Personalized Infliximab Induction Strategy with Model-informed Dosing in Patients with Crohn's Disease

(REMODEL)

Pilot & Feasibility

Protocol IRB Number: 2020-0282

National Clinical Trial (NCT) Identified Number: NCT04974099

Principal Investigator:

Phillip Minar, MD, MS – Cincinnati Children's Hospital Medical Center

Funded by:

Crohn's and Colitis Foundation

Cincinnati Children's Research Foundation (ARC)

Version Number: 4

14 Feb 2022

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation 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)

The trial will be conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval.
Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form 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.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Personalized Infliximab Induction Strategy with Model-informed dosing in Patients with Crohn's Disease.
Study Description:	This is a Pilot study to evaluate safety, feasibility and efficacy of utilizing pharmacokinetic modeling to provide an individualized infliximab induction regimen in children and young adults with moderate to severe Crohn's disease. This clinical study is designed with the hypothesis that treatment regimens that account for individual (patient) drug clearance (pharmacokinetic modeling) will not only be safe and cost-effective, but also more effective in reducing intestinal inflammation than as-labeled dosing (ALD) regimens.
Objectives:	Primary Objective: Obtain safety, feasibility and efficacy data for the optimal dosing strategy and sample size estimation to inform the design of a future, larger randomized controlled trial.
Endpoints:	Safety: Number of adverse and/or serious adverse events during the six-month study. Feasibility: Enrollment, study completion, clinician usability of dashboard and adherence (including the clinician and 3rd party insurance coverage) to dosing regimens recommended by the modeling program. Efficacy: (Primary) Rate of achieving infusion #3 (week-6) level in the target range (18-24 µg/ml).
Study Population:	20 male and female participants age 6 to 22 with Crohn's disease who are scheduled to receive infliximab.
Phase:	II
Description of Sites/Facilities Enrolling Participants:	Cincinnati Children's Hospital Medical Center
Description of Study Intervention:	Pharmacokinetic model-informed dosing recommendations are based on the subjects' weight, serum albumin, erythrocyte sedimentation rate (ESR) and neutrophil CD64 activity ratio (nCD64). The dosing recommendations are presented to the clinician with the RoadMAB™ dashboard system with the final dosing decision at the discretion of the treating physician.

Study Duration: 24 months

Participant Duration: 6 months

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screen	V1	V2	V3	V4	V5	V6	V7	V8
Timeline (infusion)		**1**		**2**	**3**	**4**	**5**	**6**	
Weeks (range)		**0**	**1**	**2**	**2-6**	**10-14**	**14-22**	**18-30**	**26-30**
Informed Consent	X								
Eligibility[1]	X								
Demographics[2]	X	X							
Medical History	X							X	
Surgical History	X							X	
Physical exam, weight[3]	X							X	
Record Clinical Lab Results[4]	X	X		X	X	X	X	X	
Prior and Concomitant Medications[5]	X	X		X	X	X	X	X	
Urine pregnancy test[6]	X								
GI Symptoms Questionnaire[7]	X	X	X	X	X	X	X	X	
Provide dashboard dosing recommendations to MD[8]		X		X	X	X	X		
Receive infliximab infusion[9]		X		X	X	X	X	X	
Blood collection[10]		X	X	X	X	X	X	X	
Stool collection[11]	--------X--------				X	X		X	
Coordinator calls[12]		X				X		X	
MRI abdomen (MRE)[13]									X
Endoscopy severity score[14]	X								X
Adverse events monitoring		X		X	X	X	X	X	X

[1] Must meet full inclusion/exclusion criteria as described in protocol; includes males and females ages ≥6 year to ≤22 years old with prior diagnosis of Crohn's Disease (CD), anti-TNF naïve, and starting infliximab (or infliximab biosimilar).

[2] Includes date of birth, date of diagnosis, gender, race, and ethnicity.

[3] Record measurements taken for clinical purposes. Includes weight, height and body mass index. Use the most recent results available.

[4] Will include all CD-related labs and those that will inform the infliximab model including serum albumin, ESR, nCD64, drug concentration, and antibody to drug concentration.

[5] All medications will be recorded.

[6] Urine pregnancy must be obtained prior to starting infliximab in all female subjects' ≥12 years of age (or younger, if menses has begun).

[7] GI symptoms questionnaire assists in the completion of disease activity scoring and will be given prior to starting infliximab. The weighted Pediatric Crohn's Disease Activity Index (clinical remission defined as wPCDAI<12.5) – combines subjective clinical evaluation (abdominal pain, stool frequency, and general well-being), and laboratory tests (albumin and ESR) with physical exam assessments (weight, perirectal disease and evaluation of extraintestinal manifestations). This will also include assessing patient reported outcomes as well.

[8] Patient weight and results of pertinent laboratory tests (serum albumin, ESR, nCD64, infliximab concentration, and antibody to infliximab concentration) will be input into the RoadMAB application. A print out with the dosing recommendation and expected PK dose/exposure curve will be supplied to the treating physician.

[9] Infusion schedule is listed in Figure2. The first 3 doses (induction) are standardized at 0, 2 and 6 weeks. The maintenance regimen (infusion4 and subsequent infusions) will be determined and then ordered by the treating physician.

[10] All attempts will be made to avoid research-only visits. Instead, sample collection will be planned to coincide with previously scheduled infusion visits, except V2, which occurs at week1 and is optional. V2 is a lab-only visit to obtain infliximab concentration, a complete blood count, ESR, nCD64 and hepatic profile. The volume of blood obtained will follow guidelines for children – the lesser of 3ml/kg or maximum of 20ml collected for research purposes.

[11] All subjects will collect stool at home and either mail the sample directly to the Minar Laboratory or bring the stool sample to the infusion visit. A total of 4 stools will be collected (screening or infusion 1 and infusions 3, 4, and 6)

[12] Coordinator calls are scheduled to evaluate for any AE or SAE and to remind participants of upcoming infusion visits.

[13] Participants will be asked to have an optional MRI scan (using oral contrast, Breeza®, or water) at V8 (approximately weeks 26-30)

[14] Endoscopy scoring is NOT feasible for this pilot study. However, if the participant has a colonoscopy six months prior to study enrollment or at any during the study period, we will perform the Simple Endoscopic Severity-Crohn's disease (SES-CD) from the video-recordings (if available with the CCHMC vaultstream application).

2 INTRODUCTION

2.1 STUDY RATIONALE

Approximately 3 million people (including >100,000 children) in the United States are living with inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC).[1] Despite advances with novel treatments, many children and adults with IBD continue to experience significant gastrointestinal symptoms (disease flares) and preventable disease complications.

Therapeutic targets for CD include monoclonal antibodies (mAb's) that antagonize circulating and tissue-bound inflammatory cytokines (anti-TNF, anti-IL12/23) and leukocyte recruitment pathways (anti-integrin). For pediatric CD, the Food and Drug Administration (FDA) has approved two anti-TNF mAb's, infliximab (and infliximab biosimilars) and adalimumab for children (>6 years old) with moderate to severe CD. Infliximab (anti-TNF) remains the most commonly used first-line biologic agent for children with moderate to severe CD. Infliximab was first FDA-approved for children (6-17 years old) with moderate to severe CD based on the results of the pivotal REACH study.[2] Based on this study[2], infliximab dosing occurs in two phases, induction and maintenance. The induction dose is 5 mg/kg at 0, 2 and 6 weeks. The maintenance dosing regimen is 5 mg/kg every 8 weeks, which is the same dosing regimen approved for adults (>18 years old) with IBD.[3,4]

Although the rates of initial *clinical response* to anti-TNF dosing regimens as-labeled exceed 80%[2, 3], rates of complete intestinal (bowel) healing only range between 36-46% with merely 19-36% of patients on maintenance therapy able to achieve deep remission (a therapeutic target that includes the combination of clinical remission and intestinal healing).[4, 5] For most patients, failure to achieve deep remission is directly related to (1) subtherapeutic drug exposure (both during induction and maintenance phases) or (2) the development of neutralizing anti-drug antibodies in the setting of low drug concentrations.[6] Moreover, in a pediatric study of 955 children receiving infliximab, the authors found the only predictors of non-remission at one year were **subtherapeutic drug concentrations at week 14** (end of induction) and **development of antibodies to infliximab.**[7] As a result, there are intensified efforts for **tighter and earlier** control of the inflammatory burden by providing individual patients with **optimized drug exposure during induction**[7] and **maintain the targeted drug exposure** through the reliable use of proactive therapeutic drug monitoring (pTDM) and subsequent dose optimization.[4]

Based on a large CD cohort who provided longitudinal biosamples to produce a real-world pharmacokinetic (PK) model, our team has developed an innovative physician support dashboard for infliximab (RoadMAB™). RoadMAB™ utilizes our population PK model that includes novel biochemical covariates (weight, albumin, ESR and nCD64) to estimate infliximab clearance to provide personalized dosing regimens for patients starting infliximab. Therefore, *we hypothesize*

that model-informed infliximab dosing that accounts for individual drug clearance with routine blood biomarkers to inform the starting infliximab dose will more accurately achieve the targeted drug exposure during induction than as-labeled dosing (ALD).

2.2 BACKGROUND

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), affect an estimated 3 million people in the United States,[1] including approximately 100,000 children and adolescents. The peak age of onset for pediatric CD is early adolescence with a rising incidence of children diagnosed with IBD before 10 years of age.[8] With the early age of onset, pediatric patients are susceptible to prolonged intestinal damage resulting in growth failure, intestinal strictures with possible bowel obstruction and significant penetrating complications (fistula or abscess formation).[9, 10] In a cohort of 989 newly diagnosed pediatric CD patients, 38% developed a CD-related complication within the first 10 years of diagnosis.[11]

Therapeutic options for moderate to severe CD include monoclonal antibodies (mAb) that antagonize circulating or tissue-bound inflammatory cytokines and leukocyte recruitment pathways. Following the pivotal REACH study,[2] mAb's targeting tumor necrosis factor-alpha (anti-TNF) are the most commonly used first-line biologic agents for children with moderate to severe CD. Although high rates of early (week 10) clinical response to anti-TNF are reported (75-88.4%),[2, 3] many children and adults continue to experience symptom flares and serious disease complications as long-term rates of mucosal healing range between 36-46% with only 19-36% achieving deep remission[5] ,The variation in treatment response likely reflects the heterogeneity of CD phenotypes, the individual differences in location and extent of inflammation and patient-specific cytokine burden. Despite this heterogeneity of disease and significant differences in drug clearance,[12, 13] initial infliximab dose selection during induction is solely based on the patient's weight and not on readily available biomarkers that can accurately predict drug clearance.[2, 14]

Although infliximab is FDA-approved for children (ages 6-17 years) with moderate to severe CD, there is significant evidence that utilizing the labeled infliximab dosing schedule of 5 mg/kg at 0, 2 and 6 weeks (induction) followed by infusions at 5 mg/kg every 8 weeks (maintenance) results in subtherapeutic drug concentrations, a 20-25% rate of immunogenicity and poor drug durability in children with CD.[12, 15-17]

Current as-labeled infliximab dosing regimens were developed prior to the routine use of therapeutic drug monitoring (TDM) and without knowledge of a well-characterized dose-exposure-response relationship. Therefore, subtherapeutic infliximab concentrations are common as availability of biomarkers to predict rapid infliximab clearance for either dose selection (starting) or dose optimization strategies are lacking. In fact, we found that 59% of patients receiving the aforementioned ALD infliximab regimens had subtherapeutic drug concentrations prior to the third induction dose.[12] In a recent retrospective review comparing outcomes between adults IBD patients who received reactive TDM (rTDM) vs. pTDM, patients with pTDM had higher rates of drug durability and a decrease in IBD-related surgery, hospitalizations, immunogenicity and infusion reactions.[6]

Moreover, in our longitudinal cohort of anti-naïve CD patients receiving infliximab induction, treatment response (clinical and biochemical) was associated with a higher infliximab concentration (Figure1a-b)[12] and infliximab exposure (Figure 1c, unpublished). We subsequently developed a real-world population PK model for infliximab with our CD cohort and found that drug clearance was affected by patient weight, serum albumin, antibody to infliximab (ATI), ESR, nCD64 and use of prednisone (Table1).

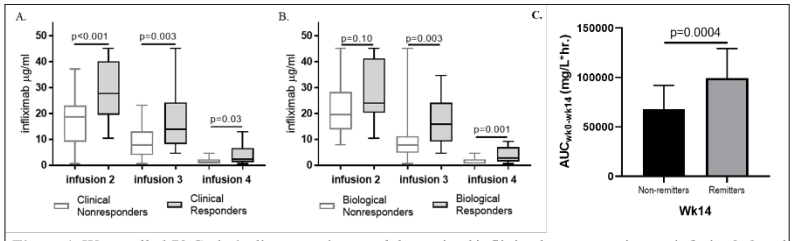

Figure 1. We enrolled 72 Crohn's disease patients and determined infliximab concentrations at infusion2, 3 and 4. A). Clinical responders (change in baseline wPCDAI at the end of induction) had higher infliximab levels at all time points. B). We found biological responders (>50% reduction in fecal calprotectin at the end of induction) had higher infliximab levels at infusion3 and infusion4 compared to non-responders. C). We also found that the total infliximab exposure (defined by area under the curve [AUC], mg/L*hr.) during induction was also higher in biochemical remitters (fecal calprotectin <250 µg/g).

These data support the hypothesis *that model-informed infliximab dosing that accounts for individual drug clearance with routine blood biomarkers to inform the starting infliximab dose will more accurately achieve the targeted drug exposure during induction than ALD.*

As noted, several treatment strategies to maximize outcomes to anti-TNF have developed and include rTDM,[18] pTDM,[6, 19] and treatment to target.[4] With our trial design, we are not only testing whether personalized dose selection will improve short-term and six-month outcomes, we are also testing the feasibility and usability of a Precision Dosing Dashboard, RoadMAB™. The **RoadMAB™ Dashboard** is a real-time decision support system that incorporates PK model-informed Bayesian estimation to provide precision dosing at the point of care. Briefly, RoadMAB™ extracts patient data (weight, concurrent medications and blood biomarker results) from the electronic medical record (EMR) and produces individual PK profiles to accurately predict drug exposure between infusions. The RoadMAB™ user-interface is intuitive and provides a visual snapshot of the predicted drug concentration (trough) at the next infusion. For this pilot study, the Dashboard will provide the starting dose with each patient set to receive the ALD induction intervals at 0, 2 and 6 weeks. During *maintenance*, the Dashboard can then be utilized for both infliximab dosing and interval (weeks) selection.

Table 1. Parameter estimates of the final population pharmacokinetic model.

Parameters	Final Estimate (RSE%)
CL (L/h/65kg)	**0.013 (5.1)**
WT for CL	0.575 (10.2)
ALB for CL	-0.852 (12.7)
ATI for CL	0.128 (10.3)
ESR for CL	0.106 (29)
nCD64 for CL	0.147 (16.3)
On prednisone for CL	1.15 (3)
V_1 (L/65kg)	**2.94 (4.4)**
WT for V_1	0.534 (20.8)
Q (L/h/65kg)	**0.0095 FIXED**
WT for Q	1 FIXED
V_2 (L/65kg)	**2.59 (3.6)**
WT for V_2	0.586 FIXED

V_1, volume of distribution in the central compartment. V_2, volume of distribution in the peripheral compartment. Q, inter-compartmental clearance. RSE, relative standard error.

Our approach will have a high impact in the field by providing critical safety and efficacy data along with implementation strategies to support a future clinical trial. Utilizing the results of this pilot investigation, our **long-term goal** is to conduct a comparative effectiveness clinical trial to evaluate short and long-term efficacy outcomes between patients receiving a personalized induction regimen with treatment to target (blood biomarkers) dose intensifications using RoadMAB™ in comparison to patients receiving ALD infliximab regimens.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks associated with this study are associated with infliximab (or infliximab biosimilar), venipuncture, magnetic resonance imaging (MRI) and breach of confidentiality.

Infliximab: Safety and efficacy of infliximab has been established in pediatric (>6 years old) and adult-onset CD patients.[2, 20, 21] There is a relative paucity of dose-exposure risks with infliximab.[22] However, risks with high dose infliximab could include:

- elevation of liver enzymes
- infection

Venipuncture: Every attempt will be made for whole blood collection to coincide with intravenous catheter placement and therefore, will be no additional risks from breaches of the skin with a needle. However, for some study participants, research-only venipuncture will occur. To reduce the risks (pain, bleeding, infection, and bruising), we will limit the number of venipunctures to obtain the blood sample to two attempts. Blood will be collected by persons experienced in drawing blood from infants and children. There is a very small additional risk of syncope associated with phlebotomy. Known risks associated with peripheral blood sampling are:

- pain
- bruising
- fainting (rare)
- infection (rare)

MRI: MRI is generally considered to be a safe, noninvasive diagnostic imaging modality. Known and potential discomforts or hazards, as stated in the suggested guidelines for the operation of clinical MRI systems established by the FDA, are associated with static magnetic field, radiofrequency magnetic field, and gradient magnetic field. The MRI scanning may induce few, if any, tangible risks in this study.

The 1.5T static magnetic field strength of the MRI scanner is below the 4.7T limit for clinical diagnostic MRI scanners set by the FDA guidelines. The FDA has concluded that magnetic field below 4.7T does not by itself impose a risk to human subjects. In short, the FDA has approved the use of magnetic field strengths of up to 4.1T for MRI scanning of humans in the research environment. While there is no biohazard associated with exposure to static magnetic fields, there are safety concerns related to ferromagnetic attraction.

The radiofrequency magnetic field used in MRI can induce heating in the subject.

The gradient magnetic field can induce peripheral nerve stimulation in the subject if the rate of change of the gradient magnetic field is too high.

The use of gradient magnetic fields generates MRI scanner noise. This noise level is dependent on the rate of change of gradient magnetic field in a given pulse sequence. Discomfort may occur due to noise produced by the MRI scanner.

Oral contrast for the MRI will be used. This includes, but may not be limited to, Breeza®, a flavored beverage that is necessary to evaluate bowel inflammation for patients with CD. Breeza® is sugar-free, gluten-free and generally considered safe (manufactured by Beekley Corporation, Bristol CT). Breeza® does contain sorbitol and mannitol which may cause diarrhea in some patients.

Known risks associated with MRI are:

- scanner (loud) noise
- ferromagnetic attraction

- diarrhea from oral contrast

2.3.1.1 ADEQUACY OF PROTECTION AGAINST RISKS:

The risks associated with MRI scanning will be addressed with the following actions:
Subjects will undergo routine screening to determine if there is any contraindication to MRI. Assuming there is no contraindication, the planned research MRI protocol is without known risk. Standard MRI procedures will be followed to minimize injury risk due to ferromagnetic projectile object(s).

MRI scanning will be performed using techniques that are substantially similar to techniques used to image other non-bowel parts of the body. FDA limits for dB/dT, specific RF absorption rate (SAR) and acoustic noise will not be exceeded.

1.5T and 3T magnets are approved by the FDA. There is no known biohazard associated with short-or long-term exposure to its magnetic field strength. MRI of the abdomen and pelvis is 1.5T or 3T is commonly performed at CCHMC in children of all ages and adults. The safety of MRI, particularly with respect to the lack of ionizing ration, is well-known.

The MRI scanner will be operated by certified technologists that have been trained to properly use the MRI scanner. These technologists also undergo training in the proper conduct of research.

The safety hazard associated with the attraction of ferromagnetic objects in the MRI environment is well-known in the radiology community and safety programs have been created to train individuals how to remain safe in this environment. MRI safety training will be required for all clinical and support staff participating in this study. Additional safety precautions include subject questionnaires and interviews

FDA guidelines regarding SAR require that the subject's core temperature rise be less than 1 degree Celsius. In the absence of core temperature monitoring equipment, the manufacturers have continued to use the previously established FDA limits of 2 W/Kg (average) and 8 W/Kg (peak). The system limits the SAR to levels at or below the conservative FDA limit for routine imaging applications: 1 W/Kg. In order to monitor this value, the RF energy at the output of the amplified is measured over a period of 10 seconds. In addition to the average output power, the peak value is also monitored. In the event that one of these values is exceeded, the transmitter power supply is turned off automatically within 3 to 5 seconds. These measures ensure that the system is well within the current FDA regulations on SAR.

The FDA suggested limit for the rate of change of magnetic field (dB/dt) is 20T/sec. This conservative limit is maintained by the system on all three gradients. The scanner measures the gradient currents in time steps of 100 microseconds. In the event that the maximum allowed values are exceeded, a signal is given to the operator console, and the scan cannot be initiated. The operator must reduce the gradient strengths by increasing the slice thickness and/or reducing acquisition matrix sizes before the scan can proceed.

Ear plug and/or earmuffs will be used for sound isolation based on institutional protocols.

Breeza® will not be given to any participants with a known allergy to any of the labeled ingredients.

2.3.2 KNOWN POTENTIAL BENEFITS

Based on results of previous studies, subtherapeutic levels of infliximab during induction were found to be strongly associated with early and late treatment failure.[7, 12, 16, 23] Therefore, personalized dose selection utilizing the individual patients inflammatory burden (assessed with blood biomarkers) and PK modeling may not only increase the rate of treatment response during induction, but optimized dosing may also improve drug durability by sustaining adequate drug exposure and minimizing the development of neutralizing antibodies.

Results of this study will provide invaluable data regarding whether model-informed dosing of infliximab is safe, feasible and effective at obtaining the targeted exposure during therapy. This knowledge will inform the design and sample size of a future, larger comparative effectiveness clinical trial. This new knowledge will be utilized to improve clinical practice.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We anticipate that the risks that participants will be exposed to during this study will be mild to moderate.

The study will mitigate risks related to model-informed infliximab dosing by assembling experienced gastroenterologists who are familiar with the profile of adverse events in this patient population to oversee the study (Medical Monitor).

Risks related to venipuncture will be mitigated by ensuring the activity is performed by expert personnel who are experienced in the care of pediatric patients.

The potential benefits of study participation outweigh the potential risks to participants.

3 OBJECTIVES AND ENDPOINTS

Table2: Primary and secondary outcomes

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Obtain data regarding safety and feasibility for the optimal dosing strategy to test in a future, larger clinical trial	**SAFETY:** Adverse events (infusion reactions, rate of infections, and/or progression of gastrointestinal symptoms) and other possible drug reactions will be recorded and provided to the medical monitor.	The FDA-approved dosing schedule during induction and maintenance has been shown to be safe and effective for the treatment of pediatric CD (>6 years old). Doses >5 mg/kg up to <15 mg/kg every 4-8 weeks (during maintenance) are safe.[24, 25] Doses >15 mg/kg every 4 weeks or >20

Table2: Primary and secondary outcomes		
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		mg every 6 weeks were found to be associated with an increased risk of adverse events.[22]
	FEASIBILITY: *Enrollment and completion*: We will evaluate the rate of recruitment including the number of patients that complete the study. We will evaluate the rate of patient adherence to stool and blood sample collections.	The pilot study will provide valuable information for patient recruitment strategies and methods to assure adherence to biospecimen collection.
	Usability: RoadMAB will generate recommended starting doses (mg/kg) during induction along with doses and dosing intervals during maintenance. We will evaluate rate of physician adherence to this recommendation along with explanation for non-adherence. We will also record 3rd party payer denials for recommended doses and/or dose intervals.	Insurance coverage for higher doses is variable and dependent on multiple factors. Prior to conducting a larger clinical trial, this pilot will inform strategies for future coverage of medication costs. This pilot study will provide additional opportunities for the RoadMAB Dashboard design team to better understand physician prescribing practices and opportunities to distribute evidence based practices.
	EFFICACY: Primary: Rate of achieving infus3 (V4) infliximab concentration between 18-24 µg/ml as a dichotomous outcome.	We have recently published infliximab induction targets that were associated with therapeutic trough values at the first maintenance dose.[12] The primary efficacy endpoint for the pilot is to investigate the accuracy of the Dashboard to achieve the desired drug exposure as well as rates of biochemical remission in patients receiving optimized drug exposure.

Table2: Primary and secondary outcomes		
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary		
Evaluate the accuracy of infliximab concentration targets	**EFFICACY**: Secondary: 1. Median difference of infus3 (V4) levels between cases and controls (historic controls that were previously enrolled and received ALD infliximab during induction. 2. Incidence of achieving infus2 (V3) level between target range of 26-34 µg/ml as a dichotomous outcome. 3. Median difference of infus2 (V3) levels between cases and controls. 4. Rates of achieving maintenance targets infus4-6 (V5-7) between 5-10 µg/ml. 5. Rate of development of anti-infliximab antibodies at any infusion between cases and controls. 6. The proportion of patients in clinical response and remission at infus4 (V5) and infus6 (V7). **Clinical response**: improvement in baseline wPCDAI by >17.5 or a wPCDAI<12.5 **Clinical remission (CR)**: wPCDAI <12.5 and off corticosteroids. 7. Rate of sustained remission: wPCDAI <12.5 and off	The results of these outcomes will provide sample size and power calculations for our future trial.

Table2: Primary and secondary outcomes		
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	prednisone for all visits from infus4 (V5) to infus6 (V7). 8. The proportion of patients in biochemical response and remission at infus4 (V5) and infus6 (V7) **Fecal calprotectin response:** ≥50% improvement in fecal calprotectin.[26] **Fecal calprotectin remission:** fecal calprotectin <250 µg/g. 9. Rate of transmural ileal, colonic and total bowel healing at infus6 (V7) by MRI. **Ileal healing**: ileum subscore stage 0 (score = 0) **Colonic healing**: all segments of colon subscore stage 0 (score = 0). **Total bowel healing**: total ileum and colonic subscore is not greater than stage 0 on either individual score.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesize that model-informed infliximab dosing that accounts for individual drug clearance with routine blood biomarkers to inform the starting infliximab dose will more accurately achieve the targeted drug exposure during induction than ALD in patients with moderate-to-severe Crohn's disease.

To test this hypothesis, we will conduct a prospective, single-center pilot study. This study will primarily include the **intervention cohort**. This cohort includes patients, age 6-22 years old who have been diagnosed with CD, are naïve to anti-TNF medications and are scheduled to start infliximab (or infliximab biosimilar).

In order to test additional (secondary) outcome measures, this study will also include an **observation (comparison) cohort**. This cohort includes patients (age 6-22 years old) who were diagnosed with CD, were anti-TNF naïve and have previously received ALD (5 mg/kg) infliximab during induction at CCHMC (IRB 2016-2046; 2017-1987). Additionally, this comparison cohort has had biospecimens (blood and stool) previously collected to compare drug concentration levels along with the various clinical and biochemical treatment outcomes.

The intervention includes utilizing Clinical and Patient Decision Support Software (RoadMAB^{TM}) that will guide the selection of the **first infliximab dose** followed by **subsequent infliximab dose and dosing interval during the maintenance phase**.

During induction, three infusions will occur at 0, 2 and 6 weeks, respectively. The RoadMAB^{TM} dashboard will utilize PK modeling software to provide an infliximab starting dose recommendation (range of 5-12 mg/kg) based on the patients biochemical profile (weight, serum albumin level, sedimentation rate [ESR], neutrophil CD64 activity ratio [nCD64] and prednisone exposure). For RoadMAB^{TM} to perform the most accurate dose calculation with Bayesian estimation, a minimum of patient weight, baseline serum albumin and nCD64 will be required for this study. As noted, dosing frequency (weeks) during induction will not be altered during this study.

For dose selections following induction (maintenance phase), we have found therapeutic targets are more reliably achieved when all covariates (weight, nCD64, serum albumin and presence of drug antibodies) are available. RoadMAB^{TM}, however, utilizes only available data to formulate a dose recommendation (it does not impute missing data). Following the first three doses, the clinician will be informed of their patients PK profile within the RoadMAB^{TM} program and with a shared document (paper). RoadMAB^{TM} will provide additional dosing recommendations after each infusion (based on the latest drug concentration measures and blood biomarkers) with the final dose and interval selected by the treating physician.

As the treating physician may alter dose and frequency for a number of reasons, an important endpoint is the rate the treating physician utilizes the Dashboard's dosing recommendation with further documentation to be recorded for reasons of non-adherence.

Every effort will be made to have the study visits coincide with a clinic visit or an infliximab infusion. If this is not possible, the subject will be seen at the Schubert Research Clinic (SRC), located on the first floor of the Clinical Sciences Pavilion (Location T.) Visit 2 and Visit 8 are optional research-only visits and not paired with a clinical infusion.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is one of the first studies to utilize population PK and blood biomarkers to inform the starting dose of infliximab. The study design is in response to multiple studies finding that early treatment response and maintenance of response to infliximab is strongly associated with infliximab exposure during induction.[7, 12, 27]

These studies will have a high impact in the field by providing critical safety and efficacy data. In addition, this pilot study will inform the sample size calculation for a comparative effectiveness trial to test the short and long-term efficacy of personalized dosing regimens.

4.3 JUSTIFICATION FOR DOSE

The current FDA-approved infliximab dosing schedule for induction (first 3 doses) is 5 mg/kg given at 0, 2 and 6 weeks. For patients with severe disease (significant inflammatory burden, low serum albumin), doses up to 20 mg/kg have been utilized.[2, 22, 28, 29] Previous data has repeated shown that infliximab 5 mg/kg during induction results in significant subtherapeutic levels in pediatric CD,[12, 30] while physicians routinely utilize patient biomarkers such as serum albumin to individualize treatment regimens to account for increased drug clearance in clinical practice. In fact, in our real-world infliximab PK study with 66 CD patients enrolled, only 33.3% of those enrolled received the ALD induction regimen (not published). The median starting infliximab dose was 6 mg/kg with a range (min-max) of 4.1 to 12.1 mg/kg.

However, empiric (off-labeled) dosing without consideration of individual drug clearance that PK modeling can provide may increase the risk of developing supra-therapeutic concentrations with a relative increase in the risk of adverse events.[22] Although influenced by a single patient, Hendler et al. found that doses >2.5 mg/kg/week (such as >15 mg/kg every 4 weeks or 20 mg/kg every 6 weeks) was associated with a higher rate of a serious infection.[22]

Importantly, based the available safety data for off-labeled infliximab dosing,[22] the RoadMAB™ Dashboard is enhanced to only provide dosing recommendations that range from 5-12.5 mg/kg with rounding up to the nearest 100 mg (each infliximab vial is supplied as 100 mg). **The PI will oversee each prescribed regimen to ensure compliance with this recommendation.**

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all study visits including the last study visit as shown in the Schedule of Activities (SOA, Section 1.2.) or has discontinued infliximab before week 26.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Written informed consent form from the patient (≥18 years old) or from parent/legal guardian if patient is <18 years old.
2. Written informed assent form from patient ≥11 years old.
3. Age criteria: ≥6 years to ≤22 years of age.
4. Diagnosis of Crohn's Disease
5. Starting infliximab (or biosimilar)
6. Anti-TNF naïve (never received infliximab, adalimumab, golimumab, certolizumab or anti-TNF biosimilar)
7. Fecal calprotectin >250 µg/g or fecal lactoferrin >10 µg/g (up to 6 weeks prior to starting infliximab) or endoscopic evidence of active Crohn's disease (up to 90 days prior to starting infliximab)
8. wPCDAI >12.5 (up to 6 weeks) prior to the first infliximab infusion
9. Negative urine pregnancy test for ALL female subjects
10. Negative TB (tuberculosis) blood test

5.2 EXCLUSION CRITERIA

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

1. Diagnosis of ulcerative colitis or inflammatory bowel disease-unspecified
2. Prior treatment with infliximab, adalimumab, certolizumab or golimumab (or anti-TNF biosimilar)
3. Active or prior evidence in past 12 months of internal (abdominal/pelvic) penetrating fistula(e)
4. Active intestinal stricture (luminal narrowing with pre-stenotic dilation >3mm), intra-abdominal abscess or perianal abscess
5. Active Clostridium difficile infection or other known bacterial/viral gastroenteritis in last two weeks
6. Current ileostomy, colostomy, ileoanal pouch, and/or previous extensive small bowel resection leading to short bowel syndrome
7. History of autoimmune disease (including autoimmune hepatitis, primary sclerosing cholangitis, thyroiditis, psoriasis or juvenile idiopathic arthritis)
8. Treatment with another investigational drug within four weeks.
9. Treatment with intravenous antibiotics within four weeks.
10. Planned continuation of 6-mercaptopurine or azathioprine (Imuran) during study.
11. Planned continuation of methotrexate during study.
12. Treatment with intravenous corticosteroids within two weeks.
13. Currently pregnant, breast feeding or plans in next 12 months to become pregnant
14. Inability or failure to provide informed assent/consent

5.3 LIFESTYLE CONSIDERATIONS

None.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but do not receive the study intervention. In order to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities, the following information about screen failures will be collected:

- Demographics
- Reason for being defined as a screen failure
- Any serious adverse event (SAE)

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects meeting Inclusion/Exclusion Criteria will be enrolled from the CD population served by CCHMC. CCHMC provides care to >800 children and young adults with IBD. The CD population is approximately 520 patients. Over the last 5 years, our center has diagnosed 50-63 CD patients each year.

Over the last year (2019), approximately 60 CD started infliximab. We anticipate that approximately 50-75% of eligible subjects would agree to participate, providing a pool of >20 subjects per year. We anticipate enrollment will be complete in two years.

Patients who meet these inclusion criteria may be identified from multiple reports. Each week, the IBD team of physicians performs population management through ImproveCareNow (ICN). Patients are also identified by the nurse (RN) and medical assistant (MA) assigned to all new biologic (anti-TNF) starts for insurance prior-authorizations. Finally, the research team is also notified of potential study participants by the team members (administrative assistants) who schedule each infliximab infusion at our center (Burnet and Liberty campuses).

All eligible patients will then be contacted at clinic visits or by phone to discuss study participation before they start infliximab (or infliximab biosimilar). We anticipate enrolling 1-2 patients per month and therefore completing enrollment over 24 months, allowing for up to 10% drop-out. The anticipated racial and ethnic composition will reflect the demographic characteristics of CD patients at CCHMC. Children are considered to be vulnerable populations due to being unable to provide consent for their participation. To mitigate this, we will seek their assent to participate if ≥11 years old.

The study coordinators will contact the patients by phone prior to each required study visit.

The study will provide a compensation for participation in the study as detailed below:

- Visit 1: $40
- Visit 2: $25
- Visit 8: $75 (includes optional MRI)
- Each infusion laboratory collection: $15 for the infusion visit
- Each stool sample provided (up to 4): $25 each.

Potential Problems and Alternative Approaches. Over 500 CD patients are cared for at CCHMC and the concept of personalized dosing to maximize efficacy is wanted not only by physicians to improve outcomes[19], but is also desirable to CD patients. Therefore, the study is not likely to be limited by low enrollment. However, if enrollment goals are not being met, we can consider adding additional pediatric academic centers including Nationwide Children's Hospital or Connecticut Children's Medical Center based on the PI's previous research collaboration with these centers.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Infliximab is a recombinant chimeric immunoglobulin (Ig)G1 monoclonal antibody (mAb) that neutralizes the biologic activity of soluble and membrane-bound tumor necrosis factor-α (TNF) and is conventionally dosed at 5 mg/kg at 0, 2, and 6 weeks during induction followed by 5 mg/kg infusions every 8 weeks during maintenance.[31] Despite the universal practice of weight-based dosing (starting at 5 mg/kg) at routine intervals, there are limited infliximab PK and pharmacodynamic (PD) studies in children.[13] Moreover, studies have found that >50% of patients

will require a dose intensification (empiric dose adjustments up to 10-15 mg/kg) to maintain therapeutic efficacy.[31, 32]

We and others have found children frequently require dose intensifications (both dose and dose interval) to maintain steroid-free clinical remission and to reduce drug immunogenicity (auto-drug antibodies).[14, 19, 30] There is emerging evidence that personalized dosing regimens informed by pTDM to assess individual drug clearance leads to improved long-term outcomes by prolonging drug durability.[6] Therefore, the prevalence of pediatric and young adult CD patients receiving "off-label" infliximab dosing regimens to maintain target drug concentrations continues to increase.[14]

The study intervention includes utilizing Clinical and Patient Decision Support Software (RoadMAB™ Dashboard) to guide the selection of the first induction dose to accurately achieve a 3rd dose (week 6) drug concentration between 18-24 µg/ml and subsequently provide maintenance dose and dosing interval recommendations to sustain infliximab concentrations 5-10 µg/ml following induction.[33, 34]

6.1.2 DOSING AND ADMINISTRATION

As noted, the starting FDA-approved dose for infliximab is 5 mg/kg. We and others have found ALD greatly underestimates individual drug clearance. Therefore, this study will look to optimize infliximab exposure with personalized dosing recommendations.

Briefly, the RoadMAB™ Dashboard is a real-time decision support system that incorporates the population PK model with Bayesian estimation to achieve personalized dosing regimens at the point of care with a PK software program (MWPharm++, MEDIMATICS, *http://www.medimatics.net/projects/mwpharm*). In contrast to off-label dosing schemes informed by "expert-opinion," Bayesian systems select an optimal starting dose to achieve the *targeted concentration* for an *individual patient*. As the targeted concentration changes during induction as compared to the maintenance phase, RoadMAB™ will provide dosing recommendations at four time points during this study (as shown in Figure2).

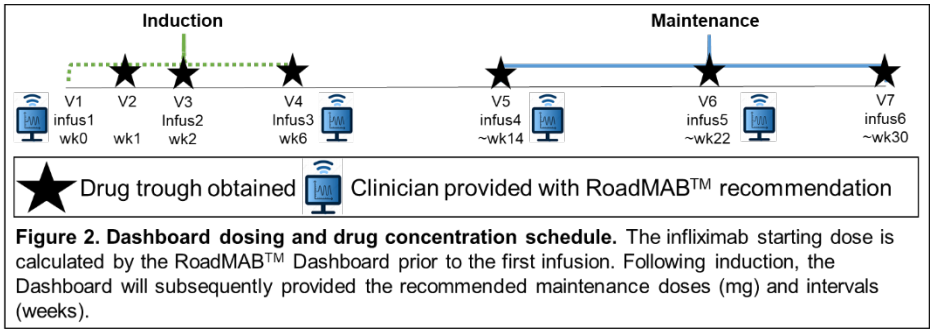

Figure 2. Dashboard dosing and drug concentration schedule. The infliximab starting dose is calculated by the RoadMAB™ Dashboard prior to the first infusion. Following induction, the Dashboard will subsequently provided the recommended maintenance doses (mg) and intervals (weeks).

Infliximab clearance has been shown to be influenced by the patients weight, serum albumin, ESR, nCD64, prednisone use and the degree of antibody to infliximab concentration.[14] With these aforementioned covariates entered into the dashboard, RoadMAB™ provides the clinician with a graphic display of up to three dosing regimens and the subsequent predicted infusion3 drug concentrations (Figure3, *below)*. Additionally, the clinician can also toggle through other infliximab doses and visualize the predicted drug concentration. For this study, the **infliximab target concentration during induction is 18-24 µg/ml prior to the 3rd dose and 5-10 µg/ml prior to each maintenance dose.**[7]

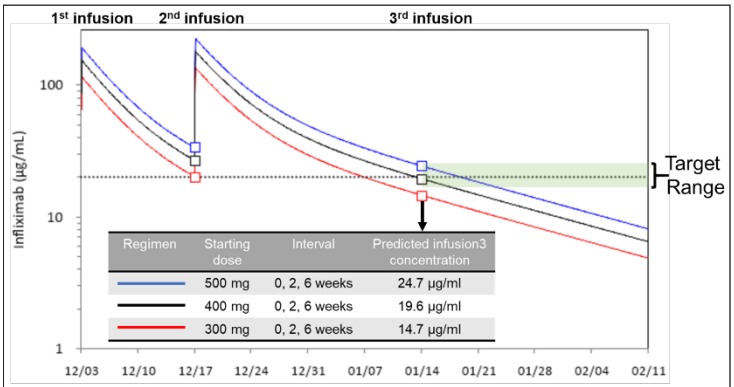

Figure 3. Dashboard dosing options and predicted drug concentrations. The RoadMAB™ dashboard provides a visual representation of predicted infliximab concentrations at infusion3 based on different starting doses. The interactive dashboard also allows the physician to simulate various starting doses to attain the targeted infusion concentration. Final dose selection is at the discretion of the treating physician.

Timing of TDM and utilization of RoadMAB™ to inform individual dosing strategies are highlighted in Figure2 (above). Serum samples to perform drug concentration monitoring are collected on the same day as the infliximab infusion and one week after the first induction dose. All serum samples will be sent to Esoterix, LabCorp specialty lab (Calabasas, CA) with results sent to the data coordination center. For the pilot study, all drug concentrations, antibody to infliximab concentrations, and covariates will be entered by the CRC into the current version of RoadMAB™. Data accuracy will be assured by a separate study coordinator and the PI. Future versions of RoadMAB™ are planned to extract these data directly from the EMR.

Dose and dosing interval selection.

Induction: For RoadMAB™ to perform Bayesian estimation during induction, a minimum of the patient's weight (in last 30 days), serum albumin and nCD64 will be required for the study. Additional covariates will be entered into the model, if pertinent (prednisone use) or are available (ESR). ATI cannot occur prior to the first dose and therefore will not be entered into the induction model. Following data extraction (results of biomarkers) the treating physician will be alerted of the dosing recommendations made by RoadMAB™ and the study team. The treating physician will then enter the infliximab starting dose into the EPIC EMR infusion plan as per policy at CCHMC.

Maintenance: For RoadMAB™ to perform Bayesian estimation prior to the first maintenance dose and during maintenance, a minimum of the patient's weight (in last 30 days), serum albumin, nCD64, previous infliximab dose (mg), date/time of last administration and the latest results of TDM will be required for this study. With frequent testing and real-world patient simulations, we have found therapeutic targets are more reliably achieved when all covariates (ESR, serum albumin, nCD64, prednisone use and presence of anti-drug antibodies) are available. RoadMAB™, however, utilizes only available data to formulate a dose recommendation (it does not impute missing data). Following data extraction (results of biomarkers) and at a minimum of **two weeks** prior to the next infliximab infusion clinicians will be alerted of the dosing recommendations made by RoadMAB™ and the study team. The treating physician will then enter the infliximab dose and interval into the EPIC EMR infusion plan as per policy at CCHMC.

As this is a pragmatic clinical trial and the study team can not ensure timely third-party insurance coverage of dosing recommendations, the treating physician will continued to be notified of the RoadMAB™ dosing recommendation throughout the study period to improve the likelihood of achieving the aforementioned drug concentration targets.

Importantly, based on previous safety data for infliximab,[22] the RoadMAB dashboard is enhanced to only provide dosing recommendations that range from 5-12.5 mg/kg with rounding up to the nearest 100 mg (each infliximab vial is supplied as 100 mg). The center PI will oversee each prescribed regimen to ensure compliance with this recommendation. However, the final dose and interval are left to the discretion of the treating physician.

Individual and Overall Study Stopping Rules.

Although infliximab is FDA-approved to be given at 0, 2, 6 weeks for induction and every 8 weeks during maintenance phase of therapy, clinicians frequently prescribe variable off-label doses and frequencies. Therefore, any patient that receives an infusion two weeks earlier than the FDA-approved induction schedule (first 3 doses) will be considered a treatment failure and evaluated in an intention-to-treat analysis using a model-predicted infusion three (week6) trough concentration. Once a treatment failure, no further dosing strategies will be presented for that individual patient. During maintenance, infusions every four-eight weeks will be permitted. Patients requiring doses >15 mg/kg every 4 weeks will be considered a treatment failure and the dashboard will no longer be utilized for dosing recommendations (study participation is complete). These patients will be evaluated in the intention-to-treat analysis.

Additionally, individual patients will be discontinued from this Dashboard study if rescue therapies are used in the event of loss of infliximab response. Rescue therapies include >3 infliximab induction infusions before week6, hospitalization for IV corticosteroids, hospitalization for severe infection or hospitalization for any surgery.

If the participant meets the stopping criteria, we will continue to record and collect subjective outcome measures and biochemical specimens up until week 26 for an intention-to-treat analysis.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Infliximab is stored and processed for administration by the CCHMC pharmacy. All infusions will occur at a CCHMC facility (Burnet or Liberty campuses).

Infliximab doses and frequency are entered in the electronic medical record (EMR, Epic) with an infusion plan (order). Patients will not be eligible for infliximab home infusions during this study.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The manufacturer of infliximab is:

Manufacturer Information:
Janssen Biotech, INC
800 Ridgeview Drive
Horsham, PA 19044
U.S. License No 1864

The manufacturer of infliximab-dyyb is:

Manufacturer Information:
Celltrion, INC
23, Academy-ro
Yeonsu-gu, Incheon, 22014, Republic of Korea

U.S. License No. 1996

Distributed by:
Pfizer Labs
Division of Pfizer, Inc.
New York, NY 10017

The manufacturer of infliximab-abda is:

Manufacturer Information:
Samsung Bioepos Co., Ltd
107, Cheomda-daero
Yeonsu-gu, Incheon, 21987, Republic of Korea
U.S. License No. 2046

Distributed by:
Merck Sharp & Dome Corp
A subsidiary of Merck & Co., Inc.
Whitehouse Station, NJ 08889

The manufacturer of infliximab-axxq is:

Manufacturer Information:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320

6.2.3 PRODUCT STORAGE AND STABILITY

Per the manufacturers, single use vials contain 100 mg of infliximab for final reconstitution volume of 10 ml. Product must be refrigerated at 2ºC to 8ºC. Do not use the medication beyond the expiration date located on the carton and the vial. Infliximab contains no preservatives.

6.2.4 PREPARATION

The treating physician will calculate the infliximab dose and order the selected dose into an infliximab infusion plan within the EPIC system. The CCHMC pharmacist will then prepare infliximab as directed by the package insert.

Following the preparation of the medication by the pharmacy:

1. Pre-medications are not necessary for the study but it is typical for patients to receive acetaminophen (10-15 mg/kg) PO 30 minutes prior to the infliximab infusion and/or diphenhydramine (0.5-1 mg/kg) PO 30 minutes prior to the infusion.
2. The infusion must be administered intravenously over a period of not less than 2 hours.
3. Prior, during and up to 30 minutes after the infusion, the patient is monitored for any infusion related adverse events.

4. If at any time during or after the infusion, the subject develops fevers, chills, pruritus, urticaria, chest pain, shortness of breath, symptomatic hypotension or hypertension or any other abnormal vital signs, the infusion is immediately stopped. For subjects at the Burnet campus, the gastroenterology team on call is notified. For subjects at the Liberty campus, the On-call Hospitalist for infusion reactions is notified. Whether the infusion is restarted or discontinued is then at the discretion of the on-call physician.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

No randomization will occur with the pilot and feasibility study.

6.4 STUDY INTERVENTION COMPLIANCE

We will obtain the actual infliximab dose prescribed by reviewing the electronic medical record. In our CRF, we will document whether the starting dose was different than ALD guidelines (5 mg/kg) and whether the selected dose (actually infused) differed from the dose recommended by the physician decision support tool, RoadMAB™.

6.5 CONCOMITANT THERAPY

Concomitant medications, including prescription medications, over-the-counter medications, and supplements will be recorded at all study visits. The following medications are not allowed – use of the drugs are cause for discontinuation from the study:

- IV antibiotics at the start of induction or during maintenance
- PO antibiotics after induction (after the 3rd dose)
- Immunomodulators including 6-mercaptopurine, azathioprine or methotrexate up to seven days before the first infusion
- Other investigational agents up to one month before the first infusion
- IV corticosteroids at the start of induction or during maintenance

Orally administered doses of corticosteroids (prednisone, prednisolone or budesonide) are permitted as long as they do not exceed >1 mg/kg or >40 mg daily.

6.5.1 RESCUE MEDICINE

Rescue medications in the event of infliximab non-response, will not be provided by the study sponsor. Participants with a treatment failure will be treated per the treating physician and will be discontinued from the dosing study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

If the study is prematurely terminated or temporarily suspended, the PI will promptly inform the CCHMC IRB, study sponsor (Crohn's and Colitis Foundation, Cincinnati Children's Research Foundation), medical monitor and provide the reason(s) for the termination or temporary suspension. Resumption of the study will not take place until the concerns related to the termination or suspension are addressed and satisfy the Sponsor, the medical monitor and the IRB.

If the study is prematurely terminated, a final visit will be scheduled for participants who are active in the study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant non-compliance with study intervention by the subject
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If 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.

Subjects who sign the informed consent or assent form and receive infliximab with/without the dose suggested by the Dashboard, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

A total of 20 subjects with CD that meet the inclusion/exclusion criteria will be enrolled.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

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

- The research coordinator will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- 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, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record or 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.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SAFETY AND FEASIBILITY ASSESSMENTS

The following assessments and procedures will be conducted to obtain safety data:

The major safety concerns for patients receiving anti-TNF biologics has been the risk of opportunistic infections and malignancy. As safety and feasibility are co-primary endpoints for this pilot trial, we will monitor all AE's regularly and we will work with a Medical Monitor to conduct interim analyses to detect any adverse safety signals. Many of the safety concerns, including malignancy are primarily long-term considerations that are beyond the duration of most clinical trials.

It is the responsibility of the Principal Investigator to oversee the safety of the study. The Principal Investigator and/or site staff is responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE).

8.1.1 DEFINITION OF AN AE

Recording of adverse events will begin at screening and monitored for during the entire study.

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 [a]).

Moreover, an AE is any unfavorable and unintended symptom, sign, illness or experience, temporally associated with the use of the study drug, which develops or worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:
- Results in study withdrawal
- Is associated with a SAE
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Leads to a change in infliximab dosing secondary to a supra-therapeutic trough level. A supra-therapeutic infliximab level is defined as a concentration >40 µg/ml at infusion3 (week 6) or any maintenance trough concentration >30 µg/ml.
- Is considered by the investigator to be of clinical significance

Preexisting Conditions
A preexisting condition is one that is present and documented at the screening visit. At baseline, any ongoing clinically significant abnormality should be recorded as a preexisting condition in the

CRF. Preexisting conditions should only be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

Anticipated (Disease Related) Events
As CD is a relapsing and remitting condition, and participants in the trial are recruited at a time of disease instability requiring initiation of a new treatment regiment, it is anticipated that many participants will have gastrointestinal symptoms or extra-intestinal symptoms (mouth sores, rashes, fevers, joint pains, and/or arthritis) during the study period. These symptoms may worsen, fail to respond or may worsen after an initial response and could lead to hospitalization, surgery and/or requirement of corticosteroids. Therefore, anticipated disease-related events will not need to be reports separately as AE's/SAE's but rather reported on the CRF's. Adverse CD-related Events are:

- Abdominal mass
- Fistula (enterocutaneous, entero-entero, perirectal, recto-vaginal, or other Crohn's-related fistula)
- Abscess (abdominal or perirectal)
- Intestinal perforation
- Intestinal obstruction
- Abdominal pain
- Fatigue
- Abdominal tenderness
- Abnormal loss of weight
- Growth failure
- GI bleeding related to CD
- Diarrhea
- Dehydration thought to be due to CD flare
- Stool urgency
- Nausea/vomiting thought to be due to CD or complications of CD
- Arthralgia/arthritis
- Uveitis/episcleritis
- Ankylosing spondylitis
- Cutaneous manifestations of CD (pyoderma gangrenosum, erythema nodosum)
- Abdominal surgery or complications of abdominal surgery due to CD
- Anemia thought to be due to CD

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an AE if any one of the following conditions are met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

8.1.2 DEFINITION OF A SERIOUS AE

AEs are classified as serious or non-serious. A serious AE is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs a hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect (in the offspring of a study participant)
- An important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

Hospitalization, Prolonged Hospitalization or Surgery
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise below. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- As discussed above in the Anticipated AE section, data regarding failure to respond and/or worsening of CD are collected as part of study outcomes and are captured in the CRFs. These anticipated disease-related events will not need to be reported separately as AEs/SAE's. However, if the PI believes the frequency or severity of a Crohn's exacerbation or complication deem it to be a SAE, then this can be reported at the discretion of the PI. All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

8.2 PREGNANCY

Any pregnancy that occurs during the study and up to 16 weeks following the last study dose must be reported on a clinical trial pregnancy report form within 2 weeks of learning of the event (self-report) and recorded as an AE. This will include any pregnancy in a female trial participant. The pregnancy must be followed in order to confirm the outcome and health status of the mother and child.

Maternal and fetal pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE per the definitions above and the instructions in the following section. Spontaneous miscarriage must be reported as a SAE.

8.3 RECORDING OF AE'S AND SAE'S

On enrollment in the study, subjects will be instructed to contact the investigator if a SAE occurs, so that appropriate measures can be taken. At each contact with the subject, the investigator must seek information on AEs by specific questioning and, as appropriate, by examination.

All AEs occurring from the date of the first dose of infliximab (or biosimilar) and for 7 days following the final dose of study medication, must be recorded. Any SAE that occurs within 14 days following the final dose of study medication should be recorded and reported according to IRB guidelines.

Information on all AEs will be recorded in the source document, and also in the appropriate AE module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document.

All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) per the reporting timelines noted above.

8.3.1 RECORDING AND EVALUATION OF AES

The following will be documented for each AE:

- Nature of the event
- Start date and stop date
- Severity
- Relationship to study treatment (causality)
- Action taken
- Outcome
- Expectedness
- Seriousness (per SAE definition)

Severity

The severity is evaluated by the investigator as follows:
Mild - event/symptom does not interfere with normal daily activities (Grade 1)
Moderate - event/symptom interferes with normal daily activities (Grade 2)
Severe - event/symptom prevents normal daily activities (Grade 3 or 4)

Relationship to Study Treatment

The relationship is evaluated by the investigator as follows:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related"

soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness
An AE is considered “unexpected” if the particular event/symptom is not listed as a common adverse reaction in the package insert of the of the study drug. An AE is also considered “unexpected” if the particular event/symptom occurs at a greater severity and/or specificity than listed in the package insert.

For the purpose of this trial, all expected AEs will be indicated on the AE CRF. The determination of the expectedness for SAEs will be made by the medical monitor based upon the appropriate package insert for infliximab.

The following will be considered expected AEs:
The most common adverse reactions caused by infliximab include:
- Infections (e.g. upper respiratory, sinusitis, and pharyngitis)
- Infusion-related reactions
- Headache Elevation of liver enzymes

In addition to the items documented for each AE (see section 8.3.1), the following will be documented for each SAE:
- Brief description of the event
- Category of the event
    - Death,
    - Life-threatening
    - Hospitalization
    - Disability / incapacity
    - Congenital anomaly / birth defect
    - Intervention required to prevent permanent impairment
    - Other (per the investigator’s discretion)
- Intervention taken
- List of relevant tests, laboratory data, history, including pre-existing medical conditions

8.4 MANAGEMENT OF AES

8.4.1 GENERAL

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious AEs that are still ongoing at the end of the study period must be followed up to determine the final outcome.

8.4.2 MANAGEMENT OF ABNORMAL LABORATORY RESULTS

All laboratory values outside of the normal range will be repeated if judged appropriate by the Primary Investigator and/or Medical Monitor to ensure the validity of the abnormal result. The investigator will document all laboratory values on the relevant page of the CRF and will assess the etiology of the clinically relevant abnormal laboratory values.

Monitoring of abnormal liver enzymes - If the AST or ALT (LFT's) increase ≥2 times the upper limit of normal (2x ULN) after the start of the study medication, the investigator will repeat the measurement of LFT's after 2-3 weeks. If LFTs normalize, the patient will continue with current dose of infliximab, however, if LFTs remain 2x ULN at the second laboratory draw, the dose of infliximab should be reduced to 5 mg/kg (rounded to nearest 100 mg) if the participant was receiving a dose of >7.5 mg/kg. If the participant was receiving a dose of infliximab <7.5 mg/kg, then another check of LFT's should be performed within 4 weeks. If the LFT's normalizes or return to less than 2X ULN, then patient should remain on the current dose and further laboratory monitoring of the LFT's should be performed in the setting of the routine laboratory draws in the context of each infusion. If LFTs remain 2x ULN upon recheck, the participant must undergo further investigations which may require additional laboratory testing (infectious causes of hepatitis, investigations for autoimmune causes of hepatitis and/or other metabolic disorders of the liver).

8.4.3 PREGNANCY

All female subjects will have a urine pregnancy done before starting infliximab as pregnancy is an exclusion for this study. Any confirmed pregnancy during the study will result in an urgent clinic visit to the primary treating physician to discuss safety of infliximab during pregnancy. Infliximab has been shown to be safe during the first and second trimesters of pregnancy,[35] with a discussion with the clinician for continued use during the final trimester. Therefore, the patient will be removed from the study but whether they will continue on infliximab will be discussed with the participant's primary physician, the PI and the Medical Monitor.

All pregnancies will be followed in order to confirm the outcome and health status of the mother and baby.

8.5 REPORTING OF SERIOUS AES

In addition to recording all AEs and SAEs in the CRF, the PI must conform to the AE reporting timelines, formats and requirements of the IRB (institutional review board), and any other

regulatory entity to which they are responsible. At a minimum those events that must be reported are those that are:

- Related to study participation
- Unexpected
- Serious or involve risks to subjects or others
- Not deemed to be a consequence of the patient's underlying CD

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Any SAE (including death, irrespective of the cause) occurring during or for up to 14 days after the end of the study must be reported without delay, i.e. within 24 hours. The Serious AE (SAE) form must be completed by the PI, and sent by facsimile to the study Safety Medical Monitor:

Within the following 48 hours, the PI must provide further information on the SAE or the unanticipated problem in the form of a written narrative. This should include a copy of the completed SAE form, and any other diagnostic information that will assist the understanding of the event, including de-identified medical and/or hospital records, where applicable. Significant new information on ongoing SAEs should be provided promptly to the study sponsor. The investigator will keep a copy of this SAE form on file at the study site.

The Safety Medical Monitor will perform a regular assessment of the number and type of SAEs.

8.5.1 INVESTIGATOR REPORTING

The PI is responsible for safety reporting to the central IRB within 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

8.6 FEASIBILITY EVALUATION

8.6.1 THIRD PARTY COVERAGE

As noted, infliximab dosing is labeled as 5 mg/kg to be given at 0, 2, 6 and then 5 mg/kg every 8 weeks. Prior to the start of infliximab, prior authorization is required by the third party payer for all participants. As children with more severe Crohn's disease frequently require doses up to 15 mg/kg to achieve intestinal healing, RoadMAB™ will calculate a starting dose and present this dose to the treating physician. If the recommended starting dose is not covered by third party payer, every effort will be made to contact the payer for justification of off-label dosing. If the dose is still denied, the physician can then petition the payer a second time before the second or

subsequent maintenance doses. All outcomes related to insurance coverage are important treatment outcome measures that may result in changes in the study design for the subsequent research trials.

Additionally, studies have suggested that infliximab infusions <8 weeks may be more effective at achieve target concentrations and improved outcomes during maintenance. Therefore, the co-primary endpoint includes a feasibility outcome measure. Specifically, we will track the following within our CRF forms:

- Rate of Insurance approval for doses >7 mg/kg during induction
- Rate of Insurance approval for doses >7 mg/kg and/or frequency <8 weeks during maintenance

8.6.2 PHYSICIAN RESPONSE TO DOSING RECOMMENDATIONS

This is a pragmatic clinical trial. All starting and subsequent dosing regimens will be presented to the treating physician utilizing the RoadMAB™ Dashboard. However, the final dose and dosing interval (weeks) will remain at the discretion of the physician. If the treating physician does not follow the prescribed dose at the first infusion, the subject will continue in the study and subsequent dose recommendations will continue as described in Figure2 and presented to the treating physician. In the CRF, we will record prior to each dose:

- Rate of physician adherence to the dashboard dosing recommendation
- Reason(s) the recommendation was not followed

8.6.3 SUBJECT ADHERENCE TO LABORATORY COLLECTIONS

It is routine at CCHMC that all patients receiving infliximab infusions undergo laboratory assessments prior to starting infliximab and prior to each subsequent infusion. The following is a list of REQUIRED pre-infliximab laboratory and with each subsequent infliximab infusion assessments for inclusion in this study

1. CBC with differential
2. Albumin, AST, ALT
3. Neutrophil CD64 activity ratio (nCD64)

The following laboratory tests will be RECOMMENDED pre-infliximab and with each subsequent infliximab infusion:

1. Erythrocyte sedimentation rate (ESR)
2. GGT

The following laboratory tests will be required to receive subsequent (after infusion3) dashboard recommendations:

1. Infliximab concentration
2. Antibody to infliximab concentration

In this study, we will be collecting additional blood specimens prior to each infliximab infusion, 5-10 days after the first infusion (lab-only visit) and a blood collection 30-60 minutes following specific infliximab infusions (infusion1, infusion2, infusion3, infusion4, and infusion6). We will track subject's adherence to:

- Blood specimen collection prior to each infliximab infusion
- Blood specimen collection 5-10 days following the first infliximab infusion

- Rate of blood specimen collection 30-60 minutes following pre-specified infusions.

8.7 EFFICACY ASSESSMENTS

Table2 in Section 3.0 is an overview of the efficacy endpoints that we are exploring during this study. The primary efficacy outcomes are infliximab trough concentrations at week6 and during maintenance, clinical response, clinical remission, fecal calprotectin response, fecal calprotectin remission, and transmural healing (as defined by MRI of the abdomen).

The following assessments and procedures will be conducted to obtain efficacy endpoint data:

Blood Collection: Participant will have up to 20 ml of blood obtained prior to each infusion, 5-10 days after starting infliximab (V2), and up to 6 ml of blood obtained 30-60 minutes after infusion1, 2, 3, 4, 6. Aliquots of blood will be utilized by the Minar laboratory for biomarker discovery testing, the Cancer and Blood Diseases Institute Clinical Laboratories at CCHMC for neutrophil CD64 activity ratio and Esoterix (LabCorp specialty lab, Calabasas, CA) for infliximab concentration and antibody to infliximab concentration testing. The remaining blood will be centrifuged and the plasma placed in -80C for future biomarker testing.

Stool Sample Collection: Participants will collect stool samples at home the day before, or on the day of the infus1 (V1), infus3 (V4), infus4 (V5) and at study end Infus6 (V7). Participants will be asked to mail their stool sample with the provided stool collection materials to the CCHMC Minar Laboratory. If the participant brings to clinic or the infusion visit, the study coordinator will transport that sample to the Minar Laboratory for storage at -80C until batched for fecal calprotectin and lactoferrin testing can be completed. Additional stool will be stored for metagenomics and/or 16S sequencing and analysis. Shipping supplies, instructions, and mailing labels will be provided. Parents and subjects will be reminded (email or by phone) of the stool collections. All collection and shipping instructions including the shipping materials will be provided to the subject.

Fecal biomarkers: Fecal calprotectin will be measured using an ELISA kit with an inter-assay precision CV 6.6-14.5% (Buhlmann, Switzerland)[36] and fecal lactoferrin measured with ELISA (CV 7.9-16%, IBD-SCAN® TechLab, Blacksburg, VA).

16S Sequencing and Analysis: DNA will be subjected to 16S rRNA amplicon sequencing (V4 region, 2x175bp). Operational taxonomic unit (OTU) clustering and taxonomic assignment will be performed with the 16S bioBakery workflow built with AnADAMA2, which incorporates ea-utils and the UPARSE pipeline (version 8.1). Microbial taxonomy is based on the Greengenes 16S rDNA database (version 13.5). Samples will be subsequently filtered based on number of assigned reads (min 3,000 reads). Shotgun metagenomics sequencing with an average of 10,000,000 paired-end reads per sample (150nt per read), will be employed. Relative pathway abundance of each sample will be quantified by HUMaN v2.0.[37]

Demographics: Information related to participant age and gender will be collected as part of the review of medical records conducted for screening (see below). Race will be collected at Visit 1.

Plasma collection: Plasma will be obtained for neutrophil CD64 surface expression, soluble CD64, and future proteomic discovery testing. In addition to the nCD64 conducted by the CCHMC CLIA-certified Immunology Laboratory, the Minar Laboratory will determine a research Neutrophil CD64 Activity Ratio (NCAR): the expression of CD64 on neutrophils is analyzed by labeling

peripheral blood with CD64, CD163 (a monocyte marker), and CD45 (a pan-leukocyte marker) and analyzing the cells by flow cytometry (FACSCantos, BD Biosciences). The CD64 expression on neutrophils is reported as an activity ratio comparing the neutrophil CD64 mean fluorescence intensity (MFI) to the negative internal control (lymphocyte CD64 MFI). Soluble CD64: Human FCGRI/CD64 ELISA will be performed according to the manufacturer's manual (LifeSpan BioSciences, Seattle, WA). Additional laboratory testing: Routine labs at each infusion includes a complete blood count, CRP, ESR, serum albumin, ALT and AST. As ESR, albumin and CRP are vital to our analyses, if these are not ordered by the treating physician, the blood collected prior to each infusion will be sent to the CCHMC CLIA-approved laboratory for testing.

MRI abdomen: Obtaining serial abdominal scans is also another method to evaluate response to treatment as transmural healing (defined by abdominal imaging) has been associated with improved patient outcomes.[38] Therefore, we will provide the option to each participant to obtain an approximately 30 minute MR scan (using oral contrast, Breeza®, or other comparable product, or water) for all study participants. If the participant has previously had a MR scan for clinical purposes, we will use the results and images for this research study. We will utilize a validated radiographic severity scoring tool (MARIAs).[39] The MARIAs will be calculated by one central reader at CCHMC (Dr. Jonathan Dillman, an experienced radiologist who has published on MR use in pediatric CD[40]). The MARIAs is based on presence/absence of intestinal wall thickening, mural edema, fat stranding and ulcerations in each segment of the colon and distal ileum with total scores ranging from 0-30.[39] Although the diagnostic accuracy of the MARIAs has not been evaluated in children with CD, we expect the tool to perform equally well in this population as the MARIAs was shown to have excellent correlation with endoscopy based assessments in adult-onset CD.[39] A strong advantage of the MARIAs is that all components of the scoring can be evaluated with imaging sequences that do not require the use of paramagnetic contrast (such as gadolinium-based contrast agents).

MR Finding	Absent	Present
Intestinal wall thickening (>3 mm)		(x1)
Mural edema		(x1)
Perienteric fat stranding		(x1)
Ulcers		(x2)

A score is tabulated for each of the 4 segments of the colon (cecum/ascending, transverse, descending, and sigmoid/rectum) and the ileum. MARIAs scores >1 identified segments with active CD with 90% sensitivity and 81% specificity (AUC 0.91). MARIAs >2 detected severe lesions with 85% sensitivity and 92% specificity (AUC 0.94).

All MRIs will be reviewed by Dr. Dillman for any abnormalities. In the case that the research MRI shows new findings that may result in harm to the patient (i.e., an abscess), these abnormal findings will be reported to both the participant and treating physician. Otherwise, results of the research MRI will not be released to participants or their treating physician.

8.8 ADDITIONAL ASSESSMENTS

Prior to enrollment the following will be performed for screening purposes.

Review of Medical Records: Existing information about potential participants will be reviewed to determine:

- Age
- Gender
- Diagnosis
- Current medications
- Medication history
- Co-morbidities
- Allergies

A HIPAA Waiver will be requested from the IRB to allow for review of records preparatory to research.

The following assessments and procedures will be performed to determine eligibility for study participation and throughout the study to obtain safety data:

Physical Exam and Vital Signs: The physical exam conducted by the primary gastroenterologist at the last clinic visit will be recorded for this study. Infus6 (V7) will also include a physical exam conducted by the PI. If the participant is seen (or a visit scheduled) by the treating physician within four weeks of the study end date, the documented exam that occurred will replace the need for PI examination (study-only visit). Vital signs will be collected and will include temperature, heart rate, respiratory rate, and blood pressure. Weight and height will also be collected at these visits.

Urine Collection: Female participants who are capable of becoming pregnant will have a urine pregnancy test at the baseline visit.

Weighted Pediatric Crohn's Disease Activity Index (wPCDAI): We will utilize the wPCDAI to measure clinical disease activity. The wPCDAI has been validated in the pediatric CD population with well-established cut-points for clinical remission and relapse (Appendix).[41] The wPCDAI will be obtained prior to each infusion and at month 6 (end of study). To be study eligible, a wPCDAI a value >12.5 will be required prior (up to 6 weeks prior) to infusion 1.

Patient-reported Outcomes: Patient reported outcomes (PRO's) are direct responses from patients (or parent proxy) and convey important aspects of health status. PRO's can evaluate symptoms, signs, functional status and are a reflection of what is most important to patients about a condition or treatment. Additionally, PRO's are becoming increasing important endpoints for clinical trials and comparative effectiveness studies. To guide the design of a future RCT, we will also collect patient-reported outcomes of abdominal pain and stool frequency for all patients prior to each infusion and infus6 (V7, See Appendix A).

IBD Disability Assessment: We will assess for CD disability and quality of life using the IBD Disk tool while eliminating the sexual function question. This tool will be exploratory and therefore, optional to complete at enrollment and study completion. This will be collected from patients ≥12 years old and completed by the parent or subject.

Endoscopic Severity Score: To guide a future RCT trial which may require endoscopic assessments, the Simple Endoscopic Score-Crohn's Disease (SES-CD) and Physician Global Assessment-Colonoscopy Score (PGA-CS) will be tabulated in participants who undergone a clinically indicated colonoscopy within six months prior to enrollment by reviewing the previously recorded colonoscopy procedure (if available) that was securely saved on VaultStream. We will also record SES-CD and PGA-CS for any patients who undergo a clinically-indicated colonoscopy during this clinical study (Appendix B).

Fecal biomarkers: We will measure fecal calprotectin and/or fecal lactoferrin to assess mucosal inflammation. To be study eligible, the subject must have evidence of active inflammation by endoscopy (performed within the last 90 days) or a fecal calprotectin >250 µg/g/fecal lactoferrin >10 µg/g. If the subject is study eligible but has not had recent fecal calprotectin/lactoferrin obtained, we will ask the treating physician to order the respective fecal testing and processed in the CCHMC Clinical Laboratory. All costs/fees of the test will be paid by the study.

8.9 UNANTICIPATED PROBLEMS

8.9.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.9.2 UNANTICIPATED PROBLEM REPORTING

Unanticipated problems (UPs) will be reported to the sponsor, reviewing Institutional Review Board (IRB), PI and to the Medical Monitor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported in an expedited manner as outlined in Section 8.3.6 – SAE Reporting.
- Any other UP will be reported at the time of regularly scheduled reporting

8.9.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The occurrence of any unanticipated problem that changes the safety profile of the study shall be incorporated into a revised version of the informed consent document(s). The IRB will make a determination as to whether enrolled participants should be re-consented.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

We **hypothesize** *that model-informed infliximab dosing that accounts for individual drug clearance with routine blood biomarkers to inform the starting infliximab dose will be safe, feasible and more accurately achieve the targeted drug exposure during induction than as-labeled (routine) dosing.*

Aim 1: **Determine the safety and feasibility of utilizing a physician support tool (RoadMAB™ dashboard) to dose infliximab during induction and early maintenance.**

Primary Endpoint

B. Rate of AE and/or SAE's during the study

C. Rate of physician, subject and third party payer (insurance) adherence to Dashboard dosing recommendations

Aim 2: Test the performance of a physician support tool to achieve infliximab concentration targets.

Endpoint(s):

A. Rate of achieving infus3 (V4) infliximab concentration between 18-24 µg/ml[33] as a dichotomous outcome.
B. Median difference of infus3 (V4) levels between cases and controls (historic controls that were previously enrolled and received ALD infliximab during induction).
C. Rate of achieving infus2 (V3) level between target range of 26-34 µg/ml as a dichotomous outcome.
D. Median difference of infus2 (V3) levels between cases and controls.
E. Rates of achieving maintenance targets infus4-6 (V5-7) between 5-10 µg/ml.
F. Rate of development of anti-infliximab antibodies at any infusion between cases and controls.
G. The proportion of patients in clinical response and remission at infus4 (V5) and infus6 (V7).
    a. **Clinical response**: improvement in baseline wPCDAI by >17.5 or a wPCDAI<12.5
    b. **Clinical remission**: wPCDAI <12.5 and off corticosteroids
H. Rate of sustained remission: wPCDAI <12.5 and off prednisone for all visits from infus4 (V5) to infus6 (V7).
I. The proportion of patients in fecal calprotectin response and remission at infus4 (V5) and infus6 (V7)
    a. **Fecal calprotectin response:** ≥50% improvement in fecal calprotectin.
    b. **Fecal calprotectin remission:** fecal calprotectin <250 µg/g.
J. Rate of transmural ileal, colonic and total bowel healing at infus6 (V7) by MRI.
    a. **Ileal healing**: ileum subscore stage 0 (score = 0)
    b. **Colonic healing**: all segments of colon subscore stage 0 (score = 0).
    c. **Total bowel healing**: total ileum and colonic subscore is not greater than stage 0 on either individual score.

9.2 SAMPLE SIZE DETERMINATION

The rational to enroll 20 participants for the test cohort is to evaluate the safety of the intervention along with the feasibility of adherence to the dosing recommendations.

In terms of our efficacy endpoints, we understand that this pilot study will be primarily descriptive. However, we have gathered data from a previously enrolled, observational cohort of 25 CD patients who received both ALD (5 mg/kg) and ALD induction intervals (at 0, 2 and 6 weeks). These 25 previously enrolled subjects are considered the **control cohort** for this study. We found 40% of the 25 subjects achieved the infusion3 target (18-24 µg/ml). We estimate a sample size of 20 subjects will have 51.9% power with the assumption the dashboard will achieve the infusion3 target in 70% of those enrolled (14 subjects). With this vital pilot data, we will be able to more effectively design our larger, confirmatory study.

Consideration of relevant biologic variables. Biologic variables which may influence infliximab concentrations include age, gender, race/ethnicity, weight, serum albumin, and extent and severity of mucosal inflammation. Of these, extent of Crohn's colitis and serum albumin are likely to have the greatest effect.[17, 44] We will evaluate these difference in our statistical analysis, however, serum albumin is already accounted for as it is a covariate in our model-based dosing scheme. If a significant effect of extent of colitis is found, we will utilize this data for our future RCT. We anticipate enrolling equal numbers of males and females between ages 6 and 22 years old and Caucasian (90%) and African-American (10%) subjects in proportion to the overall CCHMC CD population. We will exclude younger children (<6 years of age) pending identification of any un-anticipated safety signals.

Potential Problems and Alternative Approaches. With model-based dosing, the first dose will be based on patient's weight, albumin, and nCD64 using population PK and Bayesian estimation. As this is a pragmatic study, there is the potential that the prescribed dose will be denied by the third party payer. In this case, the treating physician will have the opportunity to appeal that decision. If the recommended dose is still not covered despite the appeal, another attempt will be made by the treating physician at a subsequent infusion. This will be valuable data when designing the confirmatory study as the alternative would be for the Study team to provide the additional infliximab vials needed to comply with the dashboard recommended dose.

9.3 POPULATIONS FOR ANALYSES

Our primary analysis will be on a per protocol basis, including only patients who were prescribed infusion1 as suggested by the decision support tool. Our secondary analysis will be based on an Intent to Treat (ITT) schema, with each enrolled patient included in the final analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics and graphical analyses will be used to describe rates of AE's, SAE's and feasibility assessments. In addition, rates of achieving targeted infliximab concentrations, along with rates of biochemical and clinical remission will be determined. The control group includes the 25 patients that received ALD infliximab during induction. The test cohort includes all patients enrolled in this Pilot trial.

9.4.2 ANALYSIS OF PRIMARY AIM ENDPOINTS

Primary outcome: As a pilot and feasibility study, all primary outcomes (safety and feasibility) will be reported using descriptive statistics. Rates of AE's and SAE's will be compared to those reported in previous infliximab clinical studies and the control cohort.

In the infliximab clinical trial conducted in children with CD[2], 94.2% of all patients who received infliximab after week 10 (103 patients) had an adverse event with 5.8% of patients stopping infliximab because of the adverse event. Serious adverse events were found in 14.6% with 6.8% having a serious infection. Additional safety concerns during the first 6 months of therapy include infusion reactions (17.5%), transient elevations in liver enzymes (6%) and serum sickness-like reactions (0%).[2]

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary outcomes:

1. Percent of patients achieving infliximab goal concentrations (18-24 µg/ml) at infusion3 will be compared between the Pilot (n=20) and observation cohort (n=25). Statistical differences will be assessed by the Fisher's exact test. Differences in IFX dosing and IFX clearance will be evaluated between patients who did and did not achieve infusion3 goal concentrations.

2. In addition, we will compare additional outcome measures between the pilot and observation cohort. These outcomes include infliximab concentrations, biochemical/clinical remission and rate of antibody to infliximab formation. Time to clinical remission, biochemical remission and antibodies to infliximab will be compared between the two cohorts utilizing the log rank test and Kaplan-Meier survival curves. MRI scores will be assessed for the Pilot cohort only with rates of transmural healing investigated between those with therapeutic infliximab exposure compared to those who failed to achieve the targeted infliximab concentrations.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics and graphical analyses will be used to describe clinical and demographic characteristics, baseline fecal calprotectin/lactoferrin, baseline wPCDAI and QOL.

9.4.5 PLANNED INTERIM ANALYSES

We will evaluate the safety of model-informed dosing after the first 10 patients complete induction (infusions at week 0, 2 and 6).

Safety. If three or more subjects report a serious adverse event during induction, we will determine with the Medical Monitor whether model-informed dosing is safe. We do not expect any increase safety risk as off-label infliximab dosing is commonly used[45]

As supra and sub-therapeutic levels can be associated with adverse treatment outcomes, we will also evaluate the accuracy of the model after the first 10 patients with specific attention to infusion3 (week6, 18-24 µg/ml) and infusion4 (week14, 5-10 µg/ml) concentrations. Importantly, the accuracy may be confounded by the apriori infliximab concentration targets for individual

patients and their individual dosing interval (during the maintenance phase). Therefore, both confounders will be considered during this interim analysis.
We expect that ≥6/10 patients will achieve these aforementioned targets. If these targets are not being met, we will determine with the Medical Monitor whether model-informed dosing is efficacious. If the minimum concentration is not achieved during maintenance (>5 µg/ml) for >1 infusion, a pharmacokinetic consult with Alexander Vinks, PharmD, PhD and the PI will be arranged to provide dosing guidance for subsequent infusions. Likewise, if the infliximab level exceeds 2x the upper range during maintenance (>20 µg/ml) for >1 infusion, a pharmacokinetic consult will be arranged to provide dosing guidance for subsequent maintenance infusions during the study period.

9.4.6 SUB-GROUP ANALYSES

Our primary **Aim 1** analysis will be on a per protocol basis, including only patients who received model-informed dosing at infusion1. Our secondary analysis will be based on an Intent-to-Treat (ITT) schema, with each patient included in the analysis regardless of whether the patient decision tool was utilized for dosing.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be tabulated in an unlimited fashion.

9.4.8 EXPLORATORY ANALYSES

We will test for effects of age, gender, race, infusion3 fecal biomarkers, and additional blood biomarkers (such as pre-treatment plasma proteins and pre-maintenance plasma proteins) in an exploratory manner to guide design of the larger, multi-center clinical trial

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

Consenting document(s) will be used to obtain informed consent and parental permission and assent, when required, from participants, along with a consent process note. CCHMC will provide an English consenting template(s) to be used that contain all required elements of consent including details about the study intervention, study procedures, and risks. All consent forms (and any subsequent updates) will be IRB approved prior to use in the study. Delegation for site staff to perform consenting procedures will be documented on the Delegation of Authority Log and will be signed by the PI.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the documents. The investigator or a designated study member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form(s) and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document(s) prior to any procedures being done specifically for the study. If a participant turns 18 years of age (or as defined by state law for legal age of consenting) while participating in the study, re-consent will be obtained from the participant. Once all data is collected and follow up is complete, re-consent will not be requested for analysis of the existing data.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document(s) will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Consent may take place by several methods: in-person paper consent, in-person electronic consent (using REDCap for the eConsent) or over the telephone (via paper or REDCap for remote eConsent) or video chat*. If consent takes place remotely via phone call and/or remote econsent, subjects may email, mail, text, fax, or use the eConsent platform to provide staff with the signed document. A self-addressed stamped envelope will be provided to the participant for them to return the consent through regular mail.

* When using a video chat method use tools such as FaceTime, Skype, and/or other institutionally approved methods; and, use a common-sense approach to privacy (e.g., away from your own family, delete call logs, etc.)

Signatures of the subject may not always occur on the same date as the consent discussion depending on how and when the subject returns the signed consent. The staff member who conducted the consent discussion will document this in a detailed informed consent process note, but not necessarily on the consent document itself. No matter the consenting process, study procedures will not occur prior to a fully executed consent form. Consent will be obtained following institutional SOPs. REDCap eConsent will not replace the consenting method, it will be used as an additional resource for signing the consent form. A copy of the consent form will either be given to the subject in paper form or emailed to them via REDCap depending on how the consent is completed. In all cases, the consent process will be documented on the informed consent process note and a copy of the signed consent(s) will be kept in the patient's medical record.

Staff will make sure that the eConsent database is updated as soon as possible after a new version of the paper consent is approved. Staff will also make sure paper consents are used to consent eligible subjects in the event that the eConsent database is not updated prior to eligible

subjects being available for consent approach by a member of the study staff. For the reasons described, the eConsent will not be submitted to the IRB for approval.

10.1.1.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, written notification will be provided to the IRB, Medical Monitor, and the funding agency. The Principal Investigator (PI) will promptly inform study participants, and will provide the reason(s) for the termination or suspension and will 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
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor and IRB.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records 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 CCHMC 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 requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at CCHMC. 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 CCHMC research staff will be secured and password

protected. At the end of the study, all study databases will be de-identified and archived at CCHMC.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at CCHMC. After the study is completed, the de-identified, archived data will be stored at CCHMC for use by other researchers including those outside of the study.

With the participant's approval and as approved by the CCHMC Institutional Review Board (IRB), de-identified biological samples will be stored in the Minar Laboratory. These samples could be used to research the causes of Crohn's disease, its complications and other conditions for which individuals with Crohn's disease are at increased risk, and to improve treatment. The Minar laboratory personnel will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

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

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Sponsor/Principal Investigator - CCHMC
Phillip Minar, MD, MS Associate Professor – Faculty, Gastroenterology, Hepatology & Nutrition
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue MLC 2010, Cincinnati OH 45229
513-636-7575
Phillip.minar@cchmc.org

Medical Monitor
Joel R. Rosh, MD
Atlantic Health System
55 Madison Avenue Morristown, NJ 07960
973-971-5676
Joel.rosh@atlantichealth.org

Dr. Minar will serve as the PI for this project. Dr. Minar will be responsible for oversight of the clinical trial and supervise the organization, implementation, monitoring and reporting of the clinical protocol. Dr. Minar will act as the primary medical contact for the clinical trial working closely with the CCHMC project manager to answer protocol questions and ensure appropriate interpretation of the inclusion/exclusion criteria as well as conformity to the treatment paradigm. Dr. Minar will review recruitment on a weekly basis and be in frequent communication with the project manager.

10.1.5 SAFETY OVERSIGHT

As off-label infliximab dosing is routinely utilized in Crohn's disease management, no formal Data and Safety Monitoring Board (DSMB) will be organized.

An independent Medical Monitor will be involved during the conduct of the trial for additional review of adverse and serious adverse events on a quarterly basis. Review will include the assignment of severity, expectedness, and relatedness.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Office for Clinical and Translational Research, located at Cincinnati Children's Hospital Medical Center.

- Per FDA guidance "Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, August 2013", a risk-based strategy will be implemented for monitoring. A combination of on-site and centralized monitoring may be performed. If systemic issues are identified during monitoring visits (i.e., consent process, ineligible participants, regulatory violations, missing data, etc.) re-training of the site staff will be suggested and the need for additional review will be assessed. A close out visit will be conducted once all participants have completed, withdrawn or been declared lost to follow-up and all data queries have been resolved. Any outstanding issues from previous monitoring reports will be reconciled.

- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

We will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at CCHMC under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be used as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a REDCap data capture system provided by the CCHMC DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference 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, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference 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 CCHMC staff. As a result of deviations, corrective actions are to be developed and implemented promptly.

These practices are consistent with ICH GCP:

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

It is the responsibility of the PI to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the study Sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The PI is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.10 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 after the completion of the primary endpoint by contacting the CCHMC DCC.

10.1.11 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 in conjunction with the Crohn's and Colitis Foundation 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

Not Applicable

11 REFERENCES

1. Dahlhamer JM, Zammitti EP, Ward BW, et al. Prevalence of Inflammatory Bowel Disease Among Adults Aged >/=18 Years - United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:1166-1169.
2. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007;132:863-73; quiz 1165-6.
3. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology 2012;143:365-74.e2.
4. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet 2018;390:2779-2789.
5. Nuti F, Civitelli F, Bloise S, et al. Prospective Evaluation of the Achievement of Mucosal Healing with Anti-TNF-alpha Therapy in a Paediatric Crohn's Disease Cohort. J Crohns Colitis 2016;10:5-12.
6. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. Clin Gastroenterol Hepatol 2017;15:1580-1588 e3.
7. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4:341-353.

8. Benchimol EI, Fortinsky KJ, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011;17:423-39.
9. Herzog D, Fournier N, Buehr P, et al. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. Eur J Gastroenterol Hepatol 2017;29:926-931.
10. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lemann score. Inflamm Bowel Dis 2011;17:1415-22.
11. Gupta N, Bostrom AG, Kirschner BS, et al. Incidence of stricturing and penetrating complications of Crohn's disease diagnosed in pediatric patients. Inflamm Bowel Dis 2010;16:638-44.
12. Clarkston K, Tsai YT, Jackson K, et al. Development of Infliximab Target Concentrations during Induction in Pediatric Crohn's Disease Patients. J Pediatr Gastroenterol Nutr 2019.
13. Fasanmade AA, Adedokun OJ, Blank M, et al. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 2011;33:946-64.
14. Bauman LE, Xiong Y, Mizuno T, et al. Improved Population Pharmacokinetic Model for Predicting Optimized Infliximab Exposure in Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis 2019.
15. Minar P, Saeed SA, Afreen M, et al. Practical Use of Infliximab Concentration Monitoring in Pediatric Crohn Disease. J Pediatr Gastroenterol Nutr 2016;62:715-22.
16. Singh N, Rosenthal CJ, Melmed GY, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2014;20:1708-13.
17. Frymoyer A, Piester TL, Park KT. Infliximab Dosing Strategies and Predicted Trough Exposure in Children With Crohn Disease. J Pediatr Gastroenterol Nutr 2016;62:723-7.
18. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320-9 e3.
19. Papamichael K, Vajravelu RK, Vaughn BP, et al. Proactive Infliximab Monitoring Following Reactive Testing is Associated With Better Clinical Outcomes Than Reactive Testing Alone in Patients With Inflammatory Bowel Disease. J Crohns Colitis 2018;12:804-810.
20. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029-35.
21. D'Haens G, Van Deventer S, Van Hogezand R, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 1999;116:1029-34.
22. Hendler SA, Cohen BL, Colombel JF, et al. High-dose infliximab therapy in Crohn's disease: clinical experience, safety, and efficacy. J Crohns Colitis 2015;9:266-75.
23. Bar-Yoseph H, Levhar N, Selinger L, et al. Early drug and anti-infliximab antibody levels for prediction of primary nonresponse to infliximab therapy. Aliment Pharmacol Ther 2018;47:212-218.
24. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-9.
25. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. Am J Gastroenterol 2012;107:1409-22.
26. Minar P, Lehn C, Tsai YT, et al. Elevated Pretreatment Plasma Oncostatin M Is Associated With Poor Biochemical Response to Infliximab. Crohns Colitis 360 2019;1:otz026.
27. D'Arcangelo G, Oliva S, Dilillo A, et al. Predictors of Long-term Clinical and Endoscopic Remission in Children With Crohn Disease Treated With Infliximab. J Pediatr Gastroenterol Nutr 2019;68:841-846.
28. Katz L, Gisbert JP, Manoogian B, et al. Doubling the infliximab dose versus halving the infusion intervals in Crohn's disease patients with loss of response. Inflamm Bowel Dis 2012;18:2026-33.
29. Taxonera C, Barreiro-de Acosta M, Calvo M, et al. Infliximab Dose Escalation as an Effective Strategy for Managing Secondary Loss of Response in Ulcerative Colitis. Dig Dis Sci 2015;60:3075-84.

30. Frymoyer A, Hoekman DR, Piester TL, et al. Application of Population Pharmacokinetic Modeling for Individualized Infliximab Dosing Strategies in Crohn Disease. J Pediatr Gastroenterol Nutr 2017;65:639-645.
31. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol 2009;65:1211-28.
32. Pariente B, Pineton de Chambrun G, Krzysiek R, et al. Trough levels and antibodies to infliximab may not predict response to intensification of infliximab therapy in patients with inflammatory bowel disease. Inflamm Bowel Dis 2012;18:1199-206.
33. Clarkston K, Tsai YT, Jackson K, et al. Development of Infliximab Target Concentrations During Induction in Pediatric Crohn Disease Patients. J Pediatr Gastroenterol Nutr 2019;69:68-74.
34. Hajjat T, Mosha MH, Bonkowski E, et al. 882 – Normalization of Fecal Calprotectin Requires Higher Trough Infliximab Levels in Children with Inflammatory Bowel Disease. Gastroenterology 2019;156:S-200.
35. Mahadevan U, Robinson C, Bernasko N, et al. Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report From the American Gastroenterological Association IBD Parenthood Project Working Group. Gastroenterology 2019;156:1508-1524.
36. Louis E. Fecal calprotectin: towards a standardized use for inflammatory bowel disease management in routine practice. J Crohns Colitis 2015;9:1-3.
37. Abubucker S, Segata N, Goll J, et al. Metabolic reconstruction for metagenomic data and its application to the human microbiome. PLoS Comput Biol 2012;8:e1002358.
38. Fernandes SR, Rodrigues RV, Bernardo S, et al. Transmural Healing Is Associated with Improved Long-term Outcomes of Patients with Crohn's Disease. Inflamm Bowel Dis 2017;23:1403-1409.
39. Ordas I, Rimola J, Alfaro I, et al. Development and Validation of a Simplified Magnetic Resonance Index of Activity for Crohn's disease. Gastroenterology 2019.
40. Hammer MR, Dillman JR, Smith EA, et al. Magnetic resonance imaging of perianal and perineal crohn disease in children and adolescents. Magn Reson Imaging Clin N Am 2013;21:813-28.
41. Turner D, Griffiths AM, Walters TD, et al. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. Inflamm Bowel Dis 2012;18:55-62.
42. Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2002;35:557-63.
43. Otley AR, Griffiths AM, Hale S, et al. Health-related quality of life in the first year after a diagnosis of pediatric inflammatory bowel disease. Inflamm Bowel Dis 2006;12:684-91.
44. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of Infliximab Into Feces Is Associated With Lack of Response to Therapy in Patients With Severe Ulcerative Colitis. Gastroenterology 2015;149:350-5 e2.
45. Brandse JF, Mould D, Smeekes O, et al. A Real-life Population Pharmacokinetic Study Reveals Factors Associated with Clearance and Immunogenicity of Infliximab in Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23:650-660.

12 APPENDICES:

Appendix A: Patient Reported Outcomes (Crohn’s Disease)
Appendix B: Clinical Endoscopy Findings