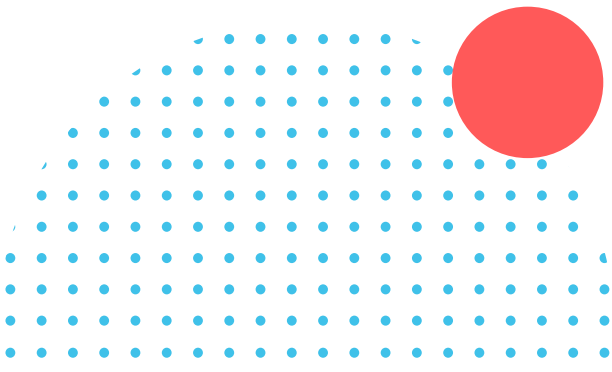
- Leveraged Cleveland Clinic's Research IT service to streamline the use of the EHR in research. The team completed programming and recruited 949 patients in 2020-2021 for interventional studies in the Heart, Vascular and Thoracic Institute, Neurological Institute and Primary Care services at Cleveland Clinic main campus and its 17 regional hospitals using the Epic's secure patient messaging functionality (MyChart). On average, we recruited >100 patients/study; without the MyChart recruitment process, the typical enrollment rate was <10 patients per year.

These two examples showcase a comprehensive EHR-based strategy to support our research mission. Aligning research processes with clinical care, and leveraging EHR-research technology (electronic consenting, secure messaging, interface with patient scheduling and procedures) can accelerate research and reduce cost.

The Clinical Problem and Pre-implementation Performance

In a fast-paced academic medical center where time is of the essence when caring for patients, identifying and enrolling patients into research studies is too often an afterthought. As a result, clinical trials under-recruit and under-deliver. A 2015 study found that more than 86% of clinical trials failed to satisfy their enrollment timelines, and of all registered clinical trials nearly one in five was terminated early due to under-recruitment.

According to the Tufts Center for the Trial of Drug Development, more than a third of sites selected for clinical trials under-enroll, and 11% fail to enroll a single subject. It is also estimated that 9 out of 10 trials require that the original timeline be doubled to meet enrollment goals. The estimated cost of subject recruitment is estimated to represent 40% of the funds of the total clinical trial budget.

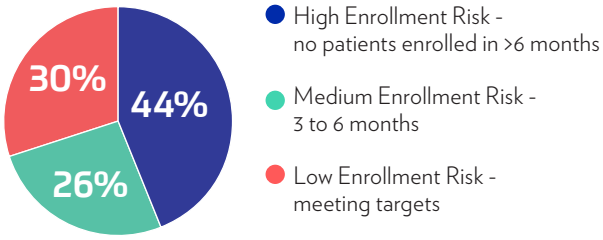


The larger societal and financial cost of these missed research opportunities is staggering:

- At the researcher level, without enough enrolled patients, important research can be left unfinished and grant funding forfeited.
- At the research sponsor/funder level, clinical trials become very costly as they require more research sites and longer study durations to enroll the needed number of patients. The median cost estimate of a clinical trial is $19 million, but can be as high as $345 million for trials that require a large number of patients, because they test new drugs that are similar to drugs already available and already proven in treating serious illnesses.
- At the patient level, any delay in clinical trial completion is a delay in making a potentially life-saving therapy available. It takes over $2.6 billion for a manufacturer to get a new drug from the laboratory onto the pharmacy shelf, according to the Tufts Center for the Study of Drug Development. The full research, development and approval process can last from 12 to 15 years.

According to research leads at Cleveland Clinic, identifying eligible patients translated into 20-25 hours per week of searching the medical records, reaching out to potential participants, one by one, via phone and hoping they would respond, or performing the lengthy recruitment process in person. Even with this time commitment, this graph shows that 70% of Cleveland Clinic studies were at risk of not enrolling a sufficient number of participants.

250 Studies Enrollment Risks



In addition to clinical trials, another pillar of clinical research that similarly struggles with under-recruitment is research bio-repositories/biobanks. Many of Cleveland Clinic's research projects are heavily reliant on the use of tissue, blood and other biospecimens collected from participants during the course of their clinical care. These biospecimens provide an invaluable resource to study essential genetic, mechanistic and translational questions that will be critical in advancing the utility and efficacy of personalized medicine. Here again, Cleveland Clinic is no exception. In 2016, prior to initiating the digital processes we will highlight within the CC-BioR, four biospecimen research studies enrolled 56 participants over the span of a year, and the average cost of enrolling a single patient in a biobanking study was $1,500. Putting that in perspective, a typical Phase 2 trial includes about 100-300 research participants, and biobanking is only one component of the study procedures. Despite performing nearly 51,000 surgeries at Cleveland Clinic every year, only 2,000 samples were stored for research annually. This highlights a significant gap between what the potential research scope could be and what it actually was.

Design and Implementation Model Practices and Governance

Use Case 1: *MyChart messaging to screen for interest in research and facilitate recruitment*

- **Composition and Governance:** A Cleveland Clinic IT Research Governance Committee was organized to facilitate the creation and implementation of EHR-based tools for research purposes. To streamline decision-making and ensure success/adoption of developed solutions, the team includes a multi-stakeholder group with members from IT, research, Internal Review Board (IRB) and ad-hoc discussions with the law department and the Research Compliance Office. To monitor performance, the committee tracks the success rate of enrollment into each study before and after the use of MyChart. This information helps the committee educate the research community and develop standard tools for study teams to utilize. The committee also coordinates with Cleveland Clinic's Bioethics group and the Office of Patient Experience to review all requests for MyChart research messages from a patient perspective: this is done to avoid overburdening patients, and to prevent "message fatigue."
- **Process:** The committee includes a research informatics concierge (a member of Cleveland Clinic's IT department) who serves as the first point of contact for study teams. The research team will request services from the Research IT Governance Committee by contacting the research informatics concierge (RIC) to describe what problem they are trying to solve. After an initial intake and high-level service definition, the RIC funnels the requests through either:
    1. Simplified approval process (the RIC summarizes the request in the weekly team meeting for awareness and approval (e.g: MyChart message to inform patients about a research study they may qualify for and gauge their interest); or
    2. A more involved process where the principal investigator of the research protocol is invited to join the weekly team meeting for a more detailed discussion of the study needs (e.g: protocols for randomized clinical trials embedded in the EHR).

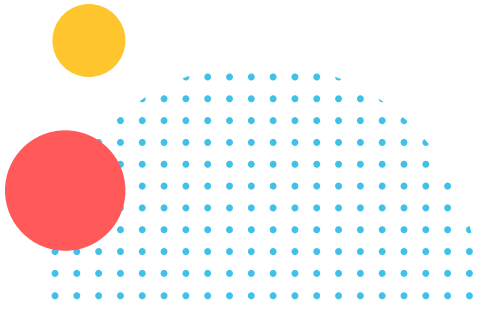
The recruitment arm of the committee operates through process one in most situations given our streamlined approach. The committee works with the study team to ensure an accurate process to identify the patients who should receive the MyChart message: this occurs by verifying a robust mechanism to identify the target recipient list through disease-based registries, or validated queries of study inclusion/exclusion criteria. The committee then assists the study team with developing regulatory documents for submission to the IRB, often providing suggestions on editing the content of the MyChart message to optimize patient understanding of the research and adoption. Once the study team gets IRB approval, the Research IT team will then build and deploy MyChart messages in Epic. MyChart recruitment statistics are collected to identify the number of new patients who received messages, responses, and recruited via MyChart. The reports are additionally used to compare recruitment prior to and post MyChart recruitment set-up.

Use Case 2: *Integration of patient consenting and tracking for Cleveland Clinic Biorepository with EHR workflow*

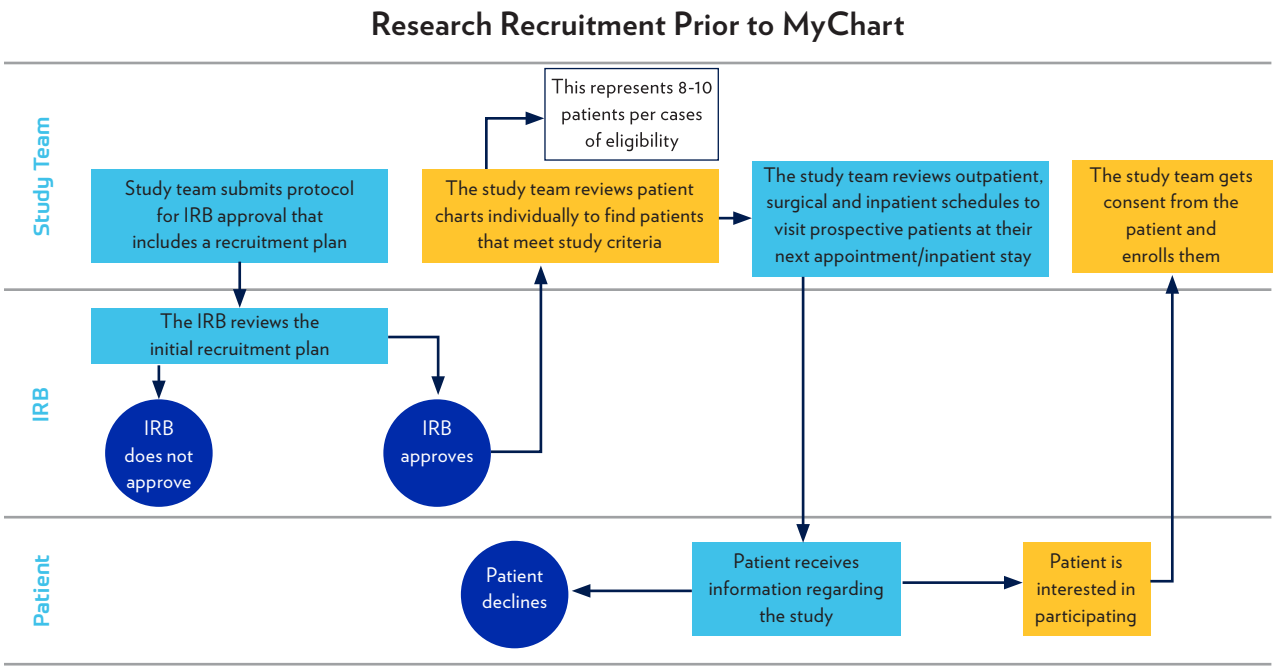
- **Composition and Governance:** The IT workstream within the CC-BioR coordinates closely with the operations workstream (research coordination and clinical department administration) and the biospecimen quality and processes workstream (pathology and laboratory medicine department and translational research cores). Overall governance of the CC BioR is through the BioRespository Steering Committee, which reviews and approves sample and data request as well as reviews available samples and adjusts the focus of sample collection to the greatest needs.

- **Process:** Three parallel workflows operate seamlessly to ensure success of the CC-BioR. The initial implementation in 2020 was in the Heart, Vascular and Thoracic Institute (HVTI).
    1. The research team, IT team and clinical operations team, worked together to flow out the clinical path of patients having open heart surgery. A flow diagram documented patient flow and was utilized to educate and communicate the CC BioR flow of patients and samples. This assisted the teams to identify opportunities to educate patients about the CC-BioR in the context of their routine clinical care (e.g: the nurse coordinator introduces it while introducing the surgical tests/appointments, and written material is included in surgical package). Most relevant, the research IT team assisted with the design and implementation of the research e-consent button within Epic. This enabled the surgeon to discuss the research study at the time of electronic consenting to the open-heart surgery. The research consent is thus also captured seamlessly in Epic.
    2. The next workflow is the collection and processing of samples during the surgery. Pathology and laboratory medicine (PLMI) identified the process for sample collection and storage. The electronic consenting for research and its automatic capture in the EHR allows us to automate the generation of daily lists of enrolled patients. Cleveland Clinic developed a process to automate the daily matching of these enrolled patient lists with the surgical schedules to automate the sample collection schedules for the PLMI team. PLMI obtains specimens from the OR, registers samples in the lab inventory management system, and aliquots tissue for storage. The Lerner Research Institute contributes by sample processing for DNA and RNA extraction. Standard operating procedures were developed for each step to educate the research and clinical teams and develop quality controls.
    3. Lastly, there needed to be an easy way for all researchers to know what samples were available for use and to request samples. The research IT team collaborated with Cleveland Clinic Business Analytics teams to design a web application that automated phenotyping and the ability to visualize available samples for each patient cohort.

The core CC-BioR leadership team meets on a weekly basis to review the operational workflow and approve the design and implementation of various CC-BioR projects. This team is made up of the PI director, co-I science coordinator, co-I medical director, co-I technical director, sr. research director for research operations, and the project manager.



Clinical Transformation Enabled Through Information and Technology



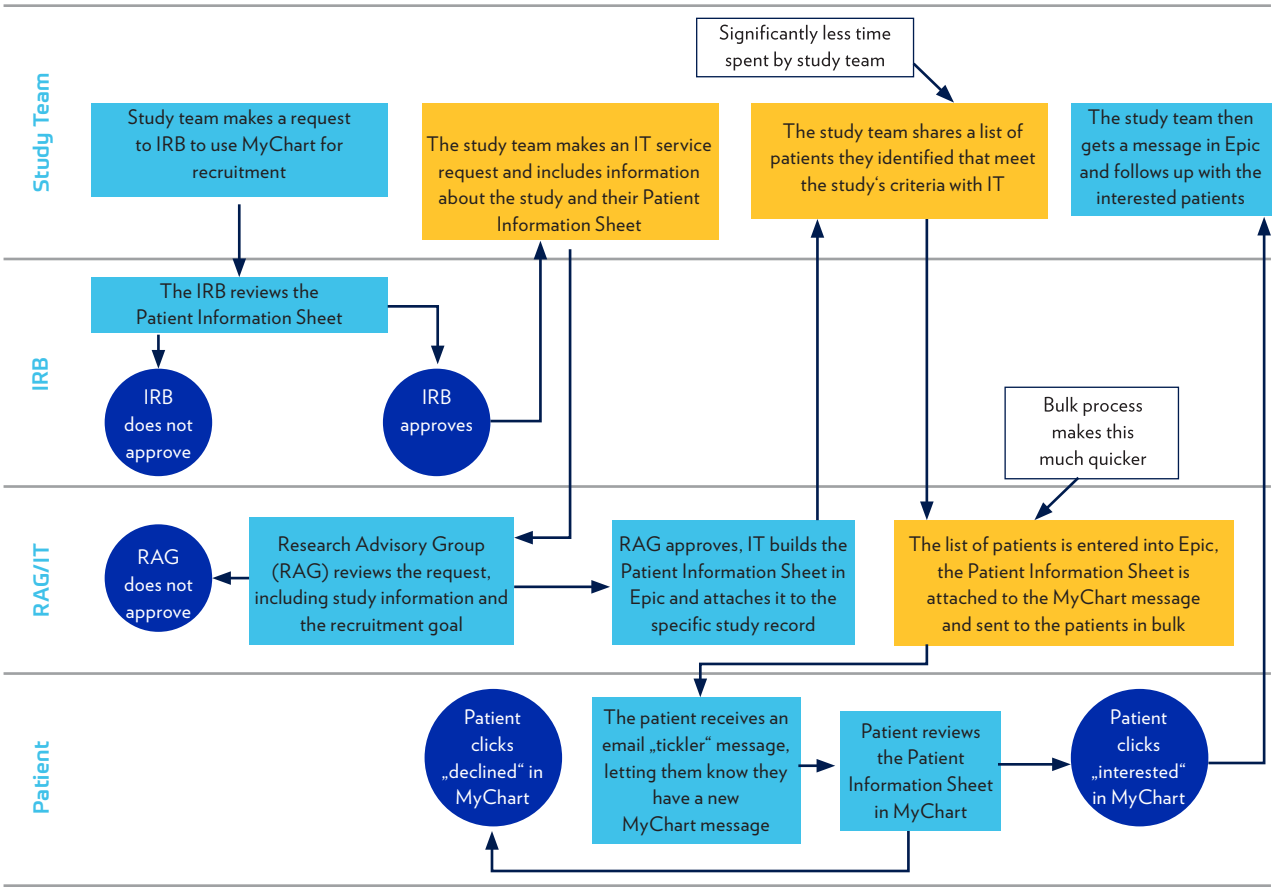
The main clinical transformation accomplished through our use of MyChart to reach patients and inquire about potential interest in participating in research studies was efficiency. This approach required minimal manpower and effort, while ensuring rapid delivery to reach patients in a method that is significantly less intrusive than phone calls.

Patients are identified in a couple of different ways. In some instances, the study team will already have a registry of patients they want to invite to the study. In other cases, inclusion and/or exclusion data are entered into a reporting workbench report and a list of patients meeting the criteria is generated and shared with the study team to verify they are appropriate candidates to recruit.

Once the study is approved by the IRB and the Research Advisory Group to use MyChart for recruitment, it is set-up through available Epic functionality. The message to be sent to the potential participant is built, then inserted into the individual record that is available for the study. The potential participants are identified in bulk by the study team. Then, a reporting workbench report within Epic is used to send the same message in bulk to multiple patients at one time. The potential participant receives an email notifying them that they have a new MyChart message. The patient can then open the message in MyChart, review it and click a button to communicate that they are either interested or not interested. Based on their response type, the study team will then get a message within Epic notifying whether or not to contact the potential participant.

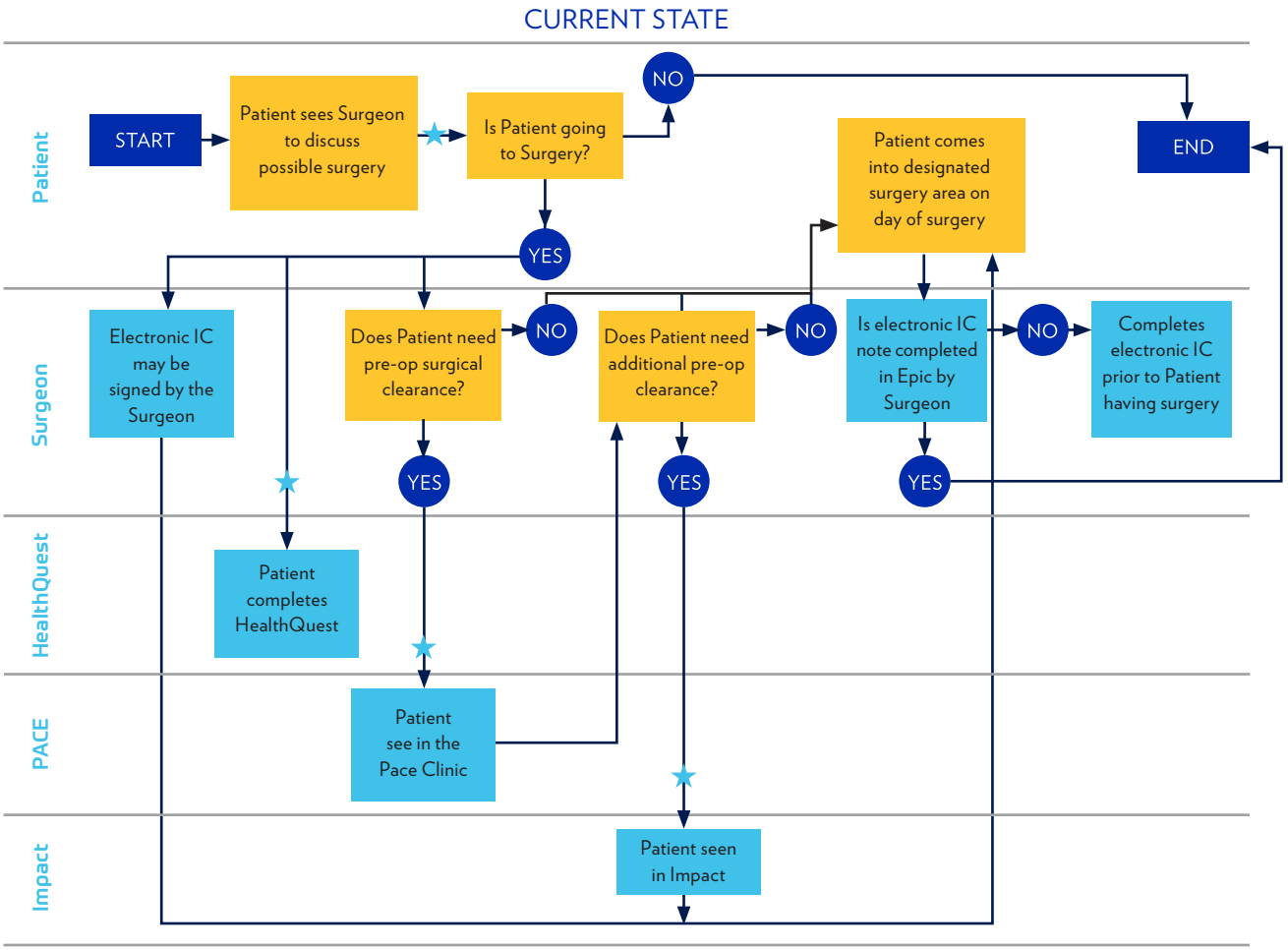
The clinical transformation that took place with the BioR enabled Cleveland Clinic to develop the enterprise-level EHR-based digital infrastructure for subject identification, electronic consenting and automated phenotyping. As many steps as possible were coordinated for the consenting and sample collection process into the clinical workflow and then leveraged the EHR. For example, after the surgeon completes the surgical consent process and discusses the BioR with the patient and the patient indicates that they would like to participate, the same encounter in Epic is utilized to access the consent activity and the research consent button is selected. This allows the consent document to be visible in Epic. The patient can then sign the consent electronically in Epic, allowing caregivers to quickly identify study participants. The following diagram identifies the surgical workflows for the participant pre-surgery. The blue stars in are opportunities for participant education about the CC-BioR.

Research Recruitment Using MyChart



Epic reports are created using discrete fields to identify the participants in the CC-BioR as well as patients that did not want to participate. These reports are used by the study team, surgeon and pathologist to quickly identify participants and easily collect and process their residual blood and tissue during the surgery.

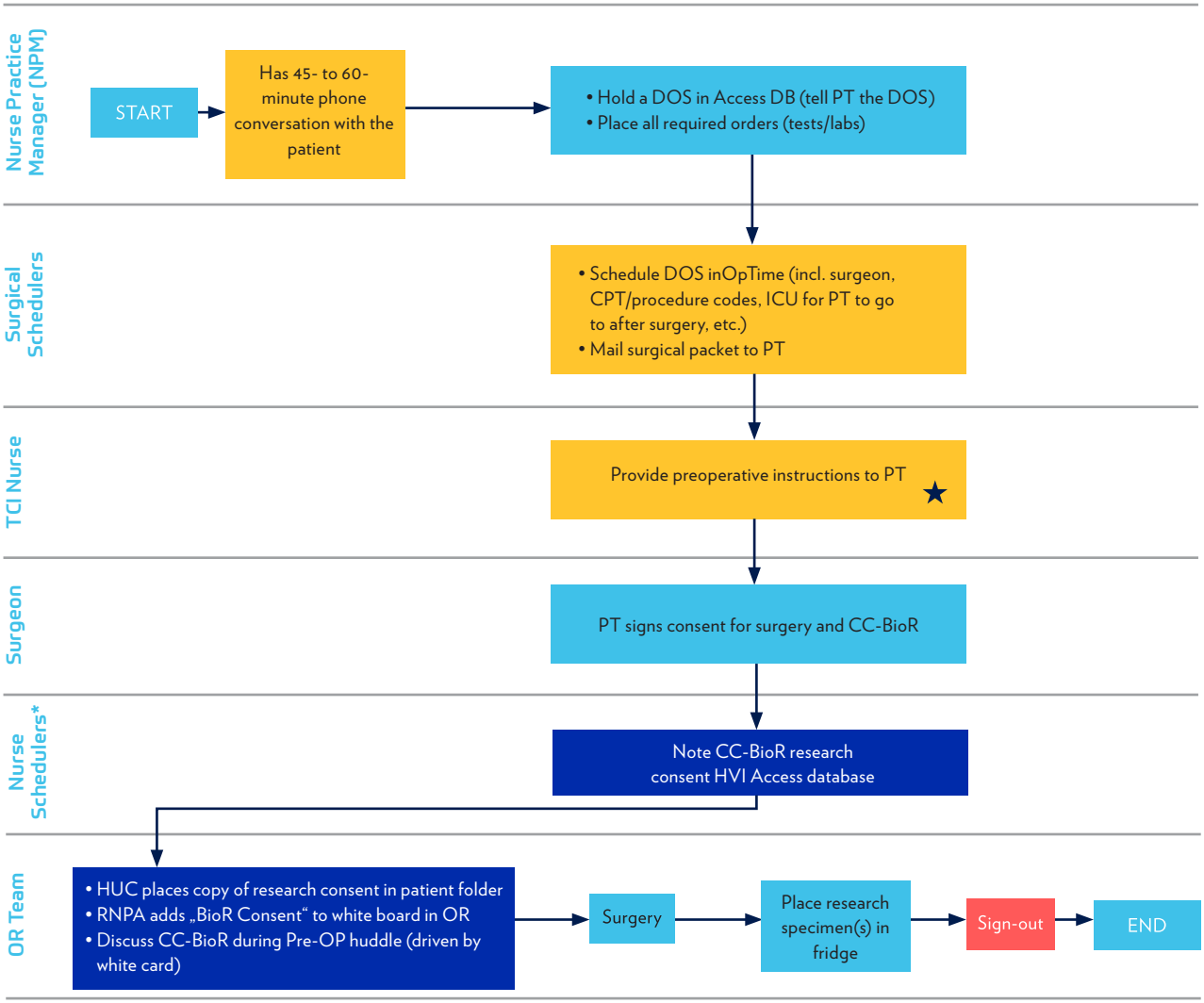
Cleveland Clinic Patient Surgical Flow #1 (Outpatient)



This diagram identifies the surgical workflow for the HVTI team and identifies opportunities for education, communication and flow through the surgical process all the way through biospecimen collection.

HVI Pilot Patient Education/Recruitment Workflow

This workflow assumes the patient has been identified by the surgeon as a candidate for surgery!

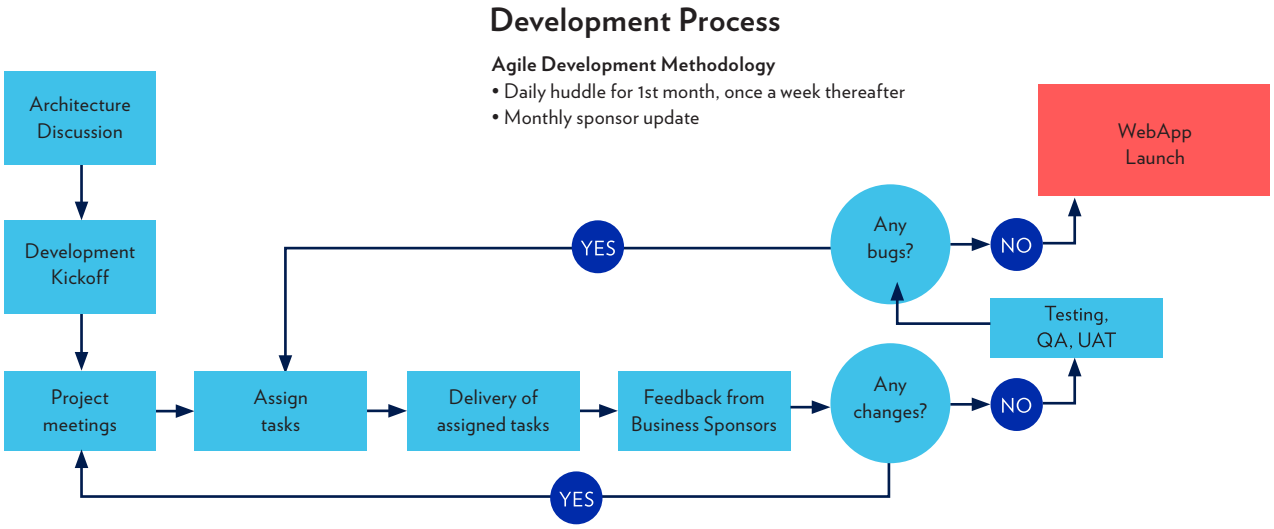


- Opportunity for CC-BioR Education
- Opportunity to communicate CC-BioR consent to OR Team
- Opportunity to confirm communication to PLMI

★ Note that the patient MAY meet with the surgeon BEFORE TCI team can discuss the CC-BioR

* This includes the TCI nurses for outpatients and the pre-op nurse practitioners for inpatients

The following diagram identifies the IT workflow that incorporates the phases for the automated phenotyping build with the web-based application called QueryBuilder.



Altogether, this coordinated and comprehensive approach transformed patient recruitment in research from a largely manual, ineffective and time-consuming process to an automated, efficient exercise that takes full advantage of the EHR technology available.

Improving Adherence to the Standard of Care

These recruitment tools enable the study team to screen, enroll and track participants to ensure compliance with the Food and Drug Administration's 21 CFR part regulations. These are the core set of regulations defining protection of human subjects in clinical research.

The IT solutions provided a transparent option to track patient recruitment, the consent process and ensure appropriate biospecimen collection. With auditing of the CC-BioR documentation and sample collection, compliance with regulatory requirements was 100%: all collected samples were traced back to informed consent documents identified in Epic under the correct filing location and all consented patients were traced back to qualifying surgeries. This is a remarkable accomplishment considering the volume of patients enrolled in the CC-BioR (1,172 subjects and collected 3,565 blood and cardiac tissue samples in 2021) and could not have been possible with the traditional manual processes for documenting informed consent and tracking study related interventions.

After each pilot, standard processes, policies and templates have been established for the study teams to ensure standardization. Study teams are also provided educational opportunities on how to operationalize these processes and utilize the tools (both online and in person).

Improving Patient Outcomes

MyChart messaging: Leveraging the MyChart functionality dramatically improved enrollment in clinical trials. For example, one research study evaluating a treatment for multiple sclerosis enrolled two or three participants a month using two study coordinators to manually review the electronic medical records. Once MyChart recruitment requests were sent to potential participants, enrollment increased to nine to 12 participants per month using one study coordinator. The table below shows our results across all studies served to date using this functionality.

MyChart messaging led to recruitment of **949 study participants** in interventional research studies at the Cleveland Clinic Health System between 2/20/2020 and 12/23/2021.

NI= Neurological Institute; HVTI= Heart and Vascular Institute, LRI= Lerner Research Institute; RI= Respiratory Institute; C5R= Cleveland Clinic Coordinating Center for Clinical Research.

Institute	Study Titles	Go Live Date	# of Messages Sent	# of subjects successfully recruited (non-white currently active or completed)	Response Rate
NI	Comparative Effectiveness of an Exercise Intervention Delivered via Telerehabilitation and Conventional Mode of Delivery (STEP4MS)	2/21/20	2960	479 (67)	16.2%
NI	The Impact of Low Flow Oxygen Therapy on Hospital Admissions and Mortality in Patients with Heart Failure and Central Sleep Apnea (LOFT-HF)	8/11/20	63	24 (9)	38.1%
NI/ Sleep Dis-orders	Impact of a Novel Sleep Apnea Management Group Intervention on Positive Airway Pressure Adherence: A Randomized Controlled Trial (SAMPAP)	10/23/20	133	30 (8)	22.6%
C5R	A randomized, double-blind, placebo controlled, first-in-human study to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic response of SLN360 in subjects with elevated lipoprotein(a) (APOLLO)	12/17/21	129	27 (3)	20.9%
C5R	HORIZON: A multicenter trial assessing the impact of lipoprotein (a) lowering with TQJ230 on major cardiovascular events in patients with cardiovascular disease	3/30/21	64	4 (1)	6.3%
HVTI	Supplements, Placebo, or RosuvastaTin Study (SPORT)	5/24/21	6109	247 (39)	4.0%
NI	A Computerized Cognitive Behavioral Therapy Randomized, Controlled, Pilot Trial for Insomnia in Epilepsy (CBTI)	8/11/21	208	16 (2)	7.7%
LRI	Elucidating the effect of systemic antibiotics on the microbiome and risk for urinary stone disease- the longitudinal cohort for microbiome and urinary stone disease (LCMU) study	8/31/21	2053	113 (36)	5.5%
RI	DNA Evaluation of Fragments for Early Interception - Lung Cancer Training Study (DELFI-L101 Study)	9/9/21	416	9 (1)	2.2%
TOTAL			**12,135**	**949 (166)**	**7.8%**

Lastly, with this method of recruitment, 18% of enrolled research subjects were under-represented minorities (as shown in the table above). This mirrors the distribution of minorities in the local community, suggesting that this tool may increase access to research in this population that has traditionally been under-represented in research.

Cost Savings with CC-BioR

Cost Per Patient - Current	Cost Per Patient - CC-BioR
$1,364	$57

CC-BioR electronic consenting and subject tracking: In the BioR process, when the patient sees their surgeon at the outpatient pre-surgical visit, the research informed consent for CC-BioR takes place in conjunction with the clinical surgical consent. The information about the BioR participation is provided to the patient in their after visit summary. This process eliminates the patient from having to wait for a research study coordinator to complete the research visit for consent. The investigator also benefits by having the high quality, well-annotated specimens readily available to do research at a cost savings. **In two-10 days, as many patients as our protocols were enrolling in one year were enrolled.**

The process supports the path to digital research transformation, which builds the data and biospecimen estate, accelerates research and innovation, and will then lead to transforming science, patient care and public policy.

Accountability and Driving Resilient Care Redesign

Effective and efficient research recruitment strategies are critical to ensure the timely and successful completion of research studies. Cleveland Clinic's approach to research informatics services shows that we can engage our patients with meaningful research opportunities early in the process, provide needed information to have a meaningful discussion with their care team, and provide transparent information for the study team and participant. These strategies are now being deployed across the Cleveland Clinic enterprise (Ohio, Florida, Nevada and London). There are also projects underway to expand these strategies to the Ohio City Wide, Clinical Translational Science Collaborative with Case Western Reserve, Metro Health Center and University Hospitals.

Clinical research has been desiegned, while providing full transparency—and thus accountability—for study teams.

In the traditional research world, endless time is spent by research personnel manually reviewing patient charts to identify potential clinical trial or biobank eligible subjects. Even more time is spent calling or mailing patients information about potential research opportunities, logging manually who was contacted and when and what their response was, and waiting for patients to call back to schedule visits to learn about the study and then enroll. All these manual time-consuming steps are fertile ground for human error (e.g.: calling patients multiple times when they have already expressed lack of interest). With our process, tracking who was contacted through MyChart or electronically consented during their surgical encounter is automated. Patients can express interest or lack of in real-time and the whole process of enrollment is more efficient.

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