

Translating Scientific Evidence into Practice Using Digital Medicine and
Electronic Patient Reported Outcomes
National Clinical Trial (NCT) Identified Number: NCT04345393
Principal Investigator: Bruce E. Sands
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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1	Added UC Davis as enrolling center	To better meet enrollment targets adding UC Davis as enrolling center.
1.3	Updated Schedule of Activities	Clarified categories (detailing what instruments are included) and updated when instruments are implemented for intervention period.
6.1.2	Updated compliance language for messaging.	Clarify messaging compliance.

CONFIDENTIALITY STATEMENT

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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Site clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site

Signed: _____ Date: _____

Name:

Title:

Affiliation:

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Translating Scientific Evidence into Practice Using Digital Medicine and Electronic Patient Reported Outcomes

Study Description: Delivery of healthcare has been traditionally limited to in-person office visits or hospitalizations, while patients spent the majority of their time at home or work. Digital Medicine has the potential to bridge this gap, but it is unclear how to implement in a mainstream clinical practice that can lead to high-level patient and provider adoption.

Through the creation of an Inflammatory Bowel Disease (IBD) Digital therapeutics Toolkit (IBDTx), the study plans to establish baseline levels of disease control and utilization and Implement precision-matched interventions to improve outcomes among 1500 patients with IBD using a stepped-wedge, cluster- randomized trial. The study will be conducted at the four IBD centers who will form IBD Digital Transformation learning Network (DTN).

Objectives: Primary Objective: 1.To improve disease control at 2 years after randomization to interventional cluster as compared to baseline

- Secondary Objectives:
- For those with unplanned care at baseline, decrease unplanned acute care for emergency visits and hospitalizations at 2 years of randomization to interventional cluster
 - To measure digital literacy
 - To decrease digital disparities
 - To quantify change in health in routine clinical care with 1-item, Overall Health Numeric Rating Scale
 - To assess improvement in Quality of Life measured by PROMIS Global scales.
 - To screen for anxiety and depression through Patient Health Questionnaire (PHQ-4) and quantify severity of depression and anxiety using Patient Health Questionnaire (PHQ-8) scores and Generalized Anxiety Disorder scale (GAD-7), respectively.

- To assess and improve mucosal healing
- To measure and improve medication adherence
- To determine and improve eligible quality metrics
- To measure usability of platform
- To measure satisfaction with the program

Endpoints:	Primary Endpoint: Percentage of patients in disease control at 2 years after randomization as compared to baseline. Disease control is defined by co-primary end points of normal inflammatory markers and normal ePROs (PRO2≤1 for UC and PRO3<13 for CD). PRO2 measures stool frequency and bleeding while PRO3 measures the number of liquid or soft stools, abdominal pain and general well-being. Inflammatory markers including Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and Fecal Calprotectin will be dichotomized using cut-offs of <30mm/hr, <5mg/L and <250 µg/g respectively for normal values.
	Secondary Endpoints: 1. Change in co-primary end points (PRO2/PRO3 and level of inflammatory markers) 2. Decrease in Digital Disparities. We will assess the impact of DTN intervention in improving digital skills and access to Internet at 2 years of randomization to interventional cluster as compared to baseline among those screening positive with previously developed digital disparities assessment instrument. 3. Behavioral health screening: We will measure the percentage of patients screening for Patient Health Questionnaire PHQ-4 at baseline. PHQ-4 is a 4 item inventory. Anxiety subscale from 0-6, depression subscale from 0-6, with full scale from 0-12, higher score indicates more symptoms. 4. Change in Patient Health Questionnaire (PHQ-8) scores at 2 years of randomization to interventional cluster as compared to baseline. PHQ-8 will be administered to those with positive PHQ-

4 at baseline, defined by a score of 3 or greater in depression subscale.

The Questionnaire Type 8 for Depression (PHQ89) is a self-administered instrument. Full scale from 0-27, with higher score indicating more severe symptoms. As needed.

5. Change in Generalized Anxiety Disorder scale (GAD-7) at 2 years of randomization to interventional cluster as compared to baseline. GAD-7 will be administered for those screening positive for PHQ-4 at baseline (defined by a score of 3 or greater in anxiety subscale).

The General Anxiety Disorder 7-item questionnaire (GAD-7) is a 7-item questionnaire. Full scale from 0-21, with higher score indicating more symptoms. As needed.

6. Percentage of participants in mucosal healing. at 2 years of randomization to interventional cluster as compared to baseline. This will be defined as the absence of inflammation on endoscopy (scoring systems) or as abstracted from imaging notes collected from physician notes (categorized as yes/no).

7. Change in Visual Analog Scale (VAS) for medication adherence at 2 years of randomization to interventional cluster as compared to baseline. The Visual Analog Scale (VAS) will be used to assess medication adherence using <80% cut-off to designate non-adherence. Full Scale from 0 to 100 with higher score indicating more adherence.

8. For subgroup of patients with unplanned care 12 months before baseline, change in unplanned acute care after intervention. Unplanned acute care is defined as the number of ED visits and hospitalizations days 12 months before the intervention and the last 12 months of DTN intervention.

9. System Usability Scale (SUS).

The system usability scale (SUS) is a 10-item Likert scale questionnaire. The range of scores is from 0 - 100 where a SUS score above 68 is considered average. This will be measured for both patients at week 52 and week 104 after randomization to interventional cluster.

10. Net Promoter Score. The Net Promoter is a 10 point scale and the full score ranges from -100 to 100 where a higher score

translates to higher satisfaction with a product. This will be measured for patients at week 52 and week 104 after randomization to interventional cluster.

- Exploratory Endpoints:
1. Change in overall Health Numeric Rating Scale [OHNRs] at 2 years of randomization to interventional cluster as compared to baseline.
 2. Change in PROMIS Global scales. PROMIS Global scale at 2 years of randomization to interventional cluster as compared to baseline. PROMIS Global scale is a 10-item measure assessing overall quality of life (QOL).
 3. Readmission rates for patients receiving intervention

Study Population: Inclusion Criteria:
 Patients with confirmed Inflammatory Bowel Disease (IBD) will be enrolled into DTN in stepped-wedge cluster randomized trial
 Age greater than or equal to 18 years
 Ability to speak or understand English or Spanish Language.
 Self-reported gaps in disease control as identified through screening questionnaire

Exclusion Criteria:
 - Condition or disease that, in the opinion of the investigators, may make it exceedingly difficult for the patient to use DTN, including, but not limited to, advanced dementia.

Phase: IV

Description of Sites/Facilities Enrolling Participants: Icahn School of Medicine at Mount Sinai, Cleveland Clinic and Northwestern University. University of California Davis will support technical validation and integration and will enroll patients in clinical trial.

Description of Study Intervention: A comprehensive patient-centric intervention will be implemented at IBD centers through digital care plans delivered through IBD Digital therapeutics Toolkit (IBDTx). Patients will be screened based on symptom scores and electronic patient reported outcomes (ePRO). Those with one or more gaps in disease control will be identified through screening questionnaire will be offered enrollment into DTN. Once enrolled, the results of ePROs and online assessments along with EHR data will be used to precision match patients to in-person care at the IBD home or to IBDTx care pathways. IBDTx provides relevant patient education, monitoring and digital self-management resources backed by human navigators and care

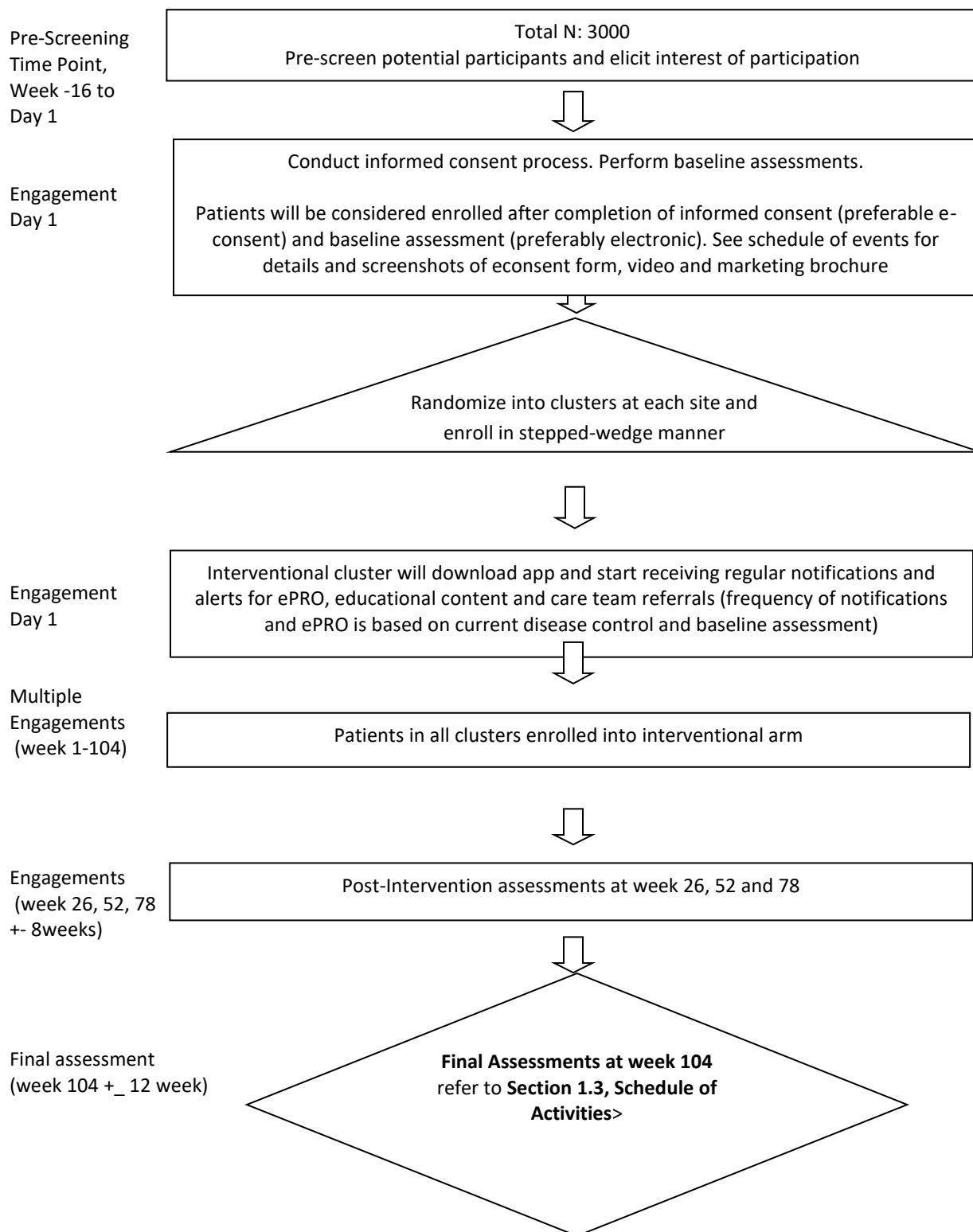
teams. For example, a patient with mild depression or anxiety may be offered an online DTx and if not useful, link to telepsychiatry or in-person psychiatry consultation. Patients will be sequentially enrolled in stepped wedged fashion in different clusters (based on physician and nurse practitioner units at each site). Ultimately, all enrolled patients will be enrolled into intervention arm and data collected before intervention will be compared to data collected 2 years after enrollment in interventional arm.

Study Duration: 4 years

Participant Duration: 2 years once entered into Intervention arm.

1.2 SCHEMA

Flow Diagram (Stepped wedge cluster randomized trial)*



* Minimum of 2 clusters per each clinical site, with clusters enrolled into recruitment every 3-6 months

1.3 SCHEDULE OF ACTIVITIES

Data type	Baseline	Week 0 - Week 104*			Interim Assessment	Interim Assessment	Interim Assessment	Final Assessment
	Week (-16 week-0 week)	Weekly	Every 3 Weeks	Every 3 Months	Week 26	Week 52Week 52	Week 78Week 78	Week 104
Pre-screening ^A	X							
Informed Consent	X							
Medical History ^B	X							
Outcome Evaluation								
Digital Disparities	X			X	X	X	X	X
Medications ^B	X			X				
Adherence ^B	X			X	X			X
Overall Health (OHNRS) ^B	X	X			X			X
PHQ4 (PHQ8, GAD-7) ^{B, C}	X		X		X	X	X	X
Hospitalized Days ^B	X			X	X	X	X	X
Emergency visits ^B	X			X	X	X	X	X
PROMIS Global ^B	X					X		X
Quality of Life (QoL)	X							
IBD Symptoms ^D	X	X			X			X
System Usability Score						X		X
Net Promoter Score						X		X
Adverse events reporting ^E					X	XX	XX	X

^A Pre-screening includes (Appendices C & D):

- Overall Disease Activity
- Initial Digital Disparity/Connectivity Question
- PRO-2 / PRO-3

^B Instrument included in the Baseline Section of Appendix E:

- Medical History
- Medications
- Adherence
- Overall Health (OHNRS)
- PHQ4
- Hospitalized Days / Emergency Visits
- PROMIS Global (either PROMIS Global or revised format of PROMIS Global in the form of QoL)

^C PHQ-8 and GAD-7 are assessed only when participants screen positive for PHQ-4.

^D IBD Symptoms includes:

- PRO-2 / PRO-3. These are asked under Pre-screening section for Baseline.

^E Participants and investigators can self-report adverse events electronically at any time during the study

2 INTRODUCTION

2.1 STUDY RATIONALE

Delivery of healthcare has been traditionally limited to in-person office visits or hospitalizations, while patients spent the majority of their time at home or work. Digital Medicine (e.g., apps, remote monitoring, telemedicine, patient reported outcomes ePRO) has the potential to bridge this gap, but it is unclear how to implement in a mainstream clinical practice that can lead to high-level patient and provider adoption. Through the creation of a Digital Transformation Network (DTN) for Inflammatory Bowel Disease (IBD), the study team plans to reduce digital disparities and scientifically address the evidence gap of digital health interventions across populations and communities.

This protocol integrates and builds upon prior efforts from three CTSA sites over the last five years in ePROs, mobile app-based remote monitoring and IBD Medical Home to support following aims: 1) Create and field test an innovative IBD Digital therapeutics toolkit (IBDTx) in English and Spanish in collaboration with patient partners, national societies, informaticists and IBD researchers. 2) Gather baseline data on disease control and social determinants of health (SDH) including digital disparities. 3) Conduct a multi-site stepped-wedge cluster randomized trial to demonstrate DTN effectiveness in addressing T3 (incorporating the optimal intervention into practice) and T4 (to provide communities with the optimal intervention) translational gaps and reducing IBD symptoms and unplanned acute care. 4) Support a Learning Health System approach for an ePRO based digital transformation network (DTN) that is sustainable through pay-for-performance and Alternative Payment Models.

2.2 BACKGROUND

Chronic conditions account for 75% of the U.S. healthcare burden, affecting almost 1 out of every 2 Americans. Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is one of the five most expensive gastrointestinal conditions in the United States, with overall direct healthcare costs standing at more than \$1.7 billion and an affected population of 1.8 million. This figure does not consider productivity loss. Furthermore, IBD symptoms (including diarrhea, weight loss, and rectal bleeding) and increased risk for colorectal cancer and surgeries, can have a profound social, professional, and emotional impact on the quality of life on those with the disease, as well as those who care for them. About 18% of patients with IBD account for more than 80% of IBD healthcare-related costs in the U.S.; with the largest contributors to this expense attributable to surgery and hospitalization. To achieve disease control and avoid unplanned acute care, proactive care through "Treat to Target" strategies (adjusting treatment iteratively to achieve normalization of patient's symptoms and inflammation as evidenced by objective findings from laboratory markers, endoscopy, or imaging) is now considered the best practice.

Digital medicine (including apps, telemedicine, electronic patient reported outcomes (ePROs)) is seen as an important tool to achieve healthcare quality. Digital therapeutics (DTx) is a subset of Digital Medicine that deliver evidence-based therapeutic interventions to patients that are driven by high-quality software programs to prevent, manage, or treat a broad spectrum of physical, mental, and behavioral conditions. What is lacking is an evidence-based approach of whether digital medicine and DTx can improve health

outcomes among a diverse group of patients and if yes, how it can be reproduced and replicated across different settings.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The testing procedures to be implemented in this study are noninvasive and pose minimal risk to study subjects. Data collection sessions will be purposefully restricted to minimize fatigue to the subjects. Since most assessments will be done digitally, there is some risk for loss of confidentiality. Every measure will be taken to ensure the security, confidentiality and privacy of the study data.

2.3.2 KNOWN POTENTIAL BENEFITS

A potential benefit of this proposal is that DTN may enhance patient-provider communication and improve patient outcomes. Although this study may not directly benefit all those who participate, it may provide important information to develop interventions to improve outcomes of patients with IBD. These benefits outweigh the minimal risks involved in this study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The potential benefit of electronic data collection improving patient-provider communication and patient outcomes, outweigh potential risks with remote possibility of data breach. All measures will be taken to ensure the confidentiality and security of the study data, minimizing the risk.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Co-Primary Objectives and End points		
1.To improve disease control before and after 2 years of randomization to interventional cluster	Percentage of patients in disease control. Disease control is defined by normalization of inflammatory markers and ePROs (PRO2<1 for UC and PRO3<13 for CD). PRO2 measures stool frequency and bleeding in UC while PRO3 measures the number of liquid or soft stools, abdominal pain and general well-being in CD. Inflammatory markers including Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and Fecal Calprotectin will be dichotomized using cut-offs of <30mm/hr, <5mg/L and <250 µg/g respectively for normal values.	Subjective symptom control through patient reported outcomes (ePRO) and objective normalization of inflammatory markers are considered central to Treat to Target goals for disease control of IBD patients.
Secondary		
1. Change in co-primary endpoints 2. To increase digital equity and decrease digital disparities 3. To screen for anxiety and depression through Patient Health Questionnaire (PHQ-4) and quantify severity of depression and anxiety using 4. Patient Health Questionnaire (PHQ-8) scores and 5. Generalized Anxiety Disorder scale (GAD-7) respectively. 6. To assess and improve mucosal healing 7. To measure and improve medical adherence 8. For patients with unplanned care at baseline, measure reduction in unplanned hospitalization days and ED visits 9. To measure usability of platform 10. To measure satisfaction with the program	• To assess and improve digital literacy using digital disparities assessment instrument, created as part of SBIR initiative • To screen for anxiety and depression through Patient Health Questionnaire (PHQ-4) and quantify severity of depression and anxiety using Patient Health Questionnaire (PHQ-8) scores and Generalized Anxiety Disorder scale (GAD-7) respectively. • To assess and improve mucosal healing • To assess and improve medication adherence measured through visual analogue scale (VAS) • To see impact on unplanned care • To measure usability of platform • To measure satisfaction with the program	Lack of access to digital technology is a major barrier to access care and interventions. Patients with behavioral health issues are more likely to be non adherent and report symptoms or access care proactively. Usability of the platform and satisfaction with the program will increase changes for participants to meaningfully engage with the digital and referral interventions.
Tertiary/Exploratory		
1. To quantify change in health in routine clinical care with 1-item, Overall Health Numeric Rating Scale	• To quantify change in health in routine clinical care with 1-item, Overall Health Numeric Rating Scale	Overall health status is dependent on many factors and

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
2. To assess improvement in Quality of Life measured by PROMIS Global scales 3. To measure readmission rates of patients in intervention arm 4. To assess impact on IBD quality indicators	• To assess improvement in Quality of Life measured by PROMIS Global scales. • To measure 30-day readmission rates for patients in home monitoring arm To see changes in IBD quality indicators as defined by AGA	not all factors are modifiable. Hence, we will explore impact of our interventions on these variables. Using structured and unstructured data from EHR, we will explore improvement in quality indicators

4 STUDY DESIGN

4.1 OVERALL DESIGN

A comprehensive patient-centric DTN will be implemented at CTSA sites (three clinical and one technical) to support multi-disciplinary, multi-modal interventions including 1) digital connectivity and digital skills, 2) SDH including language and education barriers, 3) psychosocial interventions, 4) ePRO remote monitoring, and 5) Referral to interdisciplinary care (Table 1). We will use the technology acceptance model (TAM) to guide our strategy on how users will come to accept and use DTN interventions. 54 The model suggests that when users are presented with a new technology, a number of factors influence their decision about how and when they will use it, notably: Perceived usefulness and Perceived ease-of-use.

Based on data on unmet needs and ePROs, patients will be offered targeted digital therapeutics (such as apps, telemedicine, online health education) and in-person interventions for improving biological and behavioral health and improving access to care (see Table). **Our hypothesis** is that a phased approach through clusters to implement person-specific interventions (digital skills, social determinants, behavioral health, monitoring through apps and referral to interdisciplinary care- see Table 2) and facilitating a closed-loop system (through daily alerts and monthly benchmarking) will enable sites to deliver proactive care, improve symptoms and reduce unplanned care.

Table 1. Precision-based Services Targeting Barriers to Care in IBD Digital Transformation Network

Barriers to Care	Matched Services to Address Barriers and Reduce Disparities	Service Delivery Medium
1. Digital connectivity and skills	Assess by cascaded algorithms and questionnaires based on Cleveland Model (Northstar)	Referral to community partners or resource center to be created within IBD centers for skill training and discounted connectivity and equipment
2. Social Determinants of Health	eReferral to 2-1-1, IBD medical home case managers, social workers, language barriers will be addressed through Spanish speaking community workers and Spanish health education	Interactive Voice Response (IVR), text, in person visit, phone call. Spanish version of PRAPARE and Spanish ePROs
3. Behavioral health and self-efficacy	Assess by SIBDQ, PHQ-9, IBD-SES (for self-efficacy). Targeted interventions based on gaps ⁸⁷	Mindfulness App, Telepsychiatry, IBD home, in person visit to IBD center or psychiatrists
4. Lack of regular monitoring	Assess by PRO2 and PRO3, ^{98,99} Provide and train on Personal Health Records (PHR)	App, IVR for ePRO (who do not have access to app), PHRs support timely refill of medications, secure messaging, access to medical records
5. Referral to interdisciplinary care	Interdisciplinary care available under IBD home including clinical pharmacists, nutritionists, health coaches and psychiatrists,	In-person appointments in addition to secure chat and telemedicine access

A multi-site stepped wedge cluster randomized phase 4 real-world trial will be conducted to demonstrate effectiveness of the Digital Transformation Network (DTN). A stepped wedge cluster randomized trial includes an initial period in which no clusters are exposed to the intervention. The clusters will be defined by grouping participating providers and nurse practitioner teams at each of the three sites (estimated 2-4 clusters for each site with allocation ration of 1:1). The respective clusters will group patients seen by the providers in each cluster. Subsequently, at regular intervals (the “steps”) one cluster is randomized to cross from the control to the intervention under evaluation. This process continues until all clusters have crossed over to be exposed to the intervention. We anticipate having a minimum of 2 clusters per each clinical site, with clusters enrolled into recruitment every 3-6 months.

Data collection continues throughout the study so that each cluster contributes observations under both control and intervention observation periods. Each of the 3 CTSA sites will be randomized to a specific order of implementation, and at regular intervals, DTN will be rolled out to each site. Data collected prior to implementation of the bundle will be considered “control data” and data collected at week 104 after implementation of the bundle will be considered as the “intervention data”. Interim analysis will be conducted at week 26, week 52 and week 78. Please see details in **Section 9.4.6, Planned Interim Analysis**

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The strength of this design is that it is a real-world pragmatic study design with limited exclusion criteria so the findings can be generalized (external validity). The intervention is implemented in clusters to prevent contamination between study patients. Stepped wedge implementation allows ultimately all clusters to receive intervention with baseline data before intervention serving as control. This provides greater potential for better internal validity and robust scientific evaluations that might otherwise not be possible.

4.3 JUSTIFICATION FOR INTERVENTION

Patients with IBD suffer from physical, emotional health issues as well as challenges related to access of care and care navigation, which are specific to that person. Hence, the study supports targeting interventions specific to patient needs by precision-matching digital therapeutics (such as apps, telemedicine, online health education) and in-person interventions for improving biological and behavioral health and improving access to care. Our hypothesis is that person-specific interventions and a closed-loop system (through daily alerts and monthly benchmarking) will enable sites to deliver proactive care, improve symptoms and reduce unplanned care.

To ensure all participants are able to receive the interventions digitally, participants who do not enroll into the app (including web app for patients not having Smartphone) and complete the baseline assessment (in phone or computer) will be considered screen failure. For patients without digital literacy, enrollment and baseline assessment can be facilitated by study coordinator on behalf of the patient.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has submitted the full baseline assessment and enrolled into app (or facilitated by study coordinator), received at least 1 intervention for an identified gap, completed 12-month and 24-month follow-up assessments.

The end of the study is defined as completion of the 24-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Population: Consistent with the pragmatic nature of the trial, any patient over the age of 18 years with a diagnosis of IBD whose disease control can be assessed through standard ePRO and seen at one of the three clinical IBD centers in DTN will be eligible, regardless of not having a smartphone nor internet access.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Documented diagnosis of IBD
2. Males and females; Age ≥ 18 years
3. Self-reported gaps in disease control identified through screening questionnaire
4. Provision of signed and dated informed consent
5. Stated willingness to comply with all study procedures (including symptom and other assessments during the study as well as digital interventions and referrals)
6. Access to necessary resources for participating in a technology-based intervention (i.e., computer, smartphone, internet access) or willingness to get trained on digital resources and skills

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- (1) Patients with short bowel syndrome (SBS), multiple fistulae, multiple bowel resections, stoma or other GI conditions that, in the opinion of the investigators, makes measurement of disease control through standard ePROs not feasible.
- (2) Presence of a condition or disease that, in the opinion of the investigators, may make it exceedingly difficult for the patient to enroll in DTN and participate in digital monitoring, including, but not limited to, advanced dementia; as well as subjects for whom it is otherwise impossible to give informed consent.
- (3) Inability to communicate with the investigators and comply with the study requirements.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently entered in the study. This may occur if patients do not enroll into the app and complete the baseline assessment. For patients without digital resources or skills, enrollment into the app and baseline

assessment can be facilitated by study coordinator. Individuals who do not meet the criteria for participation in this trial because of not completing baseline assessment or meeting one or more exclusion criteria that are likely to change over time may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

MSMC IBD center and its affiliates take care of around 5000 IBD patients, Cleveland Clinic takes care of 6000 IBD patients, and Northwestern IBD center takes care of around 2500 IBD patients. There are already well-established registries of IBD patients at three sites, including 2100 patients who are already enrolled in Mount Sinai Crohn's and Colitis (MSCCR) registry. Many patients in registries have already consented to be re-contacted for future studies and we will first approach these patients through Secure Text Messages, Patient portal messages (Epic My Chart), and Interactive Voice Response (IVR) through EHR connected Rx.Health platform that will host IBDTx. We plan to complete recruitment in 9 months and do outreach and advertisement through text messages, patient portals, patient brochures (electronic and paper), after visit summaries in EHR, websites as well as existing Facebook groups (for IBD centers) and engagement bots. All brochures and marketing material will be provided to IRB, and that no patient will be approached and no advertisement placed prior to approval. Each site may use a site-specific approach that will be mentioned in a separate detailed recruitment and retention plan in the Manual of Procedures (MOP) and site-specific Standard Operating Procedures (SOP) document.

Since most study related procedures and e-PROs can be collected from patients' homes by utilization of virtual trial processes and toolkit, there is no requirement to come to the IBD center per se, except for some matched in-person intervention. Hence, we feel there would be minimal barriers for study participation because of transportation, wait time, appointment scheduling, or child care issues. Considering that a substantial proportion of the clinic serving Medicaid patients are of Hispanic ethnicity, we will offer enrollment material and interventions in both Spanish and English. We anticipate that a subset of patients will not have a Smartphone or access to broadband and we would like to specifically see if interventions including digital connectivity and digital skills training can improve their access and ability to use a Smartphone for engaging with health care providers (including receiving health education, filling e-PROs, and receiving alerts); and positively impact their self-efficacy and health outcomes.

Inclusion of women/minorities:

Based on the demographics in our IBD centers, we anticipate that approximately 51.1% of eligible participants will be women and approximately 13.4% will report their ethnicity as Hispanic. These proportions are consistent with the epidemiology of IBD in the majority of participating sites and will provide adequate numbers of women and participants of Hispanic ethnicity for consideration of these important biological variables. Enrollment in the study is reported to the NIH separately; as such, the targeted enrollment form is not applicable for this application.

Inclusion of Children:

The eligibility criteria for this proposal include an age of 18 years or older. As such, children under the age of 18 years will not be included in the proposed study. The exclusion of young children from the proposed study will not limit the scientific validity, as studies of inflammatory bowel disease typically distinguish between adults and children because of differences in the epidemiology and clinical course of the disease.

Table shows estimated recruitment of minorities

Racial Categories	Female	Male	Hispanic Female	Hispanic Male	Totals
American Indian	10	10	3	3	26
Asian	60	54	0	0	114
Native Hawaiian	8	6	2	2	18
Black	120	114	25	21	280
White	455	445	70	68	1038
Multi	10	7	4	3	24
Unknown					
Total	663	636	104	97	1500

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

A comprehensive patient-centric intervention will be implemented at IBD centers through digital care plans delivered through the Rx.Health platform, HIPAA compliant platform that is implemented in multiple other health systems and partners with the American Gastroenterological Association, and IBD Digital Medicine Toolkit. This toolkit includes the remote monitoring patient facing app HealthPROMISE and prescription of the platform will occur via the IBD clinician at the time of hospitalization or office visit (one-one prescription) or via bulk prescription by IBD staff (through registry). The platforms provide education materials for common disease-related questions, share webinars and disseminate patient reported metrics for completion and collection for provider review. The collected data can be sorted and identify patients at risk for poor healthcare outcomes such as active disease and poor quality of life. Patients meeting these criteria can then be contacted via the platform for additional interventions or appointment scheduling. The frequency and exact content will be customized based on rapid-learning concepts in real-time.

6.1.2 ADMINISTRATION AND/OR DOSING

We will use the Logic model to guide our strategy on how IBD patients will come to accept and use this program. This program will be delivered in 5 steps.

1. Outreach: We will use the RxUniverse DTx Prescribing Platform (EPIC Rx Portal) to reach IBD patients through a message to their Smartphone, and inform them about the DTN program through a description and embedded video. The digital outreach will use a multi-pronged approach of email, text and/or MyChart message. For bulk outreach, sites will generate a list of eligible adult IBD patients and use the EPIC Rx Portal to outreach. Direct outreach will be done for patients who have already agreed to be contacted for future research. Individual prescription will also be possible through the EPIC Rx Portal. Smart phrases with link activation will also be generated for outreach to patients following a telehealth or office visit. Sites will also be provided with a SMS based activation, where interested patients can proactively text a short code to receive further information and initiate the enrollment process.

- a) Messaging will be in accordance to any national regulations and local regulations.

2. Screening: Patients will receive outreach messages through one of the methods described above and will be directed through an onboarding module providing further information on the research program and then directed to an e-consent module (at sites where this is acceptable). For sites which require, in person consenting will be built into the workflow to take place prior to the onboarding module. Once consent and onboarding are complete, patients will set up their profiles and be directed to download the HealthPROMISE app or use web-app to complete a baseline assessment. Patients who do not complete this process will be considered screen failure. Within the HealthPROMISE app, patients will have access to various ePRO and online assessment modules which they will be directed to fill in through automated text message reminders, app push notifications, and direct messaging by the clinical team

through the provider dashboard when needed. The expected frequencies for submission of these ePROs can be found in Section 10. Using ePROs and online assessment tools we will assess patients' IBD control as well as their barriers to care including SDH, behavioral health, lack of knowledge of quality metrics, or lack of Smartphone access or connectivity. We expect 1578 patients across three centers to be identified with at least one of the gaps to be eligible for enrollment into the DTN program.

3. Linkage to care: The results of ePROs and online assessments will be used to precision match patients to in-person care at the IBD home or to IBDTx care. RxUniverse platform allows the creation of adaptive pathways based on feedback loops that provide relevant on-demand resources based on patient care touch-points. For example, a patient with mild depression or anxiety, maybe offered an online DTx and if not useful, link to telepsychiatry or in-person psychiatry consultation. Patients who are lacking in quality metrics (like annual influenza vaccination), will be offered brief videos and linked to nearby pharmacies offering influenza vaccination.

4. Remote monitoring: All patients will receive regular monitoring through ePROs delivered via secure text messages, the HealthPROMISE app for digitally enabled population, or an Interactive Voice Response [IVR] for those without smartphone access. Based on ePRO and digital disparities, patients will be offered targeted DTx or in-person interventions for improving biological and behavioral health as well as improving access to care. Additional interventions may be incorporated over time with input from patient partners and in response to feedback from study participants once they have started to use the application. Any change in the ePRO is associated with a red-yellow-green color alert system inside RxUniverse's EHR-linked population health dashboard (provider dashboard) that provides time-trends and trigger alerts for the site population health coordinator who will then bring this to the attention of an interdisciplinary IBD medical home team for telemedicine or office visit. Site-wide steering meetings will occur on a monthly basis to review the workflow of remote monitoring leading to digital or in person interventions and adjustments and guidance will be made/given in an ongoing basis.

5. Learning Health System (LHS) for Continuous Quality Improvement (CQI): Tracking and sharing of best practices during office visits has previously been shown to be effective in a network of pediatric practices (<https://www.improvecarenow.org/>). The key distinction is that DTN builds on a traditional "provider-centered" learning network to empower patients directly and proactively through digital tools to improve care in-between office visits. Via rapid iterative closed-loop cycle, DTN uses novel approaches to LHS in supporting CQI via a) digital check-ins with the patient and remote monitoring anytime, anyplace, b) patient-centered app to guide patients daily, weekly or monthly based on their disease control status and c) real-time EHR-integrated dashboard rather than monthly or quarterly reports (through clinical decision support [CDS] hooks and alerts). In addition, to empower patients, DTN systematically assesses and improves behavioral health, digital connectivity and digital skills of IBD patients. For individuals lacking digital skills, we will provide in-person training by coordinator and IBD center staff and for individuals lacking connectivity, we will refer patients to community partners that offer free or deeply discounted wi-fi hotspots as well as refurbished phones or computers and track their adoption.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The study intervention utilizes the Rx.Health platform which will be licensed to all three clinical CTSA sites and one technical site and integrated within their respective EHRs. Study teams at each site will be trained and onboarded onto the platform with continuous technical support from the Rx.Health partner will be

made available. A regular review of usage of application and if needed, refresher training, will be provided by AppLab coordinating team, Icahn school of Medicine at Mount Sinai. A full detailed of training will be included in SOP and training manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will occur in clusters and each cluster will eventually be enrolled into interventions. This is a real-world pragmatic trial. Blinding will not be feasible for patients or providers since they will be receiving and providing interventions, once they are enrolled into interventional cluster. Blinding will be ensured at the analysis level.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Attempts will be made to regularly engage the patient for participation in study using automated and AI based digital nudging provide by Rx.Health platform. In addition, site coordinators will be provided detailed dashboard with view of each individual data points so they can further engage the patient, if necessary. Goal will be to ensure that patients are able to regularly monitor themselves using ePRO. Patients not adhering to any intervention or not submitting 52 week or 104 week assessment will be considered to have dropped out. In addition, patients submitting less than 4 times symptom ePRO in a year (8 times total during 104 week duration of study) will be considered non-adherent.

6.5 CONCOMITANT THERAPY

Not applicable. Participants may use any medication prescribed by the providers for the duration of the study.

6.5.1 RESCUE THERAPY

Not applicable

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from any IBDTx interventions but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- The participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

*Provide a list of reasons participation may be fully discontinued from the study (as compared to reasons a participant may be discontinued from the intervention as covered in **Section 7.1, Discontinuation of Study Intervention/Experimental Manipulation**). It may be appropriate to provide distinct discontinuation criteria for participants and cohorts (e.g., an individual subject may be withdrawn if the subject demonstrates a substantial increase in violence). If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. Also, note that participants may withdraw voluntarily from the study or the study intervention at any time. But, investigators should seek to minimize participant discontinuation/withdrawal from the study except for safety reasons.*

*This section should include a discussion of replacement of participants who withdraw or are discontinued early, if replacement is allowed. This section should not include a discussion of how these participants will be handled in the analysis of study data. This should be captured in **Section 9, Statistical Considerations**.*

Example text provided as a guide, customize as needed:

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)

- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the IBDTX coordinator dashboard. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced, unless interim analysis suggests otherwise. Patients will also be excluded if they changed to a different IBD center.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if after enrollment (signing eConsent, enrolling in app and completing baseline assessment), he or she

1. Changes to a different IBD center
2. Study staff are unable to contact the participant after at least 5 attempts
3. Does not complete any suggested IBDTx intervention
4. Does not complete 52 week and 104 week assessment

Patients completing 52 week and 104 week assessment but submitting less than 4 times symptom ePRO in a year (<8 times total during 104 week duration of study) will be considered non-adherent (but not lost to follow up). Subgroup analysis of patients who are adherent vs non-adherent will be done for primary, secondary and tertiary end-points.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 5 telephone calls or equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

We anticipate that the loss to follow-up rate in this study will be less than 30%. This rate is conservative as there are multiple strategies being employed by the investigator and the coordinators to optimize patient retention into the study including reimbursements for entry and exit surveys in addition to biweekly health newsletters, regular supportive automated text messages that congratulate on good outcomes and in-person reinforcement for the need for continued monitoring during office visits.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

The co-primary endpoints of the study are the proportion of patients in disease control and unplanned acute care visits, with secondary outcomes as decrease in digital disparities and improvement in behavioral health, quality metrics and quality of life. We will leverage a precision approach to implement interventions through IBDTx (digital skills, social determinants, behavioral health, monitoring through apps and referral to interdisciplinary care) will elicit improvement in disease control and secondary outcomes through proactive care coordinated with IBD medical homes. The intervention will require participation by both the patient and provider alike. Patient responses will be displayed in a series of longitudinal charts available in real-time through EHR-connected dashboards. Patient responses to ePROs will trigger cascading logical response in RxUniverse to send congratulatory notes or e-prescribe different educational content, videos, apps, telemedicine visits or shared decision-making modules (developed based on research, performance benchmarks, and focus group data) or referrals to behavioral experts, nutritionists, social worker or population health coordinators. Responses to patients' assessments are tracked within RxUniverse and if there is no appropriate follow-up action from the patient or coordinator, alerts will be escalated to treating providers. Patients will receive incentives such badges for engagement and completion of quality metrics while each IBD center will receive daily alerts and weekly overview of their alerts and responses, which will be shared across the DTN in monthly steering group meetings. This closed-loop EHR-integrated system will enable the delivery of proactive care and benchmarking of CTSA hubs to each other. Please see above sections related to end points assessment.

8.2 SAFETY ASSESSMENTS

Plan for reporting both anticipated and unanticipated adverse events: Each subject will be evaluated for adverse events. Any event that is reported to either the principal investigator or his designated research coordinator by the subject or medical staff caring for the subject and which meets the criteria will be documented as such. Any event that is reported will then generate an adverse event report, which will be submitted to the IRB. The report will include a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event or the reporting of the event. All adverse events will be graded as mild, moderate, or severe. Any severe and/or unanticipated adverse event will be immediately reported to the safety officer and IRB. All other adverse events will be reported in a timely fashion to the safety officer, and IRB, preferably within 2 weeks of the date of the event. All adverse events will be summarized annually and submitted to the IRB. Any action resulting in a temporary or permanent suspension of this study (e.g., IRB actions or actions by the investigator) will be reported to the appropriate NIH program official.

8.2.1 UNANTICIPATED PROBLEMS REPORTING

8.2.2 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoints:

Disease control: We hypothesize increase in percentage of patients in disease control, defined by normalization of inflammatory markers and ePRO2 or ePRO, 104 weeks after DTN intervention compared to before due to regular home monitoring and proactive alerting to care teams. Alternatively, our null hypothesis is that there will be no difference in the disease control at two-year post-DTN intervention.

Unplanned acute care: We hypothesize decrease in unplanned acute care in intervention cohort compared to baseline due to regular home monitoring and proactive alerting to care teams. Unplanned acute care will be measured by the number of ED visits and hospitalizations days 12 months before the intervention and the last 12 months of DTN intervention.

Secondary Endpoints:

1. **Digital Disparities.** We hypothesize reduction in digital disparities at week 104 compared to baseline due to enhanced access to digital connectivity and skills. Digital disparities will be measured by digital disparities module that assesses for Smartphone access, broadband access and digital skills.

2. **Behavioral health screening:** We hypothesize that proactive measurement and referral to appropriate virtual and in person behavioral health care will lead to improvement in percentage of patients screened for behavioral health and reduction in percentage of participants screening positive by PHQ-4.

3. **Depression scores:** For those screening positive for PHQ-4, we hypothesize that proactive measurement and referral to appropriate virtual and in person behavioral health care will lead to reduction in depression score as measured by PHQ-8.

4. **Anxiety scores (GAD-7):** For those screening positive for PHQ-4, we hypothesize that proactive measurement and referral to appropriate virtual and in person behavioral health care will lead to reduction in anxiety score as measured by GAD-7 which is a 7-item questionnaire. Full scale from 0-21, with higher score indicating more symptoms.

5. **Mucosal Healing:** We hypothesize that regular assessment, symptom monitoring and proactive alerting will lead to increase in percentage of patients in mucosal healing by week 104 compared to baseline. Mucosal healing will be assessed from endoscopy reports, physician notes and radiology reports.

6. Medication adherence

We hypothesize that increased engagement through assessment and monitoring at home will lead to increase in percentage of patients in medication adherence by week 104 compared to baseline.

The Visual Analog Scale (VAS) will be used to assess medication adherence using <80% cut-off to designate non-adherence. Full Scale from 0 to 100 with higher score indicating more adherence.

7. Proportion of patients meeting eligible quality metrics. We hypothesize that regular education and reminders about preventive health screening will lead to an increase in percentage of patients meeting eligible quality metrics by week 104 compared to baseline. Proportion of patients meeting eligible quality metrics confirmed through EHR. Composite score of metrics for skin care protection, flu vaccination, smoking cessation advice, pneumonia vaccination, bone density test, hepatitis B screen steroid sparing medication, TB test and TPMT test

8. System Usability Scale (SUS). We hypothesize that with regular feedback and iterative improvements, IBDTx platform will be user-friendly for both patients and care team members. The system usability scale (SUS) is a 10-item Likert scale questionnaire. The range of scores is from 0 - 100 where a SUS score above 68 is considered average.

9. Net Promoter Score. We hypothesize better patient experience through IBDTx will lead patients to recommend the program to others, as measured by NPS score. The Net Promoter Score is a one item questionnaire, with scores above 60 considered good for program.

Secondary Endpoints:

1. Overall Health Numeric Rating Scale [OHNRS]: We will like to explore impact of IBDTx on single item OHNRS, which measures overall health construct and not just impact of IBD.

2.. PROMIS Global scale. We will like to explore impact of IBDTx on PROMIS Global scales, which is a 10-item measure that assesses overall quality of life.

9.2 SAMPLE SIZE DETERMINATION

Three CTSA hubs IBD centers serve around 12, 000 IBD patients annually. From an automated baseline assessment of over 3000 IBD patients through the RxUniverse platform, we plan to identify and enroll 1578 patients, who will need one or more interventions specifically provided from DTN. Patients will be categorized into groups for lack of digital skills or connectivity, unfavorable determinants of health, poor disease control, increased psychiatric complexity, and/or those with increased resource utilization. We will assume a 15% effect size for the primary outcome of the proportion of patients with disease control based on our preliminary studies and other remote monitoring trials. The sample size is computed assuming patients treated at the same site will be positively correlated so the intra-class correlation (ICC) is set at 0.02. Assuming a maximum attrition rate of 30% (based on prior app-based pragmatic trial) and a two-sided type I error rate fixed at 0.05, our sample size will be a total of 1578 patients with approximately 526 patients per cluster. This will give us 80% power. The test statistic used is the two-sided Wald Z-test.

Based on prior studies, with the sample size calculated to be 1578 patients, we will be also able to detect a greater effect size (greater than 25%) for the primary outcomes of ED visits and hospitalizations while maintaining 80% power. The above calculations were performed with the Power Analysis and Sample Size Software (PASS. 15.0.5), NCSS, LLC. Kaysville, Utah, USA, (ncss.com/software/pass).

Adequate data to determine effect size for secondary outcomes is not available from existing literature.

Patients who will be enrolled into the study (completion of informed consent, filling in baseline assessment and enrollment into app) but do not complete the study (receive at least one intervention and complete assessments at 52 and 104 weeks), transfer from the IBD center or not able to be contacted after 5 attempts will be considered as lost to follow up.

We anticipate that the loss to follow-up rate in this study will be less than 30%.^{59,68,69} This rate is conservative as there are multiple strategies being employed by the investigators and the coordinators to optimize patient retention into the study including reimbursements for entry and exit surveys in addition to biweekly health newsletters, regular supportive automated text messages that congratulate on good outcomes and in-person reinforcement for the need for continued monitoring during office visits.

9.3 POPULATIONS FOR ANALYSES

We will use a modified intention-to-treat analysis where participants who completed baseline assessment and submitted data for interim analysis at week 26, 52 and 78 will be considered for analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics will be used to summarize the patient's demographic and IBD-related variables. Continuous variables will be reported using mean/standard deviation or median/interquartile range. Categorical variables will be reported by count and percentage. We will check for the normality of the continuous variable and if necessary, use log-transformation. Since the outcomes are measured as change from baseline to 2-year post-intervention, we will use a paired t-test to assess significance (p-values <0.05).

There are three different types of outcomes, continuous, binary, and count data. All of these outcomes will be using a mixed model approach to account for the clustering at the CTSA site level (random effect) and the repeated observations for patients. For the continuous outcomes, we will also use generalized linear mixed models but first, we will test the data distribution to determine the appropriate link function. Count data, i.e., ED visits and hospitalization days, will be analyzed using Poisson regression. The models will be appropriately adjusted for the following covariates: patient demographics, SDH and digital disparities, IBD phenotype, comorbidities, and system-generated utilization (including log-in, page views, click count).

Statistical analysis will be conducted using SAS v9.4 statistical software (SAS Institute, Cary, NC). We will follow the best practices of research design, conduction and reporting proposed by the Consolidated Standards of Reporting Trials (CONSORT), SPIRIT, Standards for Quality Improvement Reporting Excellence (SQUIRE), mobile health (mHealth) evidence reporting and assessment (mERA).

Type I Error and Statistical Significance: Hypothesis testing will be conducted using two-sided tests at $\alpha = 0.05$.

Point Estimation and Interval Estimation: Depending on the model applied, we will report restricted maximum likelihood estimates (REML) or quasi-likelihood estimates for point estimation. For routine reporting, two-sided 95% confidence intervals for all parameters will be prepared.

Disposition of Participants and Baseline Comparisons: Summaries of baseline characteristics of all participants enrolled and the number who complete annual visits will be provided.

Univariate Analysis: All outcome measures will be first described in a univariate analysis. For continuous variables, means and standard deviations will be used for descriptive purposes. Linear mixed effects models will be used for comparisons of continuous data. For discrete and dichotomous variables, we will use generalized estimating equations (GEE) These methods will account for the dependency of patients within a physician practice.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Analysis of the primary endpoint: The primary endpoints of the study are:

1. The proportion of patients in disease control at week 104 and
2. Decrease in resource utilization (number of ER visits and annual hospitalization days).

All outcome measures will be first described in a univariate analysis. Linear mixed effects models will be used for comparisons of continuous data. For discrete and dichotomous variables, we will use generalized estimating equations (GEE). As patients will be clustered around physician practices, should any covariate differ significantly between treatment groups at the 0.01 level, and be substantively large, we will adjust for those covariates in all analyses. The primary null hypothesis will be tested in an intent-to-treat analysis using GEE methodology with stratification by clinical center at the 0.05 level. Patients missing the 24-month assessment, for reasons other than death or illness, will have their primary outcome imputed using a multiple imputation algorithm described below. Multiple logistic regression models will be used to control for important covariates, including education level, Spanish language and lack of access to Internet, should significant imbalances be detected between the two comparative groups at baseline.

It is possible that the treatment effects may vary between different subgroups (heterogeneity of treatment effects) and if so, we will perform subgroup analyses of patients who are high utilizers (≥ 2 ER or hospitalizations in last 12 months) or lack Smartphone access or connectivity. Each ePRO will be completed in its entirety as within the app PRO responses are required field. If necessary, we will use multiple imputations and assess the possible reason for missing and then use 5 imputed datasets for analysis.

Missing Data and Imputation Procedures: Adherence to the intention- to-treat principle requires that all patients be included in the primary analysis. Reasons for missing data for each comparative group will be tabulated and compared qualitatively. The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets (for example, best-case or worst-case scenarios). Patients missing the trial's primary endpoint will be included in the analysis by modern imputation methods for missing data. Clinically reasonable imputations for the respective missing outcome for each dropout patient will be derived using a multiple imputation approach. We will use a set of repeated

imputations created by predictive models based on the majority of participants with complete data. Rubin's method of multiple (i.e., repeated) imputations will be used to estimate treatment effect. We propose to use a minimum of five datasets

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analysis of secondary endpoints is not dependent on analysis of primary endpoints. Secondary end-points include improvement in overall health numeric rating scale, PHQ-4, depression (PHQ8), anxiety (GAD-7), mucosal healing and percentage-point improvement in quality metrics from baseline to week 104. The analysis of these end-points will be conducted similarly to the analysis of the primary end-point. Since impact of intervention may vary (heterogeneity of treatment effect), we will use multivariable regression models to determine predictors (including clinical, socio-demographic, patient activation, self-efficacy, lack of Internet or Smartphone access, utilization of app and digital literacy) of meeting quality metrics, and perform subgroup analysis to identify patients who may not utilize the application so other measures to engage them will be applied.

Exploratory analysis of longitudinal assessment of health status and quality of life.: Health status data recorded electronically will be analyzed in exploratory analyses to determine which factors affect the trajectories of health status over time. Continuous variables will be analyzed using mixed effects models. Log-transformations will be used, if necessary, to normalize the variables or stabilize the variance. For binary and discrete outcomes, we will use GEE to fit logistic or log-linear models. The modeling will include assessment of potential confounders and independent risk factors. For mixed effects regression model, we will include fixed effects for the baseline/follow-up periods, the pathway/control arms, and stratifications/interaction, and random effects to account for clustering in practices.

Table below shows the primary and secondary-end points, the type of variable values and source of data

Outcome	Description	Values	Source
Primary end-points			
Disease Control (Remissions)	Ulcerative Colitis- PRO2; Crohn's Disease-PRO3	Binary, PRO2<1 or PRO3<13	App (Patient Input)
Unplanned Resource Utilization (for those with unplanned care at baseline)	Erythrocyte Sedimentation Rate (ESR)	Binary, <30mm/hr	EHR
	C-Reactive Protein (CRP)	Binary, <5 mg/L	EHR
	Fecal Calprotectin	Binary, <50 µg/g	EHR
	# of ER Visits	Continuous	EHR
	Annual Hospital Days	Continuous	EHR
Secondary end-points			

Mucosal Healing	Absence of inflammation on endoscopy or imaging reports	Binary, yes/no	EHR
Depression/Anxiety	Patient Health Questionnaire 4 (PHQ-4), PHQ-8 and GAD-7	Binary, PHQ-4 ≥ 3	App (Patient Input)
Medication Adherence	Visual Analog Scale (VAS) for medication adherence	Continuous, 1-100	App (Patient Input)
Digital Skills	Digital skills and competency assessed through module create w/ SBIR initiative	Binary, Yes/No	App (Patient Input)
Usability	System Usability Score	Binary, SUS ≥ 78	App (Patient Input)
Satisfaction	Net Promoter Score	≥ 65	App (Patient Input)
Quality Metrics	Based on national guidelines	Binary, Yes/no/unsure	App and HER
Exploratory end points			
Overall Health numeric Score	1 item score	Continuous	App (Patient Input)
PROMIS Global	Quality of Life	Continuous	App (Patient Input)
Readmission rate	30-day readmission rate	Dichotomous	App (patient input) + EHR

9.4.4 SAFETY ANALYSES

Not Applicable

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be used to summarize the patient's demographic and IBD-related variables. Continuous variables will be reported using mean/standard deviation or median/interquartile range. Categorical variables will be reported by count and percentage. We will check for the normality of the continuous variable and if necessary, use log-transformation. Since the outcomes are measured as change from baseline to 2-year post-intervention, we will use a paired t-test to assess significance (p-values < 0.05).

9.4.6 PLANNED INTERIM ANALYSES

Full interim analysis will be conducted at week 52 to analyze completion of data collected and if sample size need adjustment. Partial analysis and data-cuts will be completed at week 26 and 72 for quality assurance and quality control. Separate safety analysis is not needed as this is not a drug or device intervention trial.

9.4.7 SUB-GROUP ANALYSES

All outcome measures will be first described in a univariate analysis. Linear mixed effects models will be used for comparisons of continuous data. For discrete and dichotomous variables, we will use generalized estimating equations (GEE). As patients will be clustered around physician practices, should any covariate differ significantly between treatment groups at the 0.01 level, and be substantively large, we will adjust for those covariates in all analyses.

Since impact of the intervention may vary (heterogeneity of treatment effect), we will use multivariable regression models to determine predictors (including clinical, socio-demographic) of meeting end-points and perform subgroup analysis to identify patients who may require additional help to utilize DTN interventions. Comorbidities will be assessed through the Charlson Comorbidity Index. The extent to which patients' access DTN interventions will also be tracked and analyzed as a mediating variable. Utilization and engagement will be categorized in tertiles (low, moderate, high) for analysis. Continuous variables will be analyzed using mixed effects models. Log-transformations will be used, if necessary, to normalize the variables or stabilize the variance. For binary and discrete outcomes, we will use GEE to fit logistic or log-linear models. The modeling will include assessment of potential confounders and independent mediating variables. Mediating variables of primary and secondary outcomes will include (clinical, SDH, digital skills and connectivity, adherence measured as proportions of days covered from EHR data, language, health literacy, patient and provider utilization and provider practice.) For mixed effects regression model, we will include fixed effects for the baseline/follow-up periods, and stratifications/interaction, and random effects to account for clustering in practices.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participants data will be made available to study coordinator to match with precision-based interventions. For the purposes of analysis, each cluster with pooled participant data will be used. See Section 1.3 (schedule of activities, SoA) for details.

9.4.9 EXPLORATORY ANALYSES

Exploratory analysis of longitudinal assessment of health status and quality of life.: Health status data recorded electronically will be analyzed in exploratory analyses to determine which factors affect the trajectories of health status over time. Continuous variables will be analyzed using mixed effects models. Log-transformations will be used, if necessary, to normalize the variables or stabilize the variance. For binary and discrete outcomes, we will use GEE to fit logistic or log-linear models. The modeling will include assessment of potential confounders and independent risk factors. For mixed effects regression model, we will include fixed effects for the baseline/follow-up periods, the pathway/control arms, and stratifications/interaction, and random effects to account for clustering in practices.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and electronic documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

We will only enroll patients who seek their care at three CTSA hubs clinical IBD centers. Online informed consent will be obtained from each subject by the following process: 1) Electronic informed consent will be made available to patients electronically (through email or text) as well as in IBD centers. 2) PI, designated research associates or provider will be available to answer any questions electronically or in-person 3) subject reviews the study consent form and electronically accepts it; 4) The patient will be enrolled in the study, and is provided option to get electronic version of their signed form. We will use consent forms and terms of use approved by the Institutional Review Board. The consent form will include information on the purpose of the study, description of all research procedures, risks, the voluntary nature of the study, confidentiality, alternatives to participation, termination of participation, data sharing and contact persons.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the AppLab Data Coordinating Center, Icahn School of Medicine at Mount Sinai, New York, NY. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by AppLab Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the AppLab Data Coordinating Center.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see <https://grants.nih.gov/policy/sharing.htm>). The PI will ensure all mechanisms used to

share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

We will follow rigorous procedures to protect patients' confidentiality. Participants in the interviews and conversations will be de-identified during the analysis part. We will observe the following data safeguarding procedures: 1) train staff on data sensitivity and safeguards being employed to assure confidentiality; 2) store and process sensitive hardcopy in a centralized location; 3) secure sensitive hard copy in locked files when not in use; 4) remove names, addresses, and other direct identifiers from hard copy and computer-readable data after they are not necessary for participant tracking; 5) destroy all identifiable links to data after accuracy has been verified and final analyses have been completed; and 6) store and secure sensitive electronic data in a file secured in our file server, by encrypted password and a separate password to access the database file on the server.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at AppLab Data Coordinating Center, Icahn School of Medicine at Mount Sinai. After the study is completed, the de-identified, archived data will be transmitted to and stored at the cloud database for use by other researchers including those outside of the study. Permission to transmit data to the cloud databases will be included in the informed consent.

During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research. However, withdrawal of consent with regard to data storage may not be possible after the study is completed.

When the study is completed, access to study data will be provided through the Cloud database maintained by AppLab.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

The study will be led by monthly PI and site PI (steering committee), all key staff (executive committee). In addition, there would be technical, digital disparities and coordinator sub-committees that will meet at regular intervals based on the need. A list of all study team members will be included in the MOP along with roles and responsibilities of those involved in the conduct, management, or oversight of the trial as well as processes to report study misconduct.

10.1.6 SAFETY OVERSIGHT

In compliance with NIH requirements, we will establish a data and safety monitoring plan (DSMP). The purpose of the DSMP is to ensure the safety of patients and the validity and integrity of the data.

The proposed study does not involve greater than minimal risk (as defined in the Code for Federal Regulations 46.102). Thus, the study does not require a formal data safety and monitoring board. However, the Icahn School of Medicine at Mount Sinai requires that all human subject research protocols have a data and safety monitoring plan. The principal investigators will be responsible for the data safety and monitoring plan for the entire study.

10.1.7 CLINICAL MONITORING

Not Applicable as there will be no external team for clinical monitoring.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. There is no biological specimen collection in this trial. All sites will follow a common quality management plan. Clinical monitoring will follow internal standard of care practices along with data monitoring through a provider facing dashboard updating in real time with all patient reported data.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured directly electronically to transferred into the study database. To ensure accuracy site staff will periodically review representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

Annual review: The site investigators will review this protocol on a continuing basis for subject safety and include results of the review in the annual progress reports submitted to the safety officer and the Institutional Review Board.

Annual report: The annual report will include a list of adverse events. The annual report will address: 1) whether adverse event rates are consistent with pre-study assumptions; 2) reason for dropouts from the study; 3) whether all participants met entry criteria; 4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and 5) conditions whereby the study might be terminated prematurely.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Research material from subjects will consist of data from qualitative inquiry and data entered into online questionnaires. Any study data collected on paper will be entered into a computer database, and the datasheets will then be stored in a locked cabinet. Identifiable electronic data will be maintained in a password-protected database which will only be accessible to study investigators, clinical research coordinators, and data entry personnel. Data will be backed-up daily either to a central server and/or to an external hard drive that is kept in a locked room. The research personnel and study investigators will have completed all necessary human subjects research and HIPAA training. Data entered into an online questionnaire will be transferred through the Hypertext Transfer Protocol Secure (HTTPS) protocol, which is a combination of the *Hypertext Transfer Protocol* (HTTP) with *SSL/TLS* protocol. It provides encrypted communication and secure identification of a network *web server*. HTTPS connections are often used for payment transactions on the *World Wide Web* and sensitive transactions in corporate information systems.

Finally, data will be stored in secured database servers maintained in a secure Microsoft Azure Cloud maintained and provisioned by our technology partner, Rx.Health. Password information will be encrypted. The Microsoft Azure platform on which data and the application is hosted is HIPAA compliant and Mount Sinai has a Business Associate Agreement with Microsoft. Also, our implementation, processes and security controls have been fully vetted through and approved by Mount Sinai IT security. These include restriction of user and admin roles, auto log off with multiple wrong password entry, use of secured socket layer, detailed audit log, Web Application Firewall to protect the Web application server,

encrypted connections to the Web application server and firewall rules to restrict access to connections to the database.

Each participating site will have electronic version of medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-sponsored or NIH-affiliated study, each site will permit authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Indicate who will have access to records.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to NCATS Program Official and AppLab Data Coordinating Center, Icahn School of Medicine at Mount Sinai. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers up to 5 years after the completion of the primary endpoint by contacting Bruce E Sands, Icahn School of Medicine at Mount Sinai. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

All have sites have agreed in grant application to preferentially use SMART IRB framework. A common protocol will be submitted to Advarra Central IRB. Consistent with the pragmatic nature of trial, each site will be able to customize its digital toolkit and leverage site-specific outreach, implementation and engagement processes.

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CD	Crohn's Disease
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan

COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CQI	Continuous Quality Improvement
CRF	Case Report Form
CRP	C-Reactive Protein
CTSA	Clinical and Translational Awards
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
DRE	Disease-Related Event
DTN	Digital Transformation Network
Dtx	Digital Therapeutics
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ED	Emergency Department
EHR	Electronic Health Record
ePRO	Electronic Patient Reported Outcomes
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HIPAA	Health Insurance Portability and Accountability Act
HTTPS	Hypertext Transfer Protocol Secure
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
IBDTx	Inflammatory Bowel Disease Digital Therapeutics Toolkit
ICC	Intra-class Correlation
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
IVR	Interactive Voice Response
LHS	Learning Health System
mERA	Mobile Evidence Reporting and Assessment
MOP	Manual of Procedures
MSCCR	Mount Sinai Crohn's and Colitis Registry
MSMC	Mount Sinai Medical Center
NCT	National Clinical Trial
NIH	National Institutes of Health
NPS	Net Promoter Score
OHNRS	Overall Health Numeric Rating Scale
OHRP	Office for Human Research Protections
PASS	Power Analysis and Sample Size Software
PHQ	Patient Health Questionnaire
PI	Principal Investigator

PROMIS	Patient Reported Outcomes Measurement Information System
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
REML	Restricted Maximum Likelihood Estimates
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	Small Business Innovation Research
SBS	Small Bowel Syndrome
SDH	Social Determinants of Health
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SQUIRE	Standards for Quality Improvement Reporting Excellence
SUS	System Usability Scale
TAM	Technology Acceptance Model
TB	Tuberculosis
TPMT	Thiopurine methyltransferase
UC	Ulcerative Colitis
UP	Unanticipated Problem
US	United States
VAS	Visual Analog Scale

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Protocol Version	Affected Section(s)	Summary of Revisions Made	Date of Revisions	Rationale
Original (1.4)	1.2	Added details of ePRO and time of events	11 June 2021	
Original (1.4)	1.3	Included modifications suggested by Dr. Sands	11 June 2021	
1.5	Protocol Summary, 1.5, Study Population, 5.1	Updated inclusion criteria.	22 April 2022	Removed lab value requirements as part of inclusion criteria which is not needed to achieve Aims and Outcomes needed for the research. Corrected PRO2/PRO3 values for controlled and uncontrolled disease. Described how gaps in disease control identified.
1.5	Protocol Summary, Objectives and Endpoints, 9.4.3	Corrected PRO2 value for defining controlled and uncontrolled disease.	22 April 2022	Too high of threshold was incorrectly used for PRO2 based on the literature.
1.5	Protocol Summary, 2.3.3, 3	Corrected and clarified Objectives and Endpoints.	22 April 2022	Refined Objectives and Endpoints. Improved clarity of planned Objectives and Endpoints for the study.
1.5	1.2, 4.1	Clarified clustering at sites.	22 April 2022	Improved clarity of protocol.

1.5	1.3	Removed Quality Indicators Row.	22 April 2022	Category covered in other listed categories.
1.5	4.1, 4.3	Updated language regarding how digital connectivity skills are assessed and how the research will address connectivity barriers.	22 April 2022	Improved clarity of protocol.
1.5	6.1.2	Updated how patients will be identified for the research study. Updated flow of patients and possible research participants who connectivity barriers.	22 April 2022	Improved clarity of protocol.
1.5	7.3, 9.1, 9.4	Updated analysis plan.	22 April 2022	Added minor updates to exploratory analyses based on updated endpoints. Improved clarity of planned analysis.
1.5	Table of Contents, Investigator Signature, 4.1, 4.4, 5.2, 7.3, 8.2	Updated text formatting (e.g., removed highlighting of text).	22 April 2022	Improved clarity.
1.5	Title page and headers	Corrected version control and deleted "Protocol #1"	22 April 2022	Improved clarity and version control management. Previous Protocol version contained both 1.3 and 1.4 throughout document (with differing version dates).
1.5	Entire protocol	Corrected spelling, grammar, and formatting.	22 April 2022	Improved clarity.

1.5	10.4	Updated Protocol Amendment History Table.	22 April 2022	Improved version control
1.6	1.1	Added UC Davis as enrolling center	19 May 2023	To better meet enrollment targets adding UC Davis as enrolling center.
1.6	1.3	Updated Schedule of Activities	19 May 2023	Clarified categories (detailing what instruments are included) and updated when instruments are implemented for intervention period.
1.6	6.1.2	Updated compliance language for messaging. Updated messaging methods for Northwestern prior to consent.	19 May 2023	Clarify messaging compliance.

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