Protocol:

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Pragmatic Clinical Trial to Evaluate the Effectiveness of Low Dose Oral Methotrexate in Patients with Pediatric Crohn's Disease Initiating Anti-TNF Therapy

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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PRAGMATIC CLINICAL TRIAL TO EVALUATE THE EFFECTIVENESS OF LOW DOSE ORAL METHOTREXATE IN PATIENTS WITH PEDIATRIC CROHN'S DISEASE INITIATING ANTI-TNF THERAPY

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Sponsor:	*The University of North Carolina at Chapel Hill*
Funding Source:	*The Patient Centered Outcomes Research Institute*
Data and Site Coordinating Center:	*Cincinnati Children's Hospital Medical Center*
Study Product:	*Methotrexate*
Protocol Number:	*PCD-MTX-001*

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Amended: March 23, 2018, V7.0
Amended: December 18, 2018, V8.0
Amended: July 15, 2019, V9.0
Amended: June 23. 2021, v10

Key Roles

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Document History

Document	Date of Issue	Summary of Change
V10	June 4, 2021	The primary purpose of this amendment is to: • Update the management and maintenance of the database • Update to include particular studies being conducted under this protocol
Amendment 8, V9.0	June 17, 2019	The primary purpose of this amendment is to document changes and updates to the following: • The Central Pharmacy underwent a merger and name change. It is now called RxCrossroads by McKesson. • Section 4.3 and 7.5 – The nested trial consisting of the Enhanced and Standard Pre-Consent will be stopped. All sites will now use the Enhanced Pre-Consent procedures.
Amendment 7, V8.0	December 18, 2018	The primary purpose of this amendment is to change to a variable follow-up period with a minimum of 12 months and a maximum of 36 months. • Objective 1 – changed the treatment period to be for up to three years • Exclusion criteria – Patients expected to leave practice <12 months from enrollment should not be enrolled • Duration of administration has been changed from 24 months to 12 to 36 months. • Section 1.1.1. clarifies that long-term maintenance is now 1 to 3 years. • Section 1.1.2 now has a maximum 3-year follow-up • Section 3.1 graphic extends data collection to Week 156 • Section 3.2 Primary Outcome Induction and maintenance of steroid-free remission for up to 3 years. • Section 4.2 Exclusion Criteria – Patients expected to leave practice <12 months from enrollment should not be enrolled. • Section 4.4 Patient Follow-up – Patients will be followed for up to three years unless they have met a primary study endpoint. If the patient has met an endpoint, the follow-up period will be for a maximum of two years.

		• Section 5.2 The Treatment Regimen will continue for up to 3 years. • Clarifies the PROs can be collected in person, email, fax, U.S. mail or at the following visit. • Section 6.6 Added 4 quarterly visits in year 3, Week 117, Week 130, Week 143, and Week 156 all + / - 6 weeks. • Section 6.9 Patients will continue to be followed until the study ends. Patients who meet a study endpoint will only be followed for a maximum of two years. • Section 7 Statistical Plan has been updated • Added Section 6.11 Re-consenting current participants. Only patients who haven't yet met a study endpoint will be followed for an additional year. • Section 8.3 All SAEs will be followed until the end of the study (i.e., until week 156) • Section 8.4.4 Patients will remain in follow-up for a maximum of 156 weeks. • Section 8.6 Scheduled Unblinding at end of study has been added. • The Appendix has been updated accordingly
Amendment 6, V7.0	March 23, 2018	The primary purpose of this amendment is to document changes and updates to the following: • Key Roles – Updated the Project Manager and Central Pharmacy Information. Biologics, Inc. was purchased by McKesson Specialty Health and all clinical trial pharmacy operations are moving to Texas in late March 2018. • Primary Study Endpoints – Clarified that an elevated SPCDAI due to a non-IBD reason does not count toward the primary endpoint. Also clarified that switching from the name brand infliximab or adalimumab to the corresponding biosimilar does not constitute a study endpoint (i.e. discontinuation of the anti-TNF agent). Emphasized that any patient discontinuing their first-line anti-TNF for PCD for any reason must discontinue study medications. (Section 3.2) • Inclusion Criteria – The use of infliximab and adalimumab biosimilars is allowable for inclusion in the trial. (Section 4.1) • Exclusion Criteria – Increased the BMI cut-off from >95% to ≥98% to align with standard clinical practice of treating obese PCD patients with low dose oral methotrexate (but not morbidly obese patients). Clarified the exclusion for Clostridium difficile is only for active infection, not applicable to colonization or infection controlled by treatment. (Section 4.2)

		• Subject Recruitment – Consultation with Resource Parents (parents of current study participants) will be offered to potential patients and/or parents who are approached regarding trial participation. (Section 4.3) • Discontinuation of Study Medication – Separated this section from Early Withdrawal of Subjects. Clarified the circumstances under which study medications must be discontinued and provided reference to sections detailing discontinuation procedures and patient follow-up. (Section 4.4) • Early Withdrawal of Subjects – Clarified the term "withdrew consent" to mean that the patient / family chooses to fully discontinue participation in the trial (not just discontinue the study medications). Also clarified that patients who withdraw after shipment of study medications will not be replaced by recruitment additional subjects. Those who withdraw prior to the first study medication shipment may be replaced. (Section 4.5) • Treatment Regimen – Study providers may advise patients not to take folic acid on the day methotrexate / placebo is taken in according with their usual practice. Adjusted the window for randomization from no more than 35 days to no more than 42 days (before or after) the initiation of anti-TNF. (Section 5.2) • Prior and Concomitant Therapy – Clarified that the exclusion for prior use of anti-TNF therapy is only for the indication of Crohn's disease. Prior Anti-TNF use for another indication (i.e. juvenile idiopathic arthritis) is allowable. Added caution statements related to concomitant use of nitrous oxide anesthesia. (Section 5.7) • Visit Windows – Expanded the visit windows for visits 1-4 to accommodate a wide variety of clinical practice styles and to minimize out-of-window visit protocol deviations. (Sections 6.1, 6.3, 6.4, 6.5) • Pregnancy testing – Changed the window from within 2 weeks of the screening visit to within 30 days of randomization to ensure the testing takes place in more consistent proximity to when the patient starts taking the study medication. • Phone follow-up – Modified this to "Follow-up contact" to accommodate a variety of follow-up methods. Phone is preferred, however, email, text or in-person visit are also acceptable. (Section 6.2) • Visit 2 Laboratory tests – Given the expanded visit window and possibility of a missed visit, added a requirement to draw and confirm initial safety labs between week 1 and week 6 after the patient starts the study medication. (Section 6.3) • Study drug refill – Clarified that the request goes to the central pharmacy, not to the study site. (Sections 6.4, 6.5)

		• Additional Labs (not associated with a visit) - Added this section to provide guidance on documentation of lab values not associated with a clinic visit (i.e. routine infusion labs). Documented results are limited to those associated with a prior abnormal lab result, specialty lab test, change in clinical status, or meeting protocol-defined abnormal lab criteria for AST, ALT and WBC. (Section 6.8 and Section 8.4.3) • Study Medication Dose Change or Discontinuation – Clarified the criteria and procedures for discontinuation of study medication as well as patient follow-up for those off study medication but still in follow-up. (Section 6.9) • Withdraw of consent – Clarified the definition of "withdrew consent" includes discontinuation of both study medication and all other IRB-approved research activities (including use of routine visit information for trial purposes). (Section 6.10) • Subject Population for Analysis – Changed from an Intent to Treat to a modified Intent to Treat analysis. Only patients who were shipped the study medication will be included in the analysis. (Section 7.4) • Definition of an AE – Changed from being an event "temporally associated with the use of the study drug" to an event which develops or worsens in severity "from the date of randomization". (Section 8.1.1) • Recording of AEs and SAEs – Increased the reporting period for non-serious AEs from 7 days to 14 days following the final dose of study medication. For patients who discontinue study medication early, but remain in study follow-up, non-serious AEs do not need to be recorded after the 14 day period following their last dose of study medication. SAEs occurring from the date of randomization through the completion of the study will be recorded for all patients. For patients who continue on study medication through the end of the trial period (week 104), any SAE occurring within 14 days after their last dose of study medication should also be recorded. (Section 8.3 and Section 8.5) • Recording and Evaluation of AEs – Changed the evaluation of relationship and expectedness from solely the perspective of the study drug (per FDA guidance) to both the context of the study drug and the procedures involved in the research (per OHRP guidance). (Section 8.3.1) • General Management of AEs – Reiterated that any AE or SAE leading to a permanent discontinuation of study medication (study drug or anti-TNF intolerance or toxicity) meets the definition of a primary endpoint. (section 8.4.1) • Ethical Considerations – Added language related to the possible recruitment of Spanish-speaking patients at select study sites.

		(Section 11) • Appendix A – Modified to account for above changes.
Amendment 5, V6.0	February 28, 2017	The primary purpose of this amendment is to document changes and updates to the following: • Exclusion Criteria – Removed "Inability to swallow pills". Study medications may be dissolved in liquid prior to administration. Renumbered remaining criteria. Modified "Abdominal or pelvic abscess within the last 3 months" to "Concurrent abdominal or pelvic abscess. A recent history of abdominal or pelvic abscess, which is controlled does not exclude the subject." (Section 4) • Treatment Regimen – Provided an opt-out for the provision of ondansetron / placebo based on provider's clinical judgement of patient safety and maintenance of the blind. Allowed study medications to be dissolved and administered orally or by gastrostomy tube. Based the window of first anti-TNF administration on the randomization start date (instead of study treatment start date) and adjusted the window to 35 days. (Section 5.2) • Study Drug Dispensing, Return and Destruction – Made minor process clarifications. (Section 5,6) • Screening – Extended the window for laboratory tests used to evaluate eligibility to not more than 90 days prior to randomization. Allowed the use of a prior exam for the screening exam if the patient is recruited in an in-patient or infusion / injection-teaching setting and the prior exam is not more than 30 days prior to the randomization date. Added a supplement to the trial-specific screening form to be completed for patients screened in an inpatient setting. (Section 6.1) • Bio samples – Increased blood collection volume by 3mL to account for the size of the sourced venipuncture tubes. Clarified sample labeling with unique subject ID instead of a barcode. (Section 6.10) • Statistical methods – Added use of multiple imputation for analysis of PROs. (Section 7.3) • Pre-existing Conditions – Added documentation of the event at the screening visit as part of the definition. (Section 8.1.1) • Study Finances – Added Grifols Diagnostics Solutions Inc. and the National Institutes of Health as additional funding sources. (Section 12)

		• Appendix A – modified to account for above changes. • Other minor corrections or formatting throughout the document.
Amendment 4, V5.0	September 7, 2016	The primary purpose of this amendment is to document changes and updates to the following: • Investigator Signature Page – Incorporated a signature page to document investigator agreement with the current protocol amendment. (page vii) • Study Design Schematic – Updated to reflect secondary objectives of anti-TNF and antibody levels. (Section 3.1) • Study Drug – Updated to reflect changes in shipment configuration, provision of a 7-day pill box for patients, removal of specified methotrexate manufacturer, and addition of pharmacy counseling prior to initial shipment of study medication. (Section 5) • Statistical Plan – Removed interim analysis for nested trial of enhanced pre-consent discussion from section 7.2 and updated the interim analysis plan for the nested trial under section 7.5. Noted that full statistical plan details will be kept in separate data analysis plan. (Section 7) • Data Handling – Added a section regarding data collection and management for case report forms, patient surveys and questionnaires. (Section 9.3) • Time and Events Table – Corrected footnote c to reflect the 4-week window between initiation of the anti-TNF therapy and the initiation of the study treatment). (Section 15 – Appendix A)
Amendment 3, V4.0	June 23, 2016	The primary purpose of this amendment is to refine trial endpoints and related statistical procedures. The planned interim analyses are now consolidated under section 7.2. (Amended sections include 2, 3, 7, and 8.7)). In addition, changes were made to: • Key Roles – Changed the central pharmacy to Biologics, Inc. • Pharmacy – Removed reference to Investigational Drug Service at the University of Pennsylvania and updated packaging information per the new central pharmacy. (Section 5) • Bio samples – Changed the blood collection amount from 16 ml to 18 ml to account for additional planned testing for neutrophil CD64

		surface expression and soluble CD64. Added the laboratory of Dr. Minar at Cincinnati Children's Hospital Medical Center as a stored sample facility. (Section 6) • Subject Stipends or Payments – Corrected language regarding billing and compensation for study-related injury. (Section 12.3)
Amendment 2, V3.0	May 04 , 2016	The primary purpose of this amendment is to nest a cluster randomized controlled trial to determine whether an enhanced vs. standard pre-consent discussion increases parent/patient knowledge related to trial participation. (Amended sections include 1.1.1, 2, 3.1, 3.5, 4.3, 4.3.1, 7.2, and 8.7) In addition, changes were made to: • Key Roles – Added and clarified roles. (Cover sheet and Key Roles page) • Study Objective (aim) #4 – Changed from future use to testing for anti-TNF antibodies and trough levels for secondary outcome assessment. Leftover serum will continue to be banked for future use. (Section 2, 6.10, and 7.2) • Primary Study Endpoints – Clarified timing and definitions of treatment failure. (Section 3.2) • Secondary Study Endpoints - Removed collection of radiographic assessments. Will only collect fecal calprotectin and colonoscopy assessments, if performed. (Section 3.3, and 6.0) • Inclusion Criteria – Broke the original paragraph into individual criteria. No other changes. (Section 4.1) • Exclusion Criteria – removed prior use of other biological therapy (i.e. non-anti-TNF biologics), added prior pelvic abscess, breastfeeding, recent history of colonic adenoma or dysplastic lesions, clarified underlying C. difficile at screening, added azathioprine and 6-mercaptopurine to list of excluded concurrent treatments. (Section 4.2) • Subject Pre-screening and Recruitment – added necessity for limited waiver of HIPAA and collection of a reason for those who decline participation in the trial. (Section 4.3) • Early Withdrawal – Differentiated procedures for those who discontinue the study treatment vs. those who completely withdraw from the study. (Section 4.4)

		• Treatment Regimen - Increased Ondansetron / placebo from once weekly to twice weekly. Increased allowable time between study treatment initiation and anti-TNF administration from 3 weeks to 4 weeks. (Section 5.2, 5.4). • Study Procedures – Added windows for lab and pregnancy testing, added collection of demographics, anti-TNF initiation, perianal Crohn's history and exam (if available), added phone follow-up after each shipment of study treatment (2 phone calls to 8 phone calls), added a provision for rescreening, specified individual lab results collected, changed the window for visit 3 from 10-25 weeks to 10-22 weeks, added information related to study treatment shipment, dose change and collection of unused drug, and removed specific reasons for study treatment discontinuation. (Section 6.1 – 6.9) • Safety and AEs – Made clarifications to AE reporting and pregnancy follow-up, removed reporting requirements for pregnancy in the partner of a male trial participant. (Section 8.1 – 8.5) • Unblinding – Changed from unblinding all treatment failures to unblinding on a case by case basis. Included an option for patients who complete the study to be unblinded to their treatment assignment after week 104. (Section 8.6) • Independent Data and Safety Monitoring Board – Decreased membership from five members to three. Named the third member. (Section 8.7.1) • Ethical Considerations - Clarified the process for re-consenting subjects. (Section 11) • Study Finances – added The Leona M. and Harry B. Helmsley Charitable Trust as a funding source. (Section 12) • Conflict of Interest – Modified wording to correctly reflect IRB and sponsor responsibilities. (Section 12.2) • Subject Stipends or Payments – Added language regarding billing and compensation for study-related injury. (Section 12.3) • Appendix A – modified to account for above changes. • Other minor corrections or enhancements to procedures and formatting throughout the document.

Amendment 1, V2.0	January 14, 2016	The primary purpose of this amendment is to provide more specific information regarding bio samples, including anticipated testing, storage, and de-identification.
Original Protocol, V1.0	December 2, 2015	Not applicable

Investigator Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

PCD-MTX-001

Version 9.0, July 15, 2019

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without permission, except when necessary to protect the safety, rights, or welfare of study participants.

I agree to personally conduct or supervise this study.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations.

Lead Site Investigator: _____
(Printed name, Title)

Signed: _____ Date: _____

Table of Contents

List of Abbreviations

6MP	6-mercaptopurine
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
anti- TNF	anti-Tumor Necrosis Factor
AST	aspartate aminotransferase
BMI	body mass index
C. Difficile	Clostridium Difficile
CCFA	Crohn's and Colitis Foundation of America
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CER	comparative effectiveness research
CFR	Code of Federal Regulations
cGMP	current good manufacturing practices
CI	confidence interval
CRF	case report form
CRP	C reactive protein
CT	computerized tomography scan
dl	deciliter
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC	Ethics committee
eCRF	electronic case report form
EGD	esophagogastroduadenoscopy
EHR	electronic health record
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
g	gram
GGT	Gamma-glutamyltransferase
GI	gastrointestinal
GLIMM	Generalized linear mixed effects model
HDPE	high density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HSTCL	hepatosplenic T cell lymphoma
IBD	inflammatory bowel disease
IBS	Irritable bowel syndrome
ICH	International Conference on Harmonization
ICN	ImproveCareNow
IMM	immunomodulator
IRB	Institutional review board
IV	intravenous
kg	kilogram
L	liter
LFT	liver function test
M^2	meter squared
mg	milligram
MID	minimal important differences
mL	milliliter

MMRM	Mixed-Effect Model Repeated Measure
MRI	magnetic resonance imaging
MTX	methotrexate
NIH	National Institutes of Health
PCD	Pediatric Crohn's Disease
PCDAI	Pediatric Crohn's Disease Activity Index
PCORI	Patient Centered Outcomes Research Institute
PHI	Protected health information
PPRN	patient powered research network
PRN	as needed (pro re nata)
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcome Measurement and Information System
PS-22	pressure sensitive
QI	quality improvement
QT	Interval between the beginning of the QRS complex to the end of the T wave on an electrocardiogram
RA	Rheumatoid arthritis
RNA	ribonucleic acid
SAE	Serious adverse event
SES-CD	Simple Endoscopic Score for Crohn's Disease
SPCDAI	Short Pediatric Crohn's Disease Activity Index
sq	subcutaneous
TB	tuberculosis
ULN	upper limit of normal
WBC	white blood count
wk	week

Study Summary

Title	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PRAGMATIC CLINICAL TRIAL TO EVALUATE THE EFFECTIVENESS OF LOW DOSE ORAL METHOTREXATE IN PATIENTS WITH PEDIATRIC CROHN'S DISEASE INITIATING ANTI-TNF THERAPY
Short Title	LOW DOSE ORAL METHOTREXATE IN PATIENTS WITH PEDIATRIC CROHN'S DISEASE INITIATING ANTI-TNF THERAPY
Protocol Number	PCD-MTX-001
Phase	Phase III
Methodology	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PRAGMATIC CLINICAL TRIAL
Study Duration	4 years
Study Centers	Multi-center with estimated 50 centers
Objectives	1. To determine whether, in children with Crohn's disease (CD) initiating anti-TNF (anti-Tumor Necrosis Factor) biological therapy with infliximab or adalimumab, low-dose oral methotrexate (MTX) is more effective than placebo in the induction and subsequent maintenance of steroid-free remission for a treatment period of up to three years. We hypothesize that the addition of MTX to anti-TNF therapy will be more effective than placebo (i.e. anti-TNF monotherapy). 2. To determine whether, in children with CD initiating anti-TNF biological therapy with infliximab or adalimumab, low-dose oral MTX leads to better Patient Reported Outcomes (PROs) as compared to placebo. We hypothesize that the addition of MTX to anti-TNF therapy will result in better PROs than placebo (i.e. anti-TNF monotherapy). 3. To describe the investigator-reported adverse events (AEs) (Grade 2 or higher[1]) in PCD patients initiating anti-TNF, treated with low dose oral MTX and in a placebo comparison group. 4. To determine whether low-dose oral methotrexate, in combination with anti-TNF biological therapy, is more effective than anti-TNF monotherapy in reducing anti-TNF antibody formation resulting in higher anti-TNF trough levels. emai
Number of Subjects	425

Diagnosis and Main Inclusion Criteria	**Inclusion criteria** • PCD patients, < 21 years of age, ≥20 kg, initiating anti-TNF therapy with infliximab or adalimumab (including biosimilars) • Ability to provide parental permission and child assent (where applicable), or adult consent for patients ages 18-20 **Exclusion criteria** • Prior use of anti-TNF or other biological therapy for CD • Lack of stable home address that study medications can be mailed to • Anticipated short length of follow up at study center (plans for family to move, transition to adult GI, etc.). Patients expected to leave practice < 12 months from enrollment should not be enrolled. • Concurrent abdominal or pelvic abscess. A recent history of abdominal or pelvic abscess, which is controlled, does not exclude the subject. • Prior intra-abdominal surgery without a clinically significant relapse (i.e. patients starting on anti-TNF for post-op prophylaxis or for endoscopic recurrence only should not be included) • Receipt of a live virus vaccine within the last 30 days • Pregnancy, planning to become pregnant, or high risk of pregnancy • Breastfeeding • Refusal to stay abstinent or utilize 2 forms of birth control while on study medication (for female patients) • BMI (body mass index) ≥ 98% for gender and age • Known previous or concurrent malignancy (other than that considered surgically cured, with no evidence for recurrence for 5 years). A recent history of basal cell or squamous cell carcinoma, which is considered surgically cured, does not exclude the subject. Those with a recent history of colonic adenoma or dysplastic lesions should be excluded. • Known high alcohol consumption (more than seven drinks per week) • Patients with serum albumin < 2.5 g/dl • Patients with white blood count (WBC) < 3.0 x10 ^{9} /L • Patients with platelet count < 100 x10 ^{9} /L • Patients with initial elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times above normal limit • Patients with known active infection with Clostridium difficile (C. difficile) (untreated infection based on clinician assessment; does not apply to colonization or infection controlled with current or prior treatment) • Patients with pre-existing hepatic disease • Patients with pre-existing renal dysfunction (creatinine > 0.8 for children age<10, creatinine > 1.2 mg/dl for children age 10-18, and creatinine > 1.5 mg/dl for adults age 18 years and older). • Patients with a pre-existing chronic lung disease other than well controlled asthma • Current treatment with one of the following drugs: Probenecid (Probalan), Acitretin (Soriatane), Streptozocin (Zanosar), Azathioprine (Imuran, Azasan), 6-mercaptopurine (Purinethol, Purixan) • Other concerns about the patient/family's ability to participate in the study

Study Product, Dose, Route, Regimen	oral MTX (15 mg for children ≥ 40kg, 12.5 mg for children 30 - <40 kg, and 10 mg for children 20 - <30 kg) given once a week
Duration of administration	12 to 36 months
Reference therapy	Placebo
Statistical Methodology	The primary endpoint is time to treatment failure. Patients who fail to enter remission will be considered as a treatment failure at the visit at or just prior to week 26. To compare the distribution of time to treatment failure in the two arms we will compute stratified log-rank test stratified by anti-TNF agent prescribed (infliximab and adalimumab). There is a planned interim analysis for efficacy.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (Food and Drug Administration [FDA] Title 21 part 50, part 56 and International Conference on Harmonization [ICH] guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

1.1.1 Pediatric Crohn's Disease (PCD)

Pediatric Crohn's disease: a debilitating condition with expensive, complex, and risky treatment options

Crohn's disease is a chronic inflammatory bowel disease (IBD) that affects approximately 600,000 Americans[2] with estimated direct costs of $3.6 billion annually.[3] Typical symptoms (e.g., abdominal pain, bloody diarrhea)[4] result in substantial morbidity, including hospitalization and surgery,[5] missed work[6] and school,[7] and diminished quality of life.[8]

Pediatric CD (PCD) is a distinct disease entity, clinically different than adult CD. Since less than 10% of CD patients (~38,000) are children, PCD is recognized as a rare disease by the National Institutes of Health (NIH) Office of Rare Diseases Research.[9] PCD patients present with a more extensive distribution and rapid extension of the disease than seen in adult-onset CD and experience marked psychosocial difficulties and impairment in pubertal development and growth.[10] In a U.S. multicenter inception cohort, ~8% of children required intestinal resection during the year following diagnosis.[11] In a French cohort, the cumulative incidence of surgery was 20% at 3 years and 34% at 5 years.[12]

The primary treatment goals for all CD patients are to induce remission by eradicating intestinal inflammation and related symptoms and maintain remission by preventing disease flares and progression. Additional treatment goals for PCD include restoring physical and emotional development. Until recently, medical treatment for CD was limited to corticosteroids, aminosalicylates, and immunomodulators [6-mercaptopurine (6MP), azathioprine, and MTX]. In 1998, the FDA approval of infliximab, the first anti-TNF biologic agent, revolutionized the treatment landscape for CD. (Pediatric approval was granted in 2006). More recently, a number of additional anti-TNF and other biologics have been developed and FDA-approved based on placebo-controlled efficacy studies.[4]

As the treatment armamentarium continues to grow, there is an increasing paucity of clinical and comparative effectiveness/safety data to guide clinician and patient decision making. Treatment guidelines emphasize general management principles but fail to provide specific evidence-based treatment recommendations.[4] The lack of consensus about the best treatment strategy is confusing and frustrating for clinicians and patients resulting in widespread variation in care.[13, 14] Moreover, the uncertainty of the situation may be especially stressful for families, making it more challenging to meaningfully engage them in the decision making process.

As a result, the 2009 Institute of Medicine comparative effectiveness research (CER) report identified the introduction of biologics into the treatment algorithm for CD and other inflammatory diseases as a top quartile research priority,[15] a recommendation subsequently endorsed by the American Gastroenterological Association.[16] Additional reports from the Agency for Healthcare Research and Quality (AHRQ)[4 17] and the Crohn's and Colitis Foundation of America (CCFA),[18] the leading IBD advocacy organization, have also prioritized studies of the pharmacological management of CD as a top national priority for CER.

Chief among the research gaps highlighted by the 2014 AHRQ CER Review were "studies of pediatric patients, newly diagnosed populations, and underrepresented non-White patients."[4] This report highlighted numerous profound limitations to the existing research in PCD: 1) the small number of studies, with few participants per study, 2) the limited scope of pediatric studies, including no double-blind randomized, controlled trials, and 3) the lack of studies directly addressing the safety of children who have longer lifetime exposures to medications. The report concluded that "Comparing Crohn's disease medications directly using pragmatic clinical trials will help to understand the effectiveness of medications in clinical practice."

These gaps in evidence were reinforced by the 2014 AHRQ Future Research Needs Project on the Pharmacological Management of CD.[17] Using a multi-stakeholder approach to evaluate priorities for study populations and research questions, this report concluded that "Children were unanimously considered a high priority for all future research in the field" because: 1) few pediatric studies were identified, 2) none of the adult studies that included participants under age 18 reported the results for children separately, 3) there is a paucity of trials or observational studies to provide evidence to guide the most effective and safe treatment for children, and 4) there is no existing evidence of the effectiveness of these medications on quality of life or other PROs reported by children or their parents.

The Future Research Needs Project also identified the following question as the highest research priority: "For maintenance of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of a TNF-alpha inhibitor and thiopurine versus a TNF-alpha inhibitor alone for the outcomes of steroid reduction, PROs, Crohn's Disease Activity Index (CDAI), pediatric CDAI and mucosal healing?"

We will conduct a large, pragmatic clinical trial to answer the following, closely related, clinical question. ***Among anti-TNF naïve patients with PCD initiating anti-TNF therapy, does the addition of low dose oral MTX improve: 1) induction and maintenance of long-term (1 to 3 years) steroid-free remission and 2) PROs? We will also evaluate safety outcomes and collect serum from trial participants to determine whether low dose oral MTX is effective in decreasing anti-TNF antibody formation, an established predictor of loss of response to anti-TNF therapy.***

To successfully conduct a large, pragmatic clinical trial such as this, effective strategies to engage and inform families about study participation will be needed. There is strong evidence that use of educational materials called decision aids leads to patients[19] and parents[20] that are better informed about treatment options. Recently, a decision aid about clinical trial participation led to similar benefits,[21] but this approach has not yet been applied in the conduct of pediatric clinical trials. Therefore, we will nest a cluster randomized controlled trial to answer the question: Does a pre-consent discussion enhanced with decision aids, compared to standard

pre-consent discussion, improve parent/patient engagement in decision making by increasing parent/patient knowledge related to trial participation?

1.1.2 A Critical Research Gap

This trial will address a critical research gap recognized by the scientific community, patients, and families. By conducting this ***long-term maintenance*** study within the ImproveCareNow (ICN) Learning Health System, the maximum 3-year follow-up period (already twice the length of typical 52-week studies) can be easily extended for many years using real-world data collected through the network's registry. Additionally, as described in more detail below, we can utilize the same infrastructure to accelerate the implementation of our findings into routine clinical practice.

Patient Centeredness

Choosing to initiate therapy with an anti-TNF biologic is a high-risk/high-reward decision and one of the most difficult decisions faced by patients with PCD and their families.[19, 20] Anti-TNF agents are undoubtedly the most effective medical treatment for PCD, yet this comes with significant potential costs: a potential risk of malignancy and other serious side effects, including immune suppression and auto-immune problems, such as psoriasis and lupus-like manifestations; repeated intravenous infusions or painful injections; and the financial burden incurred by families due to high cost.

The already difficult decision of whether to initiate an anti-TNF agent is compounded by the decision of whether or not to use combination therapy with a second immunomodulator. Despite the demonstrated efficacy of anti-TNF agents, not all patients achieve remission, and a significant proportion of patients who do achieve remission lose that response over time.[21] A significant factor in the loss of response is the development of antibodies to the anti-TNF agent, and prior studies of both azathioprine and MTX suggest combination therapy reduces the likelihood of antibody formation. Thus, the potential benefits of combination therapy include an improved likelihood of response and remission, reduction in antibodies to anti-TNF, and longer maintenance of remission. The potential risks include a greater risk of malignancy, including lethal hepatosplenic T cell lymphoma (HSTCL) and additional infectious complications. Unfortunately, the relative magnitude of the benefits and risks of each approach has not been established in PCD, leading to uncertainty among patients, parents, and physicians.

Children and their caregivers must balance these complex trade-offs at a time in their life and illness when they may be least equipped to do so. First, this decision must often be made quickly, and at a time when a pediatric patient and his/her family are experiencing deteriorating health, debilitating gastrointestinal symptoms, and low emotional reserve (child and parent depression and anxiety are common comorbidities).[7] Second, this decision is often faced at or near the time of diagnosis, when patients and their families are still struggling to adjust to a severe, chronic medical condition.

Potential for the study to improve health care and outcomes

The benefits of low dose oral MTX, in addition to anti-TNF, may be both *additive* and *synergistic*. As MTX is, by itself, an effective treatment for pediatric and adult CD,[22, 23] the effects of combination therapy should, at least, be *additive*. Emerging data also suggests a

synergistic role. One mechanism underlying loss of response to anti-TNF agents is the development of antibodies against the anti-TNF agent. Antibody development has been associated with lower anti-TNF levels, loss of response, and recurrence of disease activity.[24] Combination therapy with immunomodulators such as MTX has been associated with decreased antibody production and higher anti-TNF levels.[25] Additionally, combination therapy with immunomodulators may also have a direct impact on anti-TNF clearance.

The improved efficacy of combination therapy of infliximab with thiopurines, a different class of immunomodulatory medication than MTX, has been well-established in adult CD patients who were naïve to both thiopurines and infliximab, based on a 50 week study comparing infliximab monotherapy, azathioprine monotherapy, and combination therapy.[26] Additionally, antibodies to infliximab were detected in less than 1% of those on combination therapy, compared to 14.6% of those assigned monotherapy. However, combination therapy with thiopurines remains controversial in PCD patients due to the safety concerns of HSTCL.

Instead, combination therapy with MTX as an alternative to thiopurines has become increasingly common in the management of PCD, due to a presumed lower malignancy risk. Emerging data from rheumatology and gastroenterology studies suggest that combination therapy with MTX reduces the immunogenicity of infliximab (and perhaps other anti-TNF agents), resulting in decreased antibody development.[27] One adult trial of this strategy in adult patients was inconclusive. Feagan *et al* completed a 50-week, double-blind, placebo-controlled trial comparing MTX and infliximab to infliximab alone in 126 adult patients with moderate-severe CD who also received induction therapy with corticosteroids.[28] No differences in the primary or secondary outcomes were observed. However, patients who received MTX were less likely to develop antibodies to infliximab than those who received infliximab alone (4% versus 20%) and had higher median trough levels of infliximab. This raises the possibility that this study was too short to observe differences in outcomes that might develop over time, if antibody development translates into loss of response. A number of other limitations of this study have also been noted.[45]

A recent observational study in PCD adds further support to the potential for MTX to augment response to anti-TNF. Among patients treated with concomitant MTX, the probability of remaining on infliximab therapy for 5 years was 97% versus 58% for patients treated with infliximab alone[29].

No pediatric trials have directly compared anti-TNF monotherapy and combination therapy with MTX. This evidence gap and the potential for immunologic and pharmacokinetic differences in pediatric and adult patients have led to marked practice variation in care for children with PCD. For example, we performed a preliminary analysis of the Improve Care Now registry and found that 66% of PCD patients on anti-TNF therapy were using monotherapy and 34% were using combination therapy (18% with MTX and 16% with 6MP/azathioprine). ***This demonstration of clinical equipoise indicates that a pediatric trial of anti-TNF combination versus monotherapy is an urgent and unmet need.***

In this trial, we have chosen to evaluate low dose oral MTX. The rationale for utilizing MTX over thiopurines is that physicians are more comfortable with the safety profile of MTX. In contrast, while thiopurines used in combination anti-TNF are highly effective treatment for CD, this regimen has been associated with very rare cases of HSTCL, particularly in young males. The

dosage and route of MTX were selected to minimize the known dose-dependent risks of MTX (e.g. nausea, liver toxicity) and the discomfort of subcutaneous injections. The bioavailability of oral MTX in PCD patients has been previously established[30], and combination therapy with low-dose oral MTX is commonly utilized in the care of pediatric IBD patients.

1.1.3 Study Setting

We anticipate that most study centers will be members of the ICN network, as described below. Selected additional high-volume pediatric IBD centers will also be invited to participate.

ImproveCareNow is a learning health system[31] that was built with support from AHRQ Enhanced Registries grants (R01HS20024 and R01HS22974), an NIH Transformative Research grant (DK085719), and a Patient Centered Outcomes Research Institute (PCORI) patient powered research network (PPRN) infrastructure grant. The purpose of ICN is to transform the health, care and costs for all children and adolescents with CD and ulcerative colitis by building a sustainable collaborative chronic care network that enables patients, families, clinicians and researchers to work together to accelerate innovation, discovery and application of new knowledge[32]. ICN has made significant strides in developing the social, scientific, and technological infrastructure to radically alter how patients and clinicians engage in every aspect of a learning health system. Well-developed processes and tools enable patients, families, clinicians and researchers to work together to improve care, identify gaps in outcomes, and prioritize research studies (including this proposal) when there is uncertainty about the best management practices. Once new knowledge is generated through research, quality improvement (QI) methods (e.g., decision support, pre-visit planning and transparent quality measurement) and interventions to support patient self-management can be utilized to rapidly disseminate and implement that knowledge into practice.

Use of structured QI methods to improve care and facilitate research. ICN uses collaborative learning methods based on the IHI Breakthrough Series[33] and methods of commons-based peer production[34] to enable ongoing contribution from patients, families, clinicians and researchers to improve care and outcomes and facilitate research. Network Learning Sessions are held twice each year and provide opportunities for clinical teams, patients, and parents to come together to review network performance data, share best practices, learn new QI skills, and set goals. Between Learning Sessions, care teams, patients and parents share and learn from one another through monthly webinars, an active listserv, and an online forum (www.improvecarenowexchange.org) for sharing knowledge and tools. The network is organized in a node structure in which teams are clustered into "Learning Labs" comprised of 8-10 teams with similar attributes (e.g., experience, geography, practice size). Each Learning Lab is assigned a QI coach who is responsible for coordinating efforts between and within Learning Labs. All QI efforts are based on the Model for Improvement[35]: setting aims, establishing measures, and performing iterative cycles of identifying, testing, implementing, and spreading changes that result in improved care and outcomes.

To promote the reliable implementation of chronic care processes, the Network uses QI methods and a patient registry. Specific activities include clinical performance measurement and reporting, pre-visit planning and decision support, and population management. Additional and engaging patients and families in shared decision making. Since 2007, as a result these and other processes, the proportion of patients in remission (with inactive disease) has increased from 55% to 79%[36].

Data collection/Registry In 2007, ICN established a standardized, web-based clinical registry that enabled collection of standardized, IBD-specific data about processes and outcomes of care (e.g., disease characteristics, patient well-being, laboratory results, and medications). In 2010, with AHRQ funding, ICN developed a modular, open-source, registry that can be linked to an electronic health record (EHR) to minimize the burden of manual data entry. This allows for a significant portion of registry data to be transferred electronically via a secure web portal to the registry, and stored for re-use in QI, chronic care delivery, and CER.

Data captured through EHR-linkage or web-based forms consist of discrete elements that conform to a standardized data model. Importantly, the primary and many secondary outcomes of this trial are routinely collected in the Registry, including the Short Pediatric Crohn's Disease Activity Index (SPCDAI), Physician Global Assessment, hospitalizations, surgeries, and other clinical measures.

MIGRATION OF DATA TO A THIRD-PARTY HOSTING VENDOR – The COMBINE database will transition from the original registry (hosted by CCHMC), to a new registry hosted by a third party. We expect the new registry to be operational for data entry in July 2021, and for all migration of data from the old registry to be completed by December 2021. All of the data previously collected in the COMBINE database will be migrated into the third party database. If a patient was included in the registry but is no longer a patient at the center (moved to another city, lost to follow-up, etc.), their data will still be migrated, no new data will be collected. The only data used for human subjects research will be from patients who have consented for research.

1.2 Investigational Agent

Methotrexate, which was initially developed in 1948 for the treatment of leukemia, has been clinically used for nearly 60 years as low and high dose therapy in leukemias, certain lymphomas, Wegener's' disease, psoriasis and rheumatoid arthritis. In inflammatory bowel disease the clinical efficacy has been established for steroid dependent Crohn's.[37]

MTX is an analogue of folic acid and of aminopterin, which is also a folic acid antagonist. One of the main mechanisms of action is the inhibition of dihydrofolate reductase. This enzyme is involved in the *de novo* synthetic pathway for purines and pyrimidines. The rationale for the use of high dose MTX in the treatment of cancer is that the fast proliferating malignant cells become starved of purine and pyrimidine precursors and therefore are not able to sufficiently maintain deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis leading to a decreased proliferation.

In contrast, the underlying anti-inflammatory effect of low-dose MTX in inflammatory diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel diseases is less clear, since the anti-proliferative activity of low-dose MTX is minimal. Multiple mechanisms of actions are proposed including promotion of adenosine release, inhibition of production of pro-inflammatory cytokines, suppression of lymphocyte proliferation, neutrophil chemotaxis and adherence and reduction of serum immunoglobulin's [38, 39].

MTX can be administered by oral, subcutaneous, intramuscular or intravenous routes. Orally, MTX is absorbed in the jejunum and good bioavailability is only achieved in doses below 15 mg. Above this threshold absorption rates can vary up to 30%[40].

MTX has a relatively short serum half-life of 6 to 8 hours and more than 80% of the drug in its intact form is excreted in the urine by glomerular and tubular secretion. Thus, drugs interfering with renal tubular secretion such as probenecid or the existence of low kidney function result in an increase in circulating MTX, which can lead to toxic side effects. Approximately 35% of MTX is bound to plasma proteins including albumin. Toxicity can be observed with concurrent low serum albumin concentrations or if MTX is displaced from albumin by drugs such as sulfonamides or tetracyclines.

After MTX is taken up by tissues, it is converted to MTX polyglutamates, which are long-lived derivates that retain biochemical and biological activity. The MTX polyglutamates are thought to be responsible for most of the anti-inflammatory effects. However, studies in patients with Rheumatoid Arthritis (RA) and IBD have so far not found any meaningful correlation between the clinical efficacy of MTX and serum or plasma levels of either intact MTX or its metabolites, suggesting that there is little clinical value in monitoring these levels[41].

1.3 Clinical Data to Date

The effectiveness of intramuscularly administered MTX 25 mg once weekly in steroid dependent CD in adults is well documented. In the North American Crohn's Study Group landmark trial, 39.4% of the patients receiving MTX 25 mg subcutaneously (sq) / week achieved clinical remission, as defined as a CDAI < 150 points and the discontinuation of prednisone, compared to 19.1% of the patients in the placebo group[42]. Feagan et al. also demonstrated a significant efficacy of 15 mg MTX sq once weekly in maintaining steroid free remission in CD patients (after 40 weeks 65% remission in the MTX group vs. 39% in the placebo group) [43].

Although there are no placebo-controlled, randomized trials of MTX for the treatment of PCD, the use of MTX in this patient population is increasing and the body of published observational studies is growing. Mack et al. first reported on 14 patients with a mean age of 10.6 years who had active CD and were intolerant or unresponsive to 6MP[44]. Subcutaneous administration of MTX resulted in 64% of patients with clinical improvement by as early as 4 weeks. Steroid sparing was also demonstrated. Adverse events attributed to MTX were nausea and headache leading to withdrawal of therapy in two patients. No patients demonstrated bone marrow suppression, abnormal liver chemistries, or pulmonary complications. Another single center experience demonstrated a 12-month steroid-free remission rate of about 33% which is similar to that seen in reports of adult patients with CD[45]. Good tolerance of the MTX therapy was reported.

Two multicenter retrospective studies published in 2006 and 2007 demonstrated a 40–45% 1-year steroid-free remission rate with MTX as a second-line immunomodulator in PCD patients[46, 47]. No difference in effect was seen whether the indication for the MTX was lack of thiopurine efficacy or intolerance. Again, overall good drug tolerance was demonstrated as were a steroid sparing effect and a positive effect on linear growth[46].

More recently, a retrospective cohort study 172 children who received at least 3 months of MTX without thiopurine or biologicals and had ≥1 year of follow-up was reported[48]. Twenty-seven percent of those receiving MTX as a first line immunomodulator (IMM) achieved ≥12 months of sustained clinical remission without surgery, thiopurine, biologicals, or corticosteroids, as

compared with 35% of those receiving MTX as a second line agent (p> 0.05). Fifteen percent of patients developed an ALT >60 international units/liter and 12% developed a white blood cell <4000 cells per microliter while on MTX. Only 4% of these discontinued MTX completely. A recent European multi-center retrospective cohort of 113 children with CD in remission (median age 14 years) demonstrated a slightly higher effectiveness of MTX. In this study, 52% of patients remained in steroid- and biologics-free remission 12 months after starting MTX monotherapy[49].

There are also emerging pediatric data regarding combination therapy with anti-TNF biologics and MTX. In a single center experience, PCD patients treated with low-dose oral MTX (<10 mg/wk) demonstrated no benefit in terms of infliximab effectiveness or durability as compared to children receiving infliximab monotherapy[50]. However, Grossi recently reported a retrospective, multicenter cohort study of 81 children receiving combination therapy with infliximab and MTX (60 male, 21 female). Males receiving MTX for more than 6 months showed a significantly greater likelihood of remaining on infliximab throughout the follow-up period compared to no MTX or other immunomodulator or ≤6 months MTX, with 5 year probabilities ranging from 0.41 ±0.11 among patients who received no concomitant immunomodulator to .97±.03 in patients treated with MTX > 6 months (p<0.001). Among females, the trend was in the same direction. Additionally, the durability of infliximab was significantly greater with MTX as compared to thiopurines (97±0.03 vs 0.58±0.08). In this study, the investigators were unable to identify an optimal dose or route of administration for concomitant MTX, as nearly all patients continued on infliximab regardless of MTX dose/route[29].

1.4 Dose Rationale and Risk/Benefits

For this trial, the investigators have decided on a slightly lower dose of MTX than the 15mg/M^2 given subcutaneously that has been most frequently used in MTX monotherapy for CD.[46] Specifically, we are utilizing a dose of 10mg/M^2 given orally (or to simplify 15 mg for children ≥ 40kg, 12.5 mg for children 30 to <40 kg, and 10 mg for children 20 to <30 kg). The rationale for this dosage is as follows. First, we believe the dose should be higher than 10 mg (for large size children), as one pediatric study suggested no benefit to doses less than 10 mg, and a second study failed to detect a threshold effect. As dose-dependent AEs with MTX are common, and include nausea, leukopenia, elevated liver function, and mouth sores, we plan to utilize a lower dose than the 25mg adult induction dose. We anticipate this will improve patient recruitment, tolerability, compliance, and long term retention of study subjects as well as reduce the frequency and severity of expected adverse reactions. Therefore, we have selected a dose of 15mg (in larger children) as this is the recommended maintenance for monotherapy in adult patients. We have scaled the dose downwards, based on weight, as described above.

We have selected oral administration, based upon pediatric data suggesting that oral bioavailability is comparable to that of subcutaneous administration, particularly at lower doses, and the oral formulation should substantially increase acceptability by patients and their guardians.

1.5 Standard versus Enhanced Consent

A nested study was conducted as part of this study to determine if an enhanced consent process was well received and assisted participants with understanding of the study better than a standard consent process.

As part of the enhanced consent process, select sites received materials to assist with the consent discussion that included pictures and plain language texts. Potential participants were randomized to the use of these enhanced materials or to a standardly accepted research consent process.

Data regarding the use of the enhanced consent materials was found to be null. While participants shared an appreciation for the materials, there was no indication the materials alone assisted with the participants' knowledge of the study.

Materials will be made available to all sites participating in this study to be used as an optional consenting aid.

2 Study Objectives

2.1 Primary Objective

- To determine whether, in children with CD initiating anti-TNF biological therapy with infliximab or adalimumab, low-dose oral MTX is more effective than placebo in the induction and subsequent maintenance of steroid-free remission for a treatment period of up to three years. We hypothesize that the addition of MTX to anti-TNF therapy will be more effective than placebo (i.e. anti-TNF monotherapy).

2.2 Secondary Objectives

- To determine whether, in children with CD initiating anti-TNF biological therapy with infliximab or adalimumab, low-dose oral MTX leads to better PROs as compared to placebo. We hypothesize that the addition of MTX to anti-TNF therapy will result in better PROs than placebo (i.e. anti-TNF monotherapy).
- To determine whether low-dose oral methotrexate, in combination with anti-TNF biological therapy, is more effective than anti-TNF monotherapy in reducing anti-TNF antibody formation resulting in higher anti-TNF trough levels.

2.3 Additional Objectives

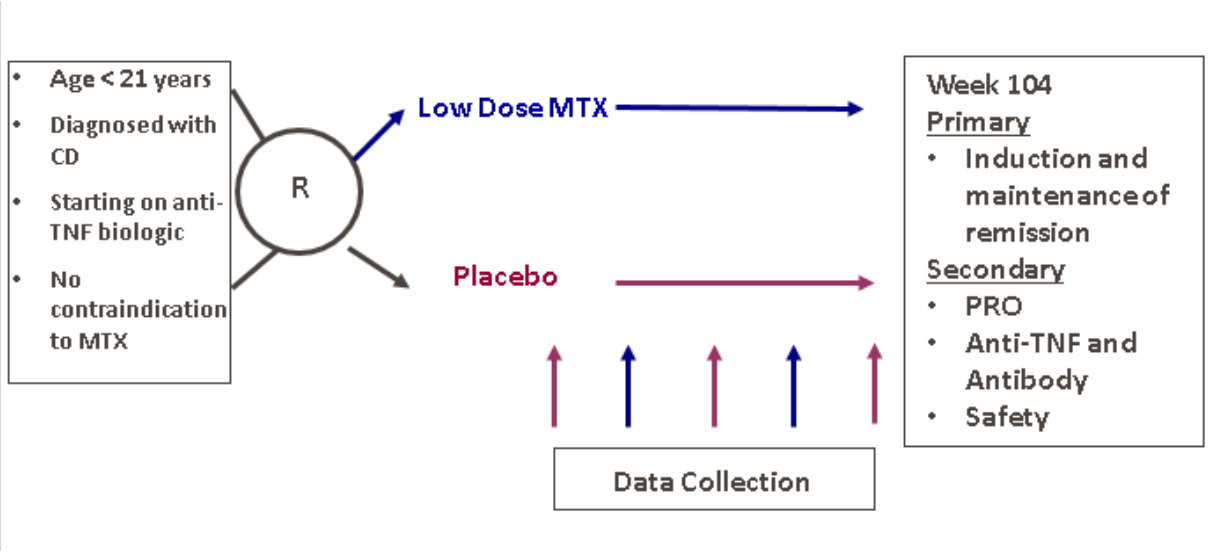
- To describe the investigator-reported AEs (Grade 2 or higher[1]) in PCD patients initiating anti-TNF, treated with low dose oral MTX and in a placebo comparison group.
- To create a registry to hold and make data and biosamples about patients initiating anti-TNF therapy to be used in future QI and research endeavors to generate new knowledge and/or improve care for patients.

3 Study Design

3.1 General Design

We will conduct a placebo-controlled, double blind, pragmatic, multi-site randomized clinical trial to determine whether, in children with CD initiating anti-TNF biological therapy, low-dose oral

MTX is more effective than placebo in the induction and subsequent maintenance of steroid-free remission. We will use randomization within each site, stratified by anti-TNF agent used (infliximab or adalimumab), to ensure balanced treatment allocation within individual sites. A randomized, double-blind trial is necessary to control for measured and unmeasured confounders, as well as potential biases that could impact the assessment of study outcomes.



Registry data sharing for Research

Research that address the objectives listed in section 2 will be performed without additional protocols and/or IRB review using the data analysis outlined in section 8.

Data and samples housed within the database and repository may be used for research activities as an ongoing effort to generate new knowledge and/or improve the care of patients at participating sites. Participating Investigators may request data and/or specimens for research activities of the existing samples and data without an additional IRB application, review, and approval. All retrospective use of data and/or samples under a limited data set will meet the ongoing approval status of this overall project. A listing of these projects and the data and/or specimens provided will be documented in this project file for reference, if needed.

If a participating Investigator proposes a research project that will require collecting data prospectively and/or with the need to contact database patients, an IRB approved protocol with IRB approval letter must be submitted for review to a member of the regulatory team. Once these documents are reviewed, approval to release the requested data and/or specimens to the Investigator will be shared with the data management team. A listing of these projects and the data and/or samples provided will be documented in this project file for reference, if needed.

Linkage of Participant Data to Visits

The COMBINE database will have the ability for a direct linkage to participating site's electronic medical record. Sites that opt to have a direct linkage will be responsible for ensuring all data elements are transferred into the COMBINE database by spot checking data elements. Manual entry of non-electronic medical record data, such as questionnaires, etc. will be required by the site's study team. COMBINE and the care center are responsible for ensuring proper agreements and protections are in place for this direct linkage.

Recruitment and Enrollment into Future Studies

The individuals included in the COMBINE database may be contacted for future research studies. These studies may originate from participating Investigators, participating sites, non-profit organizations, or for-profit organizations. All requests for patient listings must include a synopsis of the planned research study and a clear definition of inclusion/exclusion criteria. Once these are reviewed by the data management team, the patient listing and contact information will be shared with the requesting individual or organization. A listing of these requests and the data provided will be documented in this project file for reference, if needed.

3.2 Primary Study Endpoints

Primary Outcome - Induction and maintenance of steroid-free remission for up to 3 years.

This will be analyzed as time to first *treatment failure*, as defined by occurrence of any of the following:

- Failure to achieve remission (SPCDAI < 15) by the week 26 visit.
- If initiating the study on steroids for IBD reasons, failure to complete a steroid taper by week 16.
- SPCDAI ≥ 15, attributed to active Crohn's disease, at two or more consecutive visits beyond the week 26 visit. Elevated SPCDAI (≥ 15) due to a non-IBD reason (i.e. infection, IBS, normal colonoscopy or other test of mucosal inflammation) does not count toward this outcome.
- Hospitalization for active IBD or abdominal surgery after week 25.
- Use of oral prednisone or prednisolone, enteral release budesonide, or intravenous (IV) methylprednisolone for a period of over 10 weeks cumulatively, beyond week 16. Note, this does not include use of steroid as a premedication for anti-TNF administration or steroids used for conditions other than CD (e.g. asthma, poison ivy, etc.).
- Discontinuation of the anti-TNF agent and/or study drug for lack of effectiveness or toxicity.

Switching from the biologic originator to a biosimilar or vice versa does not constitute discontinuation of the anti-TNF.

Discontinuation of anti-TNF in the setting of treatment de-escalation will not be considered as a treatment failure. Neither will discontinuation of the anti-TNF or study medication for non-medical reasons (i.e. desire to switch to an alternative therapy).

NOTE: Any patient who meets a primary study endpoint as described above, or who discontinues their first-line anti-TNF for CD for any reason, must discontinue study medications. Please see section 4.4.

3.3 Secondary Study Endpoints

There are three secondary study endpoints:

1. Mean Patient Reported Outcome Measurement and Information System (PROMIS) Pain Interference T score by treatment arm. We will compare the mean of PROMIS Pain Interference T scores at week 52 and week 104 between the treatment groups.

2. Mean PROMIS Fatigue T score by treatment arm. We will compare the mean of PROMIS Fatigue T scores at week 52 and week 104 between the treatment groups.

Proportion of patients with positive anti-TNF antibody status based on the sample collected in the second year (week 91). If a sample is not collected in the second year, the sample collected in the first year will be used (week 14).

3.4 Tertiary Endpoints

Indirect and direct markers of disease activity and mucosal inflammation and healing. Objective and firm endpoints are increasingly recognized as important outcomes of explanatory trials in CD, including clinical efficacy studies designed for FDA approval. These include routine laboratory assessments including erythrocyte sedimentation rate (ESR), C reactive protein (CRP), albumin, and hemoglobin.

There are many additional tests for which there is ongoing debate regarding routine clinical use due to their high cost and/or invasive nature [calprotectin (biomarker of intestinal inflammation) and endoscopy)]. Given the pragmatic nature of this trial, we will not mandate the use of such tests by study protocol. Rather, we will collect these test results if/when they are performed in the context of each patient's routine clinical care. We will educate clinicians on one endoscopic scoring system commonly utilized to assess disease activity in clinical studies, the Simple Endoscopic Score for Crohn's Disease (SES-CD), so that they may more accurately report their endoscopic findings. As we anticipate that routine use of such testing to assess mucosal healing will increase over the next several years, this will minimize the potential for differential testing based on patient clinical status.

Change in anti-TNF dose or interval. The anti-TNF dose may be changed at the discretion of the treating provider. Changes in anti-TNF dosing will be recorded, as will the reason for these changes, and this will be analyzed as pre-specified endpoints.

Other endpoints to be analyzed include anti-TNF trough levels, induction of remission, maintenance of remission, and height velocity Z scores. We will assess induction of remission through the week 26 visit (window 22-30 weeks). Maintenance of remission will be assessed at time points following the confirmation of successful induction.

3.5 Safety Endpoints

The major safety concerns for PCD patients undergoing treatment with anti-TNF biologics (with or without combination therapy) include the risk of opportunistic infections and malignancy.

Safety concerns with MTX include bone marrow suppression, hepatotoxicity, nausea, and hair loss. Although this trial is designed primarily for CER rather than safety, we will monitor AEs regularly and we will work with a Data Safety Monitoring Board (DSMB) 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, and are better assessed from registries involving thousands of patients. However, a key strength of conducting this study in the context of ICN is that long-term safety data will continue to be collected by the network and accumulate following the conclusion of the funded trial itself. Hence, this trial will lay the groundwork for long-term safety studies.

3.6 Endpoints for Trial of Enhanced vs. Standard Pre-Consent Discussion

The primary outcome is the percentage correct on parent/patient knowledge items related to trial participation. The secondary outcome is the percentage of parents/patients who agree to enroll in the pragmatic clinical trial.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1) Diagnosis of CD established confirmed by the treating clinician, and established by standard clinical criteria (radiography, endoscopy, histology)
2) Less than 21 years of age
3) Greater than or equal to 20 kg in weight
4) Initiating anti-TNF therapy with infliximab or adalimumab (including biosimilars). Although the decision to start anti-TNF is at the discretion of the treating physician rather than by protocol, standard of care in pediatric Crohn's includes ensuring that the patient has active inflammation (generally through assessment of blood work, imaging, endoscopy/colonoscopy, fecal calprotectin, etc.) as the cause of his/her symptoms, rather than infection (viral, *C. difficile*, other), Irritable Bowel Syndrome, or complication of CD such as stricture or abscess.
5) Ability to provide parental permission and child assent (where applicable), or adult consent for patients ages 18-20

4.2 Exclusion Criteria

1) Prior use of anti-TNF therapy for CD
2) Lack of stable home address that study medications can be mailed to
3) Anticipated short length of follow up at study center (plans for family to move, transition to adult GI (gastrointestinal) provider, etc.). Patients expected to leave practice < 12 months from enrollment should not be enrolled.
4) Concurrent abdominal or pelvic abscess. A recent history of abdominal or pelvic abscess, which is controlled, does not exclude the subject.
5) Prior intra-abdominal surgery without a clinically significant relapse (i.e. patients starting on anti-TNF for post-op prophylaxis or for endoscopic recurrence only should not be included)

6) Receipt of a live virus vaccine within the last 30 days
7) Pregnancy, planning to become pregnant, or high risk of pregnancy as determined by the local investigator
8) Breastfeeding
9) Refusal to stay abstinent or utilize 2 forms of birth control while on study medication (for female patients)
10) BMI ≥ 98% for gender and age
11) Known previous or concurrent malignancy (other than that considered surgically cured, with no evidence for recurrence for 5 years). A recent history of basal cell or squamous cell carcinoma, which is considered surgically cured, does not exclude the subject. Those with a recent history of colonic adenoma or dysplastic lesions should be excluded.
12) Known high alcohol consumption (more than seven drinks per week)
13) Patients with serum albumin < 2.5 g/dl
14) Patients with WBC < 3.0 $x10^9$/L
15) Patients with platelet count < 100 $x10^9$/L
16) Patients with initial elevation of AST or ALT > 1.5 times above normal limit
17) Patients with known active infection with Clostridium difficile (C. difficile) (untreated infection based on clinician assessment does not apply to colonization or infection controlled with current or prior treatment)
18) Patients with pre-existing hepatic disease
19) Patients with pre-existing renal dysfunction (creatinine > 0.8 for children age<10, creatinine > 1.2 mg/dl for children age 10-18, and creatinine > 1.5 mg/dl for adults age 18 years and older).
20) Patients with a pre-existing chronic lung disease other than well controlled asthma
21) Current treatment with one of the following drugs: Probenecid (Probalan), Acitretin (Soriatane), Streptozocin (Zanosar), Azathioprine (Imuran, Azasan), 6-mercaptopurine (Purinethol, Purixan)
22) Other concerns about the patient/family's ability to participate in the study

4.3 Subject Pre-screening and Recruitment

Participant identification and pre-screening. Potential subjects will be identified through the standardized pre-visit planning process. Care teams (physicians, nurses, study coordinators, etc.) use the process to anticipate patient needs and pre-arrange/coordinate services. Pre-visit planning also includes a review of research studies a patient may be eligible for (or enrolled in). This allows necessary staff to have recruitment or study visit materials available at the time of the encounter.

A limited waiver of HIPAA is necessary to pre-screen patient's medical record / EHR data to look for indications that a patient may be heading toward anti-TNF therapy initiation (i.e. recent negative trends in sPCDAI, lab values, imaging, and endoscopic assessments) as well as to review past medical history for other inclusion and exclusion criteria.

Recruitment. All potential patients / parents identified during pre-screening, who are approached for the trial, will take part in a pre-consent discussion that introduces the study using IRB approved recruitment materials.

In addition to asking questions of study investigators and research coordinators, potential patients / parents who are approached for the trial will be given the opportunity to connect with Resource Parents – parents of current study participants – to learn about what it is like to participate in this research study. The process for the identification, training, and coordination of Resource Parents will be detailed separately and will include procedures for maintaining patient confidentiality.

Informed consent. In order to inform overall trial recruitment efforts, we will attempt to collect a reason from those who decline to participate / sign a consent form. For those who decide to participate, informed consent (and assent where applicable) will be obtained prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for this study. All sites will have access to materials for an enhanced consent process. The use of these materials for each site is optional.

4.4 Discontinuation of Study Medication

Dose discontinuation: Any patient who meets a primary study endpoint or who discontinues their first-line anti-TNF for CD for any other reason, must discontinue study medications. Upon request, the treating physician will be unblinded if there is a clear case that knowledge of that patient's treatment assignment would impact future treatment decisions.

In the event of medical emergencies that require immediate unblinding, treating physicians will have access to a 24-hour pager. Patients who experience Serious Adverse Events or abnormal laboratory values may also discontinue study treatment based on assessment by the Safety Medical Monitor and/or a local site investigator.

Patients who become pregnant over the course of the study will also discontinue study treatment.

At any point in time, the clinician/investigator and/or the patient/caregiver may choose to discontinue study treatments for any reason. Reasons may include poor study follow-up, change of mind, logistics, etc.

See section 6.9 for procedures related to discontinuation of study medication.

Patient Follow-up: Patients discontinuing study treatment will continue to be followed for up to 3 years unless consent is withdrawn for the remaining study procedures, or they have met a primary study endpoint. If the patient has met an endpoint, the follow-up period will be for a maximum of two years. See section 6.9 for details related to follow-up of patient off study medication. The subsequent treatments and outcomes of these patients will be utilized in secondary analyses.

4.5 Early Withdrawal of Subjects

Early Termination: Patients/caregivers may also withdraw consent. The term "withdrew consent" means that the patient/family chooses to fully discontinue participation in the trial. This includes discontinuation of study treatment and all other IRB-approved research activities (including use

of routine follow-up visit information for trial purposes). Efforts should be made to collect study data up to the date of withdrawal and to make a follow-up plan for any ongoing adverse events or pregnancy. Patients at ICN study centers will continue to have routine clinical data collected through the ImproveCareNow Registry, but will not undergo any additional follow-up or data collection that is specific for this trial. Subjects who withdraw after shipment of study medications will not be replaced by recruitment of additional subjects.

5 Study Drug

5.1 Description

Methotrexate (MTX), which was initially developed in 1948 for the treatment of leukemia, has been clinically used for nearly 60 years as low and high dose therapy in leukemias, certain lymphomas, Wegener's' disease, psoriasis and rheumatoid arthritis. In inflammatory bowel disease the clinical efficacy has been established for steroid dependent Crohn's.

MTX is an analogue of folic acid and of aminopterin, which is also a folic acid antagonist. One of the main mechanisms of action is the inhibition of dihydrofolate reductase. This enzyme is involved in the de novo synthetic pathway for purines and pyrimidines.

Although there are no placebo-controlled, randomized trials of MTX for the treatment of pediatric CD, the use of MTX in this patient population is increasing and the body of published observational studies is growing. Oral MTX is absorbed in the jejunum and good bioavailability is achieved in doses below 15 mg.

Our study will utilize MTX 2.5mg pills or matching placebo.

5.2 Treatment Regimen

1) Oral MTX or placebo: The weekly dose will be 15 mg for children ≥ 40kg, 12.5 mg for children 30 to <40 kg, and 10 mg for children 20 to <30 kg.
2) Ondansetron or placebo: A twice per week, 4mg dose of ondansetron for the MTX group (or matching placebo for the placebo group) will be provided as pre-treatment to prevent nausea. The first dose of ondansetron or placebo should be taken one hour before the weekly dose of MTX or placebo. The second dose should be taken the morning after the weekly dose of methotrexate or placebo. In consultation with the provider, the patient may skip the second dose of ondansetron or placebo. **The study provider may opt-out of the provision of this component of the study treatment based on clinical judgement. See below.*
3) A 1 mg dose of folic acid per day for all patients (those receiving MTX or placebo) will be provided. This will help to reduce the risk of side effects in the MTX group.

Table 1: Treatment Regimen Summary

Arm 1	Arm 2
MTX (10, 12.5, or 15 mg, once weekly)	Placebo (once weekly)
Ondansetron (4 mg, twice weekly)	Placebo (twice weekly)
Folic Acid (1 mg, daily)	Folic Acid (1 mg, daily)

In special circumstances, the study medications may be dissolved and administered orally or by gastrostomy tube (G-tube). Instructions will be provided for dissolving the methotrexate / placebo in a closed system.

As nausea may be a symptom of CD (even in the absence of MTX), all patients should be given a prescription by their treating physician for an age based dose of ondansetron to be used on an as needed (PRN) basis, as is consistent with standard of care (4mg for patients < 12 years of age; 4 or 8mg for patients 12 years of age and older). Note that for patients who receive ondansetron as a study medication and as a PRN prescribed by their physician, the maximum dose of 16mg will not be exceeded. The prescription of ondansetron by each patient's physician will be in accordance with best clinical practices. As ondansetron has been reported to very rarely cause cardiac arrhythmias in patients with prolonged QT syndrome or medications that prolong the QT interval, clinicians will be educated about not utilizing ondansetron in these populations. Of note, oral ondansetron utilized in a single dose has not been reported to cause cardiac arrhythmias.

Ondansetron / placebo Opt–Out. Because nausea is a common side effect of methotrexate, ondansetron is included as part of the treatment regimen to help protect the blind. The study provider may opt-out of sending the ondansetron / placebo portion of the study treatment regimen and may prescribe another anti-emetic per routine clinical care. The decision to opt-out will incorporate clinical judgement in regard to patient safety and maintenance of the blind.

Folic Acid. At their discretion, the study provider may advise patients not to take folic acid on days where methotrexate / placebo is taken, according to their usual practice.

Anti-TNF. Since the decision to start anti-TNF is at the discretion of the treating physician, all patients will have the anti-TNF agent (infliximab or adalimumab) prescribed and dose adjusted according to their physician's usual practice, not a pre-specified study protocol. Selection of anti-TNF agent is at the discretion of the treating physician. Standard best practice guidance will be provided to all participating physicians, including 1) the identification of appropriate patients to start on anti-TNF, and 2) appropriate screening for tuberculosis and other infections prior to starting anti-TNF.

As described below, the patient should be randomized to study treatment as close to the start of anti-TNF as possible, but no more than 42 days (before or after) the initiation of anti-TNF.

Treatment will continue for up to 3 years.

5.3 Method for Assigning Subjects to Treatment Groups

Participants will be randomized to one of the two treatment arms with a 1:1 allocation ratio. We will utilize a centralized, stratified, randomization approach in which randomization in each stratum will occur in a constrained block with maximum imbalance of 3. We will stratify within sites and by anti-TNF agent prescribed (infliximab or adalimumab).

5.4 Packaging

MTX and matching placebo tablets will be packaged in 1-Clic Clear Vu 40-dram prescription vials. Vials are USP 671 compliant (light, moisture, and child resistance) and contain an audible click enclosure to ensure the vials are properly secured. Each shipment will contain enough tablets for 13 doses and vials will be labeled with clear instructions for how many tablets to take at each dosing day (once weekly).

Ondansetron and matching placebo tablets will be packaged in 1-Clic Clear Vu 40-dram prescription vials. Vials are USP 671 compliant (light, moisture, and child resistance) and contain an audible click enclosure to ensure the vials are properly secured. Each shipment will contain enough tablets for 13 twice-weekly doses and vials will be labeled with clear instructions for how many tablets to take at each dosing day (one hour before MTX/placebo and the morning after the weekly MTX/placebo dose). In consultation with the provider, the patient may skip the second dose of ondansetron or placebo.

Folic acid 1mg tablets will be packaged in 1-Clic Clear Vu 40-dram prescription vials. Vials are USP 671 compliant (light, moisture, and child resistance) and contain an audible click enclosure to ensure the vials are properly secured. Each shipment will contain enough tablets for 13 weeks of daily dosing, with instructions to take one tablet by mouth once daily.

Patient-specific supplies will be packaged together in a box kit, which will be shipped to the participant. Additional instructions will be included with the kit, detailing the entire regimen and when each of the three medications should be taken. A 7-day pill box will be provided to assist with proper dosing.

5.5 Blinding of Study Drug

For MTX, a commercial 2.5mg tablet will be purchased in bulk and repackaged into smaller bottles as described above, at the time of dispensing. Similar-appearing placebo tablets, consisting of microcrystalline cellulose and binding and coloring agents, will be manufactured by the cGMP (current Good Manufacturing Practices) Laboratory at the Temple University School of Pharmacy, using a tableting die plate made to create tablets with the same size/shape and similar markings to the original MTX tablet. Those placebo tablets will also be repackaged into smaller bottles as described above, at the time of dispensing.

For ondansetron, a commercial 4mg tablet will be purchased in bulk and repackaged into smaller bottles as described above, at the time of dispensing. Similar-appearing placebo tablets, consisting of microcrystalline cellulose and binding and coloring agents, will be manufactured by the cGMP Laboratory at the Temple University School of Pharmacy, using a tableting die plate made to create tablets with the same size/shape and similar markings to the original ondansetron tablet. Those placebo tablets will also be repackaged into smaller bottles as described above, at the time of dispensing.

For folic acid, commercial 1mg tablets will be purchased in bulk bottles of 500 or 1,000 tablets and will be repackaged into smaller bottles as described above, at the time of dispensing.

5.6 Receiving, Dispensing, Storage and Return

5.6.1 Receipt of Drug Supplies

The central pharmacy will purchase the three commercial medications either through pharmaceutical wholesalers or directly from the manufacturers. These products will remain in their original manufacturers' containers prior to repackaging for individual subjects. Placebo manufactured by the Temple University School of Pharmacy, will be shipped to the central pharmacy in bulk. Perpetual inventories will be maintained by the central pharmacy using a 21 CFR (Code of Federal Regulations) Part 11 compliant electronic drug accountability system.

5.6.2 Storage

Both active and placebo tablets, will be stored in an investigational drug storeroom at the central pharmacy, under tight security (research pharmacy staff only) and controlled room temperature conditions (20-25 Celsius).

5.6.3 Dispensing of Study Drug

As this is a pragmatic clinical trial, it is important that participating practices are not required to have an on-site research pharmacy. Additionally, we do not want dispensing of study drugs to interrupt routine clinical practice. Therefore, upon randomization, the central pharmacy will distribute study drugs by mail to each participant's home.

Enrollment and randomization of a subject at the clinical site, will trigger an alert from the data management system, to the central pharmacy, that a treatment kit is needed, along with the treatment condition, dosing information (and weight for the pharmacist to confirm this with) and the subject's and parent's contact information so that the product can be shipped. Prior to the initial shipment of study medication, the pharmacist will contact the subject (or parent) to confirm the subject's information and provide counselling according to a script. Any discrepancies or inconsistencies discovered during the call will be resolved with the clinical site prior to processing the initial shipment. The bottles will be filled by a research technician and labeled, then checked by a licensed pharmacist before the box kit is sealed and sent to the subject. The pharmacy will track the package until receipt by the intended recipient and will notify the sponsor of any problems. The site study coordinator will be able to access shipment details via a report within the trial electronic data capture system.

Each drug kit will contain a 3-month supply of medication. Refills will also be provided by the central pharmacy according to the study dosing schedule. All drug kits will contain dosing instructions.

Following each shipment, a physician, nurse, or study coordinator will contact the patient/parent to ensure they received the drug kit in good condition, review dosing instructions, and answer any questions. The date the patient began study drug will be recorded.

5.6.4 Return or Destruction of Study Drug and Subject Compliance Monitoring

Any unused study medication will be returned to the clinical site and given to the study team at the next regularly scheduled visit after a new kit is received, or upon completion of the treatment phase of the trial. The site study team will document compliance by counting the quantity of tablets unused when the bottles were returned. Once quantities are documented in the electronic CRF (eCRF), the study medication may be destroyed in biohazard waste following the site's policies for investigational drug destruction. For sites that do not have a suitable method of destruction, arrangements may be made on an individual site basis, to return product to the central pharmacy for incineration.

If a subject forgets or is unable to bring pills to the clinic appointment, reasonable efforts will be made to collect study medication at a later date. However, if after reasonable effort the coordinator is not able to collect remaining pills or verify that no pills remain, this will be documented in the case report form (CRF).

All analyses will be conducted using an intent to treat basis, without regards to compliance.

5.7 Prior and Concomitant Therapy

Prior and current use of other immune suppressant medications for the treatment of IBD will be recorded. Current use of all medications will also be recorded. This includes prednisone, methylprednisolone, 6MP, azathioprine, MTX, cyclosporine, and tacrolimus.

- Prior use of anti-TNF therapy for Crohn's disease will not be allowed (i.e. prior use of anti-TNF for other conditions, such as juvenile idiopathic arthritis, is allowable).
- Patients receiving 6MP, azathioprine, or MTX must discontinue treatment with these agents at the time of or prior to randomization. No specific wash-out period will be required.
- Patients treated with prednisone, methylprednisolone, or other systemic steroids or with budesonide at the time of randomization, must be initiated on a taper of these agents. The taper will be at the discretion of the treating physician. Failure to discontinue steroids by week 16 will be considered a treatment failure. These patients will discontinue treatment with study drugs.
- The following drug groups <u>are not permitted</u> as concomitant medication:
    - Other immune suppressants such as cyclosporine, tacrolimus, mycophenolate mofetil, etc.
    - Other biologic agents such as vedolizumab, ustekinumab, etc.
- No live vaccines should be administered during the trial
- If during the study a patient needs to be started on a medication that has a potential interaction with MTX (e.g. Probenecid, Acitretin, Streptozocin, nitrous oxide anesthesia), the site investigator should contact the Principal Investigator, Dr. Michael Kappelman, to discuss whether the patient should continue in the study.
- Use caution when administering methotrexate after a recent history of nitrous oxide administration as it may result in potential increased toxicity (i.e. stomatitis, myelosuppression, and neurotoxicity).

Consistent with pragmatic clinical trial design, concomitant medications not specifically excluded above will be allowed. These include aminosalicylates, antibiotics, and probiotics.

6 Study Procedures

Study visits will be divided into <u>Screening and Randomization Phase</u> and a <u>Blinded Treatment Phase</u>. Consistent with pragmatic clinical trial design, all study visits will be conducted in the context of routine clinical care. As all study participants have a high-risk condition and are being treated with a high-risk medical regimen, enrolled patients will have close medical follow-up and assessment of outcomes. Every effort will be made to ensure that patients have at least one follow-up at approximately 4 weeks following enrollment, at approximately Week 14 (to assess induction of remission), at approximately week 26, and quarterly thereafter.

<u>Data collection and management.</u> As part of routine care, data on primary study outcomes are already being collected and incorporated into the ICN registry through EHR or web-based data capture forms. For this study, standard ICN registry data will be expanded to include additional relevant laboratory and other test results (colonoscopy), AEs, reasons for dose changes or discontinuations of anti-TNF therapy, and reasons for study withdrawal. All non-ICN sites will have access to the same systems in place for electronic data capture.

The descriptions below and in the Time and Events Table (Appendix A) describe the minimum number of visits and requirements at each visit. As any additional clinic visits will be considered study visits, it is expected that each participant will have more visits than the minimum standard as described here. These additional visits will also be captured and utilized for this study. For all visits data collection will include Clinical Documentation and Standard AE reporting.

6.1 Visit 1 (Week -4 to week 0)

Screening:

Informed consent (and assent where applicable) will be obtained prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for this study. An enhanced consent process may be utilized.

At this visit, inclusion and exclusion will be reviewed and documented on an Inclusion/Exclusion form. Laboratory tests used to evaluate and confirm exclusion criteria should be performed as close to the screening visit as possible, and not more than 90 days prior to randomization. For females ≥ 12 years of age (or younger, if menses has begun), a negative pregnancy test will be documented (either sent to clinical lab or documented by a provided urine pregnancy kit). The pregnancy test must be performed within 30 days of randomization. Reproductive counseling will be given to patient/family by the treating provider and documentation of this will be collected.

**In addition, the following clinical documentation will be collected:

From the existing ImproveCareNow Visit Form:
Demographics, including race and ethnicity
History (to calculate SPCDAI)
IBD Medications
Examination including abdominal exam, height and weight (to calculate PCDAI)
Physician Global Assessment
Laboratory tests (CRP, ESR, HCT, and albumin)
Documentation of negative Tuberculosis (TB) screening within the past year

From a Trial-Specific ImproveCareNow Supplemental Screening Form
Inclusion and exclusion criteria checklist
Prior IBD Medications
Anti-TNF initiation (actual or expected)
Confirmation it is clinically acceptable to start study medications
Laboratory Testing and Recording: ALT, AST, Creatinine, WBC, Platelets, HGB
ULN for liver function tests (LFTs) and CRP
Documentation of fecal calprotectin, if performed
Documentation of colonoscopy if performed
Documentation of perianal Crohn's disease history, if applicable
Documentation of perianal exam, if performed
Documentation of all ongoing preexisting conditions
Documentation of all baseline medications
Documentation of mailing address and email address (es)

**If the patient is recruited as an inpatient or in the setting of an anti-TNF infusion or injection teaching, a prior exam may be used to fulfill the screening exam. The prior exam should be as

close to the randomization date as possible, and not more than 30 days prior to the randomization date.

If an inpatient consents to trial participation, a supplement to the Trial-specific Screening Form will be completed because an ImproveCareNow visit form is not completed in this setting. The Trial-specific Screening Form will include collection of elements to calculate PCDAI, document lab tests (CRP, ESR, HCT, albumin), and to record the Physician Global Assessment. In both of these scenarios, it remains that no trial-specific procedures be performed until consent is obtained.

In addition, patients will complete a survey of baseline PROs. This survey may be completed in person, or obtained by email, fax, or U.S. mail. If PRO collection is missed at this visit, it can also be done at the following visit.

Patients will also be provided with a study diary. Completion of the diary is not required, but will be encouraged to assist with treatment compliance and monitoring as well as recall of symptoms and AEs.

Randomization and Treatment Initiation:
If the patient is determined eligible to participate in the study at this visit, the patient will be randomized to treatment. Randomization will trigger the central pharmacy to prepare the appropriate treatment kit and mail it to the patient's address.

If the patient is determined not eligible to participate in the study at this visit due to outstanding laboratory results, the patient will be randomized upon confirmation that all inclusion and no exclusion criteria are met. There must be no more than 42 days between initiation of the anti-TNF therapy and the randomization date. Re-screening is allowed if the patient postpones initial treatment with anti-TNF therapy.

If the patient is determined not eligible to participate because he/she does not meet the inclusion/exclusion criteria, he/she will be considered a screen failure. In order to inform recruitment efforts, we will collect the reason(s) for ineligibility for those who fail screening.

6.2 Follow-up contact (After each shipment of study medication)

A physician, nurse, or study coordinator will contact the patient/parent to ensure they received the drug kit in good condition, review dosing instructions, inquire about adverse effects and answer any questions. Preferred method of contact is by phone, however, this contact may also accomplished via email, text or in-person visit. The date the patient began study drug will be recorded. Nausea should be specifically asked about. If nausea is documented, then taking the ondansetron (or other anti-emetic) should be recommended. Compliance with the folic acid will also be reinforced.

*6.3 Visit 2 (Week 4 +/- 4 weeks**)*

The following clinical documentation will be collected:

From the existing ImproveCareNow Visit Form:
History (to calculate SPCDAI)
IBD Medications
Examination including abdominal exam, height and weight (to calculate PCDAI)
Physician Global Assessment
**Laboratory tests (HCT, CRP, ESR, and albumin)
Anti-TNF level and antibody if performed

From a Trial-Specific ImproveCareNow Supplemental Form
Date of first anti-TNF induction dose
Non-IBD Reason for SPCDAI ≥15 (i.e. infection, irritable bowel syndrome [IBS], normal colonoscopy or other test of mucosal inflammation)
Reason for anti-TNF discontinuation (if applicable)
Date of steroid initiation (if done)
Reason for anti-TNF escalation (if done)
Confirmation it is clinically acceptable to continue study medications
**Laboratory Testing and Recording: ALT, AST, WBC, Platelets, HGB
**ULN for CRP, LFTs
Documentation of fecal calprotectin, if performed
Documentation of colonoscopy if performed
Documentation of perianal exam, if performed
Documentation of all medications

AEs and Serious Adverse Events Reporting-
AEs and Serious Adverse Events will be ascertained at each study visit and reported as described in Section 8 below.

Other Anticipated (Disease-related) AEs not recorded elsewhere

> ***Note:** Regardless of the visit 2 date, initial safety labs need to be drawn and checked between week 1 and week 6 after the patient began taking the study medications. In the event visit 2 is not performed (i.e. patient does not show or has a scheduling conflict) initial safety labs still need to be collected, assessed and recorded in the Non-visit Labs eCRF. All results (normal and abnormal) should be entered for the initial safety labs.

6.4 Visit 3--Week 14 (week 9 to week 22)

This visit is timed with the end of anti-TNF Induction. Must be at least 2 weeks after 3rd anti-TNF dose.

The following clinical documentation will be collected:

From the existing ImproveCareNow Visit Form:
History (to calculate SPCDAI)
IBD Medications
Examination including abdominal exam, height and weight (to calculate PCDAI)
Physician Global Assessment
Laboratory tests (HCT, CRP, ESR, and albumin)
Anti-TNF level and antibody if performed

From a Trial-Specific ImproveCareNow Supplemental Form
Non-IBD Reason for SPCDAI ≥15 (i.e. infection, IBS, normal colonoscopy or other test of mucosal inflammation)
Reason for anti-TNF discontinuation (if applicable)
Date of steroid initiation or discontinuation (if done)
Reason for anti-TNF escalation (if applicable)
Confirmation it is clinically acceptable to continue study medications
Laboratory Testing and Recording: ALT, AST, WBC, Platelets, HGB
ULN for CRP, LFTs
Documentation of fecal calprotectin, if performed
Documentation of colonoscopy if performed
Documentation of perianal exam if performed
Documentation of all medications

AEs and Serious Adverse Events Reporting-
AEs and Serious AEs will be ascertained at each study visit and reported as described in Section 8 below.

Other Anticipated (Disease-related) AEs not recorded elsewhere

In addition, we will collect data to confirm that the patient has successfully **achieved a clinical remission.**

For visits after week 16, we will collect data to confirm that the patient has **successfully completed a steroid taper** (if on steroids at the start of the study)

In addition, patients will complete a survey of PROs. This survey may be completed in person, or obtained by email, fax, or U.S. mail. If PRO collection is missed at this visit, it can also be done at the following visit.

Bio sample collection #1: The collection of bio samples will be considered optional but will be strongly encouraged. For patients undergoing blood collection for clinical purposes, additional tubes of blood will be drawn and banked for future use. This will include 2 serum separator tubes and 2 EDTA tubes (up to 18 ml total). If the bio sample collection is not feasible at this visit, it may be collected at Visit 4.

Study Drug: Collection of any unused study drug from the prior shipment will be documented. Approximately 2 weeks prior to shipment of the next refill, a notification will be sent to the central pharmacy. Any change to the study drug dose (including discontinuation) must be documented in the dose change eCRF per section 6.8 below.

6.5 Visit 4--Week 26 (week 22 to week 32)

The following clinical documentation will be collected:

From the existing ImproveCareNow Visit Form:
History (to calculate SPCDAI)
IBD Medications
Examination including abdominal exam, height and weight (to calculate PCDAI)
Physician Global Assessment
Laboratory tests (HCT, CRP, ESR, and albumin)
Anti-TNF level and antibody if performed

From a Trial-Specific ImproveCareNow Supplemental Form
Non-IBD Reason for SPCDAI ≥15 (i.e. infection, IBS, normal colonoscopy or other test of mucosal inflammation)
Reason for anti-TNF discontinuation (if applicable)
Date of steroid initiation or discontinuation (if done)
Reason for anti-TNF escalation (if done)
Second-line anti-TNF use (if applicable)
Confirmation it is clinically acceptable to continue study medications
Laboratory Testing and Recording: ALT, AST, WBC, Platelets, HGB
ULN for CRP, LFTs
Documentation of fecal calprotectin, if performed
Documentation of colonoscopy, if performed
Documentation of perianal exam, if performed
Documentation of all medications

If the week 14 visit (end of induction) was completed prior to week 16, documentation of a **successfully completed a steroid taper** (if on steroids at the start of the study) will be needed at this visit

In addition, patients will complete a survey of PROs. This survey may be completed in person, or obtained by email, fax, or U.S. mail. If PRO collection is missed at this visit, it can also be done at the following visit.

Note: For patients who **did not have bio samples collected at Visit 3:*
Bio sample collection #1: For patients undergoing blood collection for clinical purposes, additional tubes of blood will be drawn and banked for future use. This will include 2 serum separator tubes and 2 EDTA tubes (up to 18ml total).

AEs and Serious AEs Reporting-
AEs and Serious AEs will be ascertained at each study visit and reported as described in Section 8 below.

Other Anticipated (Disease-related) AEs not recorded elsewhere

Study Drug: Collection of any unused study drug from the prior shipment will be documented. Approximately 2 weeks prior to shipment of the next refill, a notification will be sent to the central pharmacy. Any change to the study drug dose (including discontinuation) must be documented in the dose change eCRF per section 6.8 below.

6.6 Visit 5-14 (Week 39, 52, 65, 78, 91, 104, 117, 130, 143, 156 (all +/- 6 weeks)

These visits will include Clinical Documentation, AE/Serious AE reporting, and documentation of study drug returns and changes as described above.

Week 52 and 104 will also include PRO collection. An additional PRO will be collected during the last study visit between weeks 117 and 156. The PRO may be completed in person, or obtained by email, fax, or U.S. mail.

Week 91 or 104 will also include bio banking. The collection of bio samples will be considered optional but will be strongly encouraged. Practically speaking, a single sample collection will be obtained between week 85 and 110). For patients undergoing blood collection for clinical purposes, additional tubes of blood will be drawn and banked for future use. This will include 2 serum separator tubes and 2 EDTA tubes (up to 18 ml total)).

6.7 Additional Visits

Any clinic visits in addition to the above will be considered additional study visits. For all additional study visits, data collection will include Clinical Documentation and Standard AE reporting.

6.8 Additional Labs (not associated with a visit)

Any laboratory results collected outside of the study visits noted above will be documented in the Non-Visit Labs eCRF only if the following criteria are met:

- The lab test was ordered as a follow-up to a prior abnormal lab result.
- The lab test is a specialty lab - fecal calprotectin, anti-TNF antibody level, anti-TNF trough level.
- The lab test was ordered due to a change in clinical status (i.e. Crohn's flare or other AE).
- The lab test result meets the abnormal criteria for AST, ALT, WBC as defined in section 8.4.3 - Management of Abnormal Laboratory Results.

Note that routine labs which do not meet the above criteria (i.e. labs drawn during infusions not associated with clinical visits) do not need to be recorded as additional labs.

6.9 Study Medication Dose Change or Discontinuation

Any patient who meets a primary study endpoint or who discontinues their first-line anti-TNF for CD for any other reason must discontinue study medications. Occasionally patients may choose to discontinue medications without meeting an outcome.

Any change in the MTX / placebo dose will be documented by a provider in the trial-specific eCRF along with a reason for the change. It is important to complete the dose change eCRF promptly since refill shipment / dosing is based on the most recent information entered into the EDC system. If a patient discontinues the study medication, the date of last dose, reason for treatment discontinuation, as well as any outcomes met will be documented.

Patient Follow-up Off-study Medication: Patients discontinuing study treatment will continue to be followed for the entire study period unless consent is withdrawn for the remaining study procedures. The following study procedures will take place for patients in follow-up, but off study drug:

- Study Visits: Continue to see the patient and collect data in accordance with the study visit schedule.
- PRO collection: Continue to collect at appropriate time points.
- Bio sample collection: Collect the first sample post-treatment discontinuation. The second collection post-treatment discontinuation may be skipped.
- Lab results: if ordered based on the discretion of the treating provider.
- Adverse Events: Continue to collect and record for 14 days following final dose of study medication.
- SAEs: Collect and record for the entire duration of follow-up (i.e. until week 104 visit completed or the patients withdraws from the study).
- Follow female participants for pregnancy for 16 weeks after final dose.

The patient should continue to be followed throughout the entire trial period, and data collected per protocol, unless the patient withdraws consent, is lost to follow-up, dies, or the study ends. Patients who meet a study endpoint will only be followed for a maximum of two years.

6.10 Withdraw of consent/loss to follow up

For the purposes of the COMBINE trial, the term "withdrew consent" means that the patient/family chooses to fully discontinue participation in the trial. This includes discontinuation of study treatment and all other IRB-approved research activities (including use of routine follow-up visit information for trial purposes).

For patients who are lost to follow up or withdraw consent for the study, we will collect the following data on an early termination form:

- Date of last MTX/placebo dose (if known)
- Date of last contact (e.g. visit, phone, email, etc.)
- Any known AEs, pregnancy, medication use, lab and/or colonoscopy results since last study visit. If possible, a plan will be made to following any ongoing AEs or pregnancy present at early termination.
- Any study outcomes met since last study visit

If possible, unused study medication should be collected and documented. The dose change eCRF should be completed to discontinue refill shipments of the study drug.

6.11 Re-consenting current participants

Current study participants who initially provided consent for a 2-year follow-up period, and who have not yet met a study endpoint, will be asked to participate in the longer follow-up period beginning at Visit 9, Week 91 (+/- 6 weeks). Re-consented patients will continue with quarterly study visits up to Visit 14, Week 156 (+/- 6 weeks) or until the study stops.

6.12 Bio samples

For trial participants who provide consent for sample collection for research purposes, blood samples will be collected at two time points (Visit 3 and Visit 9). This collection is considered optional (i.e. it will not preclude participation in the clinical trial), but will be strongly encouraged.

To avoid a separate venipuncture, the research blood will be collected at the time of a clinical blood draw or prior to an infliximab infusion (if applicable). When possible, up to four additional tubes of blood will be collected to include 2 serum separator tubes and 2 EDTA tubes. Up to 21mL (approximately 1.5 Tablespoons) of blood will be collected at each time point. If the collection is not feasible at Visit 3 or Visit 9, the samples may be collected at the following visit (Visit 4 and Visit 10, respectively).

Samples will be collected at the study site and shipped to a central laboratory for processing and testing. De-identification of samples will be accomplished by labeling the samples with the participant's unique subject identification number for the trial.

Planned research testing includes measurement of anti-TNF antibodies, anti-TNF trough levels as well as neutrophil CD64 surface expression and soluble CD64.

Any leftover blood samples will be stored at the central laboratory, in a secure location, at -80 degrees Celsius, for future research purposes. The central laboratories responsible for stored samples include the BioSpecimen Processing Facility at the University of Chapel Hill as well as the Laboratory of Dr. Minar at Cincinnati Children's Hospital Medical Center. Future research using these samples will be reviewed by an IRB prior to use.

Future testing on these samples may relate to IBD or other un-related conditions. Testing may include, but is not limited to, the following:

- Genotyping
- Whole exosome sequencing
- Immunological tests
- Additional assays that may be developed in the future

The stored samples may be banked for an indefinite period of time and may be destroyed at any time. Test results will not be reported back to participants and/or their parents or legally authorized representatives. There are no plans for subjects to share in financial proceeds that may accrue from development of future technologies. Samples may be withdrawn from the repository at any time by withdrawing consent for future studies, however, any data that have already been derived from testing will not be withdrawn.

7 Statistical Plan

7.1 Sample Size Determination

Our sample size calculation is based upon our primary aim and outcome—induction and maintenance of steroid free remission. We estimate our needed sample size on the following assumptions:

1. *Induction and maintenance of steroid-free clinical remission through week 104 will occur in 50% of the monotherapy group in 2 years*. This is based on the two adult trials of anti-TNF combination versus monotherapy in CD[26,28]. In these trials, treatment success rates in the monotherapy group at the end of year 1 were 40% and 56%. We anticipate that treatment success will diminish somewhat over the 2nd year of follow-up. Therefore, the actual rates of treatment success in our trial may be somewhat less than 50%. However, as 50% is among the possible values, we used it in our power calculations. This is a conservative assumption, as any deviations from this will result in greater statistical power.

2. *True difference between the two treatment arms will be 15% or more.* We believe that a 15% difference is the minimum clinically important difference, as smaller effects will not warrant the incremental toxicity of combination therapy. The two adult studies[25 26] were powered only to detect a 20% and 25% difference; however, we believe that a smaller difference would still be clinically meaningful. We think a 15% differences is a reasonable estimate of the treatment effect. In the SONIC study (combination therapy with 6MP), the observed difference at 1 year was 16%[26], and we anticipate a greater difference over an additional year of follow-up. Although no difference in treatment arms was observed in the COMMIT study (combination therapy with MTX)[28], this may have resulted from a number of methodological limitations that have been addressed by our trial design[52].

3. *We anticipate a loss to follow up of 20%.* Based on data from 2013, loss to follow up in the ICN network is approximately 6% per year, or 12% over a two-year trial. For this trial, we assume an additional 5% loss to follow-up to account for withdraws of consent or other reasons for study drop-out. We also expect that about 25% of patients who did not have an event by year 2 will not sign the consent for an additional year of treatment and follow-up.

One hundred ninety subjects have been accrued in the first 2 years of the study. Assuming the accrual of 9 subjects per months for the remaining 27 months of the study, 190+27*9 = 433 subjects will be accrued. Based on the assumptions above, we will observe about 152 treatment failures and achieve 82% power with two-sided 0.05 level test. These power calculations are based on the assumption that time to failure is exponentially distributed.

7.2 Planned Interim Analysis

We will perform an interim analysis for efficacy using O'Brien-Fleming boundary after 76 patients experience a treatment failure (half of the required treatment failures). The null hypothesis will be rejected if the p-value is less than 0.005. The final analysis will be done at 0.048 α-level to ensure that the overall α-level does not exceed 0.05.

7.3 Statistical Methods

An overview of the statistical analysis can be found below. Full details will be incorporated into a separate data analysis plan.

Primary analyses. The primary endpoint is time to treatment failure. Patients who fail to enter remission will be considered as a treatment failure at the visit at or just prior to week 26. To compare the distribution of time to treatment failure in the two arms we will compute stratified log-rank test stratified by anti-TNF agent prescribed (infliximab and adalimumab).

Additional analysis of the primary endpoint. We will also perform the un-stratified log-rank test. Cox model with treatment (MTX versus placebo), site, anti-TNF agent prescribed (infliximab and adalimumab) and important covariates (see Potential confounders below) will be considered. Since some sites will recruit a small number of patients, we will combine sites based on the geographic location to have a total of 6-8 site clusters.

The Kaplan Meier method will be used to estimate the probabilities of treatment failure, induction rates, and the maintenance of steroid free remission rates at various time points (week 26, 52, 104, 156) in the two groups (MTX versus placebo). Survival curves will be presented for time to induction and time to relapse. We will also evaluate the probability of treatment failure through week 156.

Analysis of the secondary endpoints. The three secondary endpoints will be tested using the Bonferroni multiple comparison procedure. Since the three secondary endpoints are likely to be positively correlated, Bonferroni is a conservative approach to controlling for multiplicity here. The first secondary endpoint is the average of PROMIS Pain Interference T scores at weeks 52 and 104. We first compare the average of PROMIS Pain Interference T scores at week 52 and week 104 between the treatment groups. If this comparison is significant at 0.05/3 level, we will compare the treatment groups based on PROMIS Pain Interference T score at week 52 and separately based on week 104 at 0.05/3 level each. To perform this analysis, the means and the variability of the PROMIS scores at 52 and 104 weeks will be estimated by fitting mixed model for repeated measures (MMRM) to PROMIS scores at all available time points adjusted for important covariates. The second secondary endpoint is the average of PROMIS Fatigue T scores at weeks 52 and 104. We will compare the averages of PROMIS Fatigue T scores at week 52 and week 104 between the treatment groups. If this comparison is significant at 0.05/3 level, we will compare the treatment groups based on Fatigue T score at week 52 and separately based on week 104 at 0.05/3 level each. To perform this analysis, the means and the variability of the PROMIS scores at 52 and 104 weeks will be estimated by fitting MMRM to PROMIS scores at all available time points adjusted for important covariates. The third secondary analysis is the comparison of proportions of patients with positive anti-TNF antibody status based on the sample collected in the second year (week 91). If a sample is not collected in the second year, the sample collected in the first year will be used (week 14). The proportions in the two groups (MTX versus placebo) will be compared using logistic regression with adjustment for important covariates using 0.05/3 significance level.

Analysis of additional endpoints. Additional pre-specified endpoints, listed below, will be analyzed using appropriate statistical methods: Wilcoxon rank-sum test to compare mean anti-TNF levels and dose and chi-squared test to compare proportions. Parameter estimates for PROs will be obtained from the MMRM.

1. Mean anti-TNF levels form the specimen collected during 2nd year of follow up.
2. Proportion of patients with normal ESR and mean ESR at various time points (week 26, 52, 104).
3. Proportion of patients with normal CRP at various time points (week 26, 52, 104).
4. Proportion of patients at various time points (week 26, 52,104) with the following (on anti-TNF, requiring dose escalation of anti-TNF, without hospitalization, without surgery,

without any steroid for IBD, without steroid for IBD > 10 weeks cumulatively (beyond week 16).
5. Proportion of patients achieving steroid free remission by the week 26 visit (+/- on original anti TNF and study drug).
6. Proportion of patients in steroid free remission at week 104 (+/- on original anti TNF and study drug).
7. Proportion of patients with height velocity Z score at week 104 that is better -1.
8. Proportion of patients with normal calprotectin (< 150) at week 104 (select measurement between week 52 and 104, closest to 104).
9. Proportion of patients with endoscopic healing (defined by SES-CD and/or PGA) at week 104 (select measurement between week 52 and 104, closest to 104).
10. PROMIS Positive Affect, and IBD Symptom PRO T score (continuous variable, mean in general population = 50, SD = 10) at week 26, 52, 104.
11. PROMIS Fatigue and Pain Interference at week 26.
12. Mean anti-TNF dose (per kg) at week 26, 52, 104 in the two groups.

Potential confounders. Adjusted models will consider the following potential confounders, as assessed at baseline: the anti-TNF agent used, SPCDAI score, current or prior use of prednisone and other steroid medications, prior use of MTX, prior use of 6 mercaptopurine or azathioprine, time from diagnosis (< 2 or ≥ 2 years), elevation of baseline CRP or ESR as a measure of inflammation and disease activity, age (< or ≥ 12 years), gender, and race.

Multiplicity adjustment. A multiple comparison procedure that preserves the type I error rate for the study is to perform the test of the primary endpoint using the primary analysis specified in the protocol. The primary test is declared to be significant if its p-value is less than 0.05. A comparison based on each of the three secondary endpoints is declared to be significant if this comparison is significant at 0.05/3 level and if the primary comparison is significant at 0.05 level. We will ascertain whether or not the analysis of primary and secondary endpoints is significant based on this strict procedure that preservers the study's overall type I error rate at 0.05.

Pre-specified subgroup analyses. We will perform analysis in the following subgroups: type of anti-TNF, time from diagnosis (< 2 or ≥ 2 years), baseline disease activity (SPCDAI score ≥ 30) at enrollment, and elevation of baseline CRP or ESR as covariates. Other covariates to consider are gender, age (< or ≥ 12 years), race/ethnicity, CD subtype based on the Paris Classification, and other relevant clinical/phenotypic characteristics (i.e. presence of perianal lesions). Additional subgroup analyses based on anti-TNF starting dose will be performed, if applicable.

An additional subgroup analysis will be based upon whether the anti-TNF dose was prescribed according to a traditional weight-based dosing model or whether the dose was adjusted based upon measurement of trough levels. We will ascertain the use of level-based dose adjustments and will evaluate whether this practice results in higher induction/maintenance of remission or is an effect modifier of the combination versus monotherapy comparison.

For each subgroup analysis, we will: 1) test for an interaction of treatment by subgroup, 2) estimate the treatment effects within each subgroup, and 3) use a graphical approach to display treatment effects within appropriate subgroups (i.e., meta-analysis forest plot). Although the study will not have adequate power for each of these subgroup analyses, estimating the effect size and precision will provide very useful hypothesis-generating data, even in the absence of statistical significance.

Missing data. Some components in the definition of the primary outcome - treatment failure- might not be available in some instances. For example, one or more components of the SPCDAI may be missing for some visits. Subjects who are missing more than 10% of the SPCDAI components across visits will be excluded from the analysis. Subjects who are missing 10% or less of the components across visits will be included in the analysis. The missing components of the SPCDAI will be imputed based on the estimated joint distribution of the SPCDAI components using multiple imputation[59]. Missing covariates in our models will be imputed using multiple imputation. We will use the Mixed-Effect Model Repeated Measure (MMRM) method if some of the repeated measures for secondary outcomes are missing.

Observational CER study of patients treated with thiopurine combination therapy. Some patients in the network will decline study participation and some will undergo treatment with combination therapy of anti-TNF and 6MP or azathioprine, either due to patient and/or provider preference. By conducting this trial within ICN, we will be able to perform an observational cohort study of these patients. Specifically, we will compare the baseline characteristics of trial participants with patients treated with anti-TNF + 6MP/azathioprine combination therapy. We will also be able to perform unadjusted and adjusted analyses comparing the two study arms with this 3rd observational arm.

Additional analysis of PROs. PROs include PROMIS domains, which are continuous measures, calibrated using a T-score metric to the US general population with a mean of 50 and standard deviation of 10. Minimal important differences (MIDs) for many PROMIS domains are in the range of 2 to 6. Our analysis plan will take advantage of the longitudinal nature of selected PROs, and the MMRM will be used for analysis. Additionally we will use multiple imputation to impute missing covariates and missing outcomes. Groups will be compared over a given set of time points.

AEs and safety analyses. We will use descriptive statistics (e.g., proportions, 95% confidence intervals (CI)) to summarize physician reported AEs [grade 2 (moderate) or higher]. We will also compare the following safety outcomes between the two treatment groups by estimating relative risk and 95% CI: elevated liver enzymes (> 2X upper limit of normal), leukopenia (WBC < 3.5), serious infections, malignancies, and nausea. Interim and final analyses will be reviewed by the DSMB at regular intervals (see Protection of Human Subjects). In addition to safety monitoring during the study period, we will also perform longer-term safety monitoring after the conclusion of the study, as data will continue to be collected on trial participants as part of routine clinical care in ICN.

7.4 Subject Population(s) for Analysis

We will conduct a modified Intent to Treat Analysis. Any subject randomized into the study, who was shipped study drug, will be included in the analyses.

8 Safety and AEs

8.1 AEs

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. Each investigator will be trained in good clinical practices. This safety monitoring will include careful assessment and appropriate reporting of AEs as outlined below. The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE (AE) or serious adverse event (SAE).

8.1.1 Definition of an AE

An AE is any unfavorable and unintended symptom, sign, illness or experience, which develops or worsens in severity from the date of randomization.. 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 MTX/placebo dosing
- 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 PCD 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 either worsen or fail to respond initially, or may have a worsening of disease after an initial response. Indeed, the trial outcomes include measures of disease activity, hospitalization, surgery, requirement for corticosteroids, etc. As most data regarding failure to respond and/or worsening of PCD are collected through trial CRFs, these anticipated disease-related events will not need to be reported separately as AEs/SAE's. A listing of Anticipated Adverse (Disease Related) Events is provided below:

- Abdominal mass
- Fistula (enterocutaneous, entero-entero, perirectal, recto-vaginal, 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 Crohn's
- Diarrhea

- Dehydration thought to be due to Crohn's flare
- Urgency
- Nausea/vomiting thought to be due to Crohn's or complications of Crohn's
- Arthralgia/arthritis
- Uveitis/episcleritis
- Ankylosing spondylitis
- Cutaneous manifestation of Crohn's (pyoderma gangrenosum, erythema nodosum)
- Abdominal surgery or complications of abdominal surgery due to Crohn's
- Anemia thought to be due to Crohn's

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

Refer to section 8.3.3 for the management of abnormal lab values.

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 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. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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 PCD are collected as part of study outcomes and are captured in the existing ImproveCareNow eCRFs. These anticipated disease-related events will not need to be reported separately as AEs/SAE's. However, if the site investigator 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 site investigator.

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. 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 AEs and SAEs

On enrollment in the study, the patients 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.

Patients in Follow-up, **ON** Study Medication:

- All non-serious AEs occurring from the date of randomization through 14 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 immediately (see section 8.5).

Patients in Follow-up, **OFF** Study Medication:

- All non-serious AEs occurring from the date of randomization and for 14 days following the final dose of study medication, must be recorded. Any non-serious AEs that occur after day 14 following the final dose of study medication do not need to be recorded.
- All SAEs occurring from the date of randomization through the completion of study follow-up (i.e. until week 156 visit completed or the patients withdraws from the study), must be recorded in the eCRF and on the SAE report form and reported immediately to the Safety Medical Monitor (see section 8.5).

Information on all AEs should be recorded immediately 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, though should be grouped under one diagnosis.

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 and/or procedures involved in research (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 and/or Procedures Involved in Research

The relationship is evaluated by the investigator as follows:

Definitely Related:

- Reason to conclude that event was at least partially caused by the study medications and/or procedures involved in research

Possibly Related:

- A reasonable possibility that event was at least partially caused by the study medications and/or procedures involved in research

Not related:

- Solely caused by the underlying disease, disorder or condition of the patient (including background medication/anti-TNF)
- Solely caused by other circumstances unrelated to the study medications and/or procedures involved in research

Expectedness

An AE is considered "unexpected" if it meets the following criteria:

- Adverse reactions listed in the package inserts for the study medications - Methotrexate, Ondansetron and Folic Acid – ***that occur at a greater severity, frequency and/or specificity than stated***.
- Adverse reactions listed in the package inserts for the respective anti-TNF (infliximab or adalimumab) - ***that occur at a greater severity, frequency and/or specificity than stated***.
- Progression of PCD or other pre-existing condition ***that is unusual*** in terms of the frequency, intensity or character.

- Events not identified as known adverse reactions in the package inserts of the study medication or background medication.

An AE is considered "expected" if it meets the following criteria:

- Common adverse reactions listed in the package inserts for the study medications - Methotrexate, Ondansetron and Folic Acid.
- Common adverse reactions listed in the package inserts for the respective anti-TNF (infliximab or adalimumab). These anti-TNFs are not study medications, however, patients must be starting treatment with one of these medications to be eligible for the trial. As such, we expect patients may experience common adverse reactions associated with these background medications. This includes infusion or injection-site reactions.
- Events related to the natural progression of PCD or other pre-existing condition (Note: these events are not to be reported as adverse events per protocol section 8.1.1).

For the purpose of this trial, all expected AEs will be indicated in a pull-down menu on the AE eCRF. Selection of an event from the pull down menu will automatically assign a determination of "expected". For all other events, the nature of the event will be entered as free text in the AE eCRF and the expectedness determination will automatically be assigned as "unexpected".

The determination of the expectedness for SAEs will be made by the sponsor's safety medical monitor based upon the appropriate package insert (MTX, adalimumab, infliximab) and criteria provided above.

The following will be considered expected AEs:

Common adverse reactions caused by MTX include the following:

- anorexia, nausea, vomiting
- elevation of liver enzymes (AST, ALT, ALP [alkaline phosphatase] or GGT [gamma-glutamyltransferase])
- stomatitis
- malaise
- fatigue
- abdominal discomfort
- chills
- fever
- dizziness
- diarrhea
- anemia
- thrombocytopenia
- leukopenia
- rash
- pruritus
- alopecia
- photosensitivity
- abortifacient, teratogenic

The more common side effects caused by ondansetron include[1]:

- confusion
- dizziness
- fast heartbeat
- fever
- headache
- shortness of breath
- weakness

The most common adverse reactions caused by infliximab include:

- Infections (e.g. upper respiratory, sinusitis, and pharyngitis)
- Infusion-related reactions
- Headache
- Abdominal pain

The most common adverse reactions caused by adalimumab include:

- Infections (e.g. upper respiratory, sinusitis)
- Injection site reactions
- Headache
- Rash

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.

Any AE or SAE leading to permanent discontinuation of study medication is considered a primary endpoint (i.e. study drug or anti-TNF intolerance or toxicity) and should be documented as such in the CRF.

[1] http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045342/#DDIC603313.side_effects_section accessed December 2, 2015

8.4.2 Management of Nausea

All patients will receive an age- based dose of ondansetron or matching placebo along with their MTX (or matching placebo). This will be taken at the same time as the MTX/placebo to prevent nausea.

In addition, each participant's treating prescription will provide a prescription for an age based dose of ondansetron to be taken on a PRN basis if symptoms of nausea develop. Note that for patients who receive ondansetron as part of their study medication AND take a PRN dose prescribed by their physician, the total dosage will not exceed the maximum dosage for this medication.

For significant nausea not relieved with ondansetron, the patient's physician will use their clinical judgment to determine whether they think the nausea is related to the study drug or is due to a different etiology (underlying Crohn's or complication of Crohn's, infection, etc.) and will evaluate as appropriate.

Nausea that occurs only on the day of or 24 hours following study drug administration will be suspected as being related to the study drug. In this instance, the following week's dose of study drug will be skipped to further evaluate for causation. If nausea continues in the absence of receipt of study drug, it will not be considered to be drug related. If nausea subsides with holding the study drug, it will be considered highly likely to be a consequence of the study drug. The patient will be tried on study drug for 1 additional week. If nausea develops, it will be determined to be related to study drug. If nausea is significant enough, the patient, caregiver, or treating physician may choose to discontinue treatment with study medication.

8.4.3 Management of Abnormal Laboratory Results

All laboratory values outside of the normal range will be repeated if judged appropriate by the investigator to ensure the validity of the abnormal result. The investigator will assess the etiology of the clinically relevant abnormal laboratory values and will document relevant laboratory values in the CRF as outlined in section 6.0.

Monitoring of abnormal liver enzymes and complete blood count
- If the AST or ALT (LFT's) increase ≥ 2 times the upper limit of normal (ULN) after the start of the study medication, the investigator will repeat the measurements of LFTs after 2-3 weeks. If LFTs normalize the patient will continue with current dose of MTX/placebo, however, if LFTs remain elevated ≥ 2 times the upper limit at second draw, the dose of MTX/placebo should be reduced to ½ of the participant's starting dose. Another check of LFT's should be performed after 4 weeks at the lower dose. If the LFT's normalizes or return to less than 2X upper limit of normal, then patient should remain on ½ of the starting dose and further laboratory monitoring of the LFT's should be performed in the setting of the regular lab draws in the context of the regular study visits. If LFTs remain elevated > 2x ULN upon recheck, participant must stop therapy with MTX/placebo.

-If WBC below 3.5 x10 ^{9}/L but above 3.0 x10 ^{9}/L, the investigator should repeat CBC within 2 weeks. If WBC > 3.5 x10 ^{9}/L, it is acceptable to continue MTX/placebo. If WBC below 3.5 x10 ^{9}/L but above 3.0 x10 ^{9}/L, the dose of MTX/placebo should be reduced to ½ of the participant's starting dose. Repeat CBC should be obtained in approximately 2 weeks.

- If WBC below 3.0 x10 ^{9}/L, the investigator should stop therapy with MTX/placebo and perform another blood draw within 14 days. If repeat WBC is ≥ 3.5 x10 ^{9}/L, then patient may resume MTX/placebo therapy at ½ of the participant's starting dose. If WBC is between 3.0 and 3.5, CBC should be repeated within 2 weeks. If repeat WBC is ≥ 3.5 x10 ^{9}/L, then patient may resume MTX/placebo therapy at ½ of the participant's starting dose. If WBC remains less than 3.5, participant must stop therapy with MTX/placebo. If WBC should drop again below 3.0 x10 ^{9}/L, participant must stop therapy with MTX/placebo.

Stop of study medication in case of following pathologic laboratory values:
- Renal dysfunction as defined by 1) creatinine > 0.8 for children age<10, creatinine > 1.2 mg/dl for children age 10-18, and creatinine > 1.5 mg/dl for adults age 18 years and older or 2) increase of 0.5 mg/dL compared to baseline value).
- Hepatic dysfunction as defined as an increase of AST or ALT ≥ 3 times upper limit of normal after the start of study medication or persistent elevation > 2X normal as described above
- Drop of WBC below 3.0 x10 ^{9}/L despite dose reduction of MTX after the start of study medication.

8.4.4 Pregnancy

Any pregnancy in a female trial participant will result in immediate discontinuation of study medication. The participant should be unblinded to determine potential risk to the mother and fetus. Pregnancies amongst those participants receiving MTX will be followed in order to confirm the outcome and health status of the mother and baby. The patient will remain in follow-up for up to the 156-week trial period.

8.5 Reporting of Serious AEs

In addition to recording all AEs and SAEs in the appropriate CRF module, investigators and the protocol sponsor must conform to the AE reporting timelines, formats and requirements of the DSMB, 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 (see definitions, section 8.1.2),
- 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
- Study Center
- 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) must be reported without delay, within 24 hours, in accordance with the guidelines in section 8.3. The Serious AE (SAE) form must be completed by the investigator, and sent by facsimile to the study Safety Medical Monitor:

Hans Herfarth, M.D.
University of North Carolina at Chapel Hill
Fax: 919 843-6633
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Within the following 48 hours, the investigator 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

Investigators are responsible for safety reporting to the central and/ or local IRBs. Investigators are responsible for complying with the central and/or local IRB's reporting requirements, though must submit the required reports no later than 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

8.5.2 Sponsor reporting

The study sponsor will notify all participating investigators, as well as the central IRB, of relevant DSMB safety reports as described in section 8.7.1.

8.6 Unblinding Procedures

Every attempt will be made to preserve blinding during and after completion of the trial. However, unblinding will be allowed in certain instances where knowledge of the treatment assignment will significantly impact a patient's subsequent treatment. As such, unblinding will be considered for participants who meet a study endpoint on a case by case basis, upon the request of the patient's treating physician. All requests for unblinding will be reviewed by a committee of expert IBD physicians. Additionally, patients who become pregnant over the course of the study will be unblinded. Unblinding will also be permitted for certain AEs or SAEs for which unblinding is necessary to manage the AE or SAE or if it will affect future treatment

decisions. In the event of medical emergencies that require immediate unblinding, physicians will have access to a 24-hour pager.

Scheduled unblinding at end of study

Patients who complete the study and are still undergoing treatment with study medication will be offered the opportunity to be informed of their treatment allocation while participating in the trial. This will occur at either at Visit 14, Week 156 (+/- 6 weeks) or when the study closes. Specifically, the Study Completion eCRF and the week 156 (Last Visit) form will be completed. The patient's treatment assignment will be available within the online Unblinding Report within 24 hours. Patients who originally consented to the 24 month trial and do not wish to re-consent for the additional year of follow up will be offered unblinding at the end of their two year follow-up, provided they are still taking study medication.

8.7 Stopping Rules

We decided against early stopping for futility as a full two years of follow up may be necessary to observe treatment effects. By the time sufficient patients complete two years of follow up to complete a futility analysis, the trial will be too far along to make early stopping worthwhile.

We will consider early stopping for efficacy. As discussed above, we will perform an interim analysis using O'Brien-Fleming boundary after 73 patients experience a treatment failure (half of the required treatment failures). The null hypothesis will be rejected if the p-value is less than 0.005. Any decision for early stopping for efficacy will be the decision of the DSMB as discussed below.

If serious safety concerns arise, the coordinating investigator can terminate or interrupt the study by agreement with the sponsor. If new information on the risk-to-benefit ratio of the drug or on the treatment methods used in the study is obtained in the meantime, the coordinating investigator reserves the right to interrupt or terminate the project by agreement with the sponsor. Premature termination is also possible if the coordinating investigator, or the investigators and the sponsor determine that patient recruitment is insufficient and cannot be expedited by appropriate measures.

We will also consider stopping our nested trial of enhanced vs. standard pre-consent discussion as outlined in section 7.5.

8.7.1 Independent Data and Safety Monitoring Board

An independent DSMB will regularly review interim data to monitor safety and effectiveness and recommend whether the trial should continue. The DSMB has overall responsibility for interpreting data on AEs. This group reviews unblinded data every six months and makes recommendations to the Study Leadership Committee regarding actions to ensure that participants are not exposed to undue risks. Summary reports of the meetings are sent to the site investigators and the central IRB.

Committee Members

Members are independent experts chosen on the basis of their expertise and scientific rigor. They are not associated with the trial or with the pharmaceutical companies that supply the study agents. Committee members' areas of expertise span the disciplines relevant to the conduct of this pragmatic clinical trial, including epidemiology, clinical trials, pharmacology, biostatistics, and clinical care, including treatment with anti-TNF biologics and MTX. Members of

the Committee are named below. Additional/alternate members that may be identified by PCORI will also be included.

- Committee Chair: Dr. Brian Smith, Duke University, pediatric clinical trials expert
- Dr. Todd MacKenzie, Dartmouth Geisel School of Medicine, biostatistician
- Dr. Jenifer Lightdale, University of Massachusetts, pediatric gastroenterologist and division chief

Committee Mandates

The Committee has the responsibility to review the research protocol and to evaluate the progress of the trial overall and at each participating clinical center. This includes accrual, data quality and completeness, episodes of hospitalization, mortality, other toxicities, and protocol violations. Serious unexpected events will be disclosed to the committee between meetings. The Committee will also review interim endpoint data (both primary and secondary endpoints).

The Committee will begin its work on this trial by identifying key data points that will be monitored at each of the interim meetings. The DSMB will work closely with the investigators and biostatistician to develop study-wide stopping rules.

Concurrently, the Committee will evaluate participant risk vs benefit as the trial progresses, considering evolving scientific discoveries or treatment options that may affect the desirability of continued treatment. At the conclusion of each meeting, the Committee will recommend whether the trial be continued. If study medication proves to be more harmful than expected in terms of mortality or severe morbidity, we will stop the trial early. This decision will be made by the study investigators on recommendation of our Safety and Data Monitoring Committee.

Frequency of Committee Meetings

The Committee will confer at six-month intervals, generally by telephone or webinar.

Committee Meeting Structure

The study's principal investigator, Michael Kappelman, MD, MPH, and the study's statistician, Anastasia Ivanova, PhD, and on occasion other key personnel, will participate in the meetings' open sessions, which includes consideration of trial progress, general scientific issues, etc. The Committee's voting members will discuss in closed session unblinded data regarding endpoints and toxicities and other material that should be kept confidential from the investigators. This will likely include comparisons of the following safety outcomes by estimating relative risk and 95% CI: elevated liver enzymes (> 2X normal), leukopenia (WBC < 3.0), serious infections, malignancies, and nausea.

Frequency and content of reports to the Safety and Data Monitoring Committee

Every six months, the lead programmer at the coordinating center will prepare a report for DSMB review. The report will contain the following categories of information aggregated by masked treatment group.

- Current enrollment status and timeline for completion of follow-up
- AEs reported, including hospitalizations and any mortality
- 1st and 2nd order protocol violations
- Endpoint data
- Numbers of patients whose study medication is discontinued

Unexpected serious events are reported to the Safety and Data Monitoring Committee between meetings.

Frequency, content, and distribution of meeting reports

Following each meeting of the Safety and Data Monitoring Committee, its chair will prepare a report on the questions raised by Committee members, monitoring recommendations, and recommendations for the continuation of the trial. This report will be distributed confidentially to meeting participants. The Committee's secretary also prepares a redacted summary of this report, focusing on safety issues, for distribution to clinical center co-investigators and their IRBs.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Data Collection and Management

9.3.1 Case Report Forms

As part of routine care, data on primary study outcomes are already collected and incorporated into the ICN registry through EHR or web-based data capture forms. In addition, electronic CRFs will be used for data collection in order to capture trial-specific information. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. The site investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. In the event of incomplete or inconsistent data, correction and/or clarification will be requested from the site. The names of all persons authorized to make entries and/or corrections on CRFs must be maintained in a delegation log. Registry and electronic CRF data collection and management activities will be performed by the data and site

coordinating center. The trial data set will be transferred to the UNC biostatistics core for data analysis and reporting.

9.3.2 Patient Surveys and Questionnaires

Participant knowledge surveys for the nested trial of pre-consent discussion will be administered to participants via a paper form. The paper forms will be scanned at the local study site and transmitted electronically to the data and site coordinating center. Dr. Lipstein and Dr. Brinkman from Cincinnati Children's Hospital Medical Center will oversee data collection, entry, analysis, and reporting for the nested trial.

PRO surveys will be administered to patients via a paper form. The paper surveys will be scanned at the local study site and transmitted electronically to the Children's Hospital of Philadelphia for data entry and scoring. PRO results will be transferred to the data coordinating center and the UNC statistical core for data analysis and reporting.

9.4 Records Retention

The investigator must retain all study records and source documents for the maximum period required by their institution or as required by local and national governing regulations, whichever is longer. Study records include consent forms, distribution and inventory of investigational drug (as applicable), and source documentation. The investigator must contact the sponsor prior to destroying any records associated with the study.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

Representatives of the study sponsor will monitor compliance with the current protocol / amendment(s) and with applicable regulatory requirements. A Risk Based Monitoring strategy will be taken and monitoring will be conducted remotely unless a site visit is warranted. Monitoring efforts will focus on elements that have been identified as being critical to the research goals, data integrity, and protection of study participants.

The Investigator will ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related source documents. To provide remote access to critical source documents, this may involve printing, redacting, coding, scanning and emailing or uploading the documents for the monitor's review.

If a site visit is warranted, the Investigator will ensure that the monitor has direct access to study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. The investigator will allocate adequate time for all monitoring activities.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) by the IRB, the sponsor, government regulatory bodies, and any compliance and quality assurance groups from the investigator's institution. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by the IRB, the sponsor, government regulatory bodies, and any compliance and quality assurance groups from the investigator's institution. If informed of such an inspection, the investigator should notify the sponsor immediately.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 50, part 56 and ICH guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a centralized, properly constituted independent Ethics Committee (EC) or IRB, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The sponsor and investigator will maintain a list of the central EC/IRB members and their affiliates in their files.

All subjects (and/or the subject's legally authorized representative) for this study will be provided a consent form describing this study and providing sufficient information for subjects (and/or their legally authorized representative) to make an informed decision about their participation in this study. The sponsor will provide the investigator with appropriate sample informed consent forms. These consent forms will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject (and/or the subject's legally authorized representative), using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject (and/or the legally authorized representative), and the investigator-designated research professional obtaining the consent.

Spanish-speaking patients may be recruited for this trial at study sites with a significant Spanish-speaking population. The informed consent and other essential patient-facing recruitment and study materials will be translated to Spanish and certified by back translation. The translated documented will be submitted to a properly constituted independent Ethics Committee (EC) or IRB, for formal approval. The decision of the EC/IRB concerning the translated materials will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before being used for recruitment of Spanish-speakers.

All subjects enrolled as children and who turn 18 during the study will be consented as adults at the earliest opportunity (but no later than 6 months after reaching age of consent). The same process will be followed if parents/patients need to be re-consented during the study for any other reason (i.e. new information becomes available).

12 Study Finances

12.1 Funding Source

This research study is partially funded through a Patient- Centered Outcomes Research Institute (PCORI) Award (PCS-1406-18643). The Patient-Centered Outcomes Research Institute (PCORI) is an independent, nonprofit organization authorized by Congress in 2010. Its mission is to fund research that will provide patients, their caregivers, and clinicians with the

evidence-based information needed to make better-informed healthcare decisions. PCORI is committed to continually seeking input from a broad range of stakeholders to guide its work.

Additional funding is provided by the ImproveCareNow Network, The Leona M. and Harry B. Helmsley Charitable Trust, Grifols Diagnostics Solutions Inc and the National Institutes of Health.

ImproveCareNow is a 501(c) 3 non-profit organization. Its purpose is to transform the health, care and costs for all children and adolescents with CD and ulcerative colitis by building a sustainable collaborative chronic care network, enabling patients, families, clinicians and researchers to work together in a learning health care system to accelerate innovation, discovery and the application of new knowledge.

The Helmsley Charitable Trust supports leading research institutions across the globe in an unprecedented effort to find a cure—and until then better treatments—for IBD and Crohn's disease.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned study specific conflict management plan that has been reviewed and approved by the IRB providing oversight for that investigator prior to participation in this study. This information shall also be made available to the study sponsor upon request or as required under any separately executed agreement between the sponsor and study site.

12.3 Subject Stipends or Payments

Patients will be reimbursed $25 for each of two blood collections that are sent to the biobank and $10 for each completed PRO form. The maximum reimbursement will be $110 per patient over the course of the study.

The majority of study procedures are performed as part of routine care and will be billed to the patient or their insurance. Procedures performed solely for research purposes will not be billed to the patient, nor their insurance, but will be covered by the study (i.e. pregnancy tests, tubes for serum bio samples, PRO collection). Neither the University of North Carolina at Chapel Hill, nor PCORI, has set aside funds to pay patients for any study-related reaction or injury, or for the related medical care.

13 Publication Plan

Dissemination of study results is an essential component of this research project. Regardless of the outcome of the trial, we submit study findings to high-impact, peer-reviewed journals and present results in the form of abstracts at scientific meetings. We will also make our research findings publicly available on the ICN and PCORI websites, including lay summaries of relevant findings.

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15 Appendix A – Time and Events Table

NOTE – Patients who discontinue study medication but remain in follow-up will have a modified events schedule. See footnote "f" and section 6.9 for details.

Study Period	Screening	Randomization and Treatment Initiation	Blinded Treatment Phase											End of Study[g]	Additional Visits	Early Termination[d]
Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	AV	ET
Study Week	W-3 to W0	W0[a]	W4 (+/- 4 wks)	W 14 (wk 9 to wk 22)[b]	W26 (wk 22 to wk 32)	W 39 (+/- 6 wks)	W 52 (+/- 6 wks)	W 65 (+/- 6 wks)	W 78 (+/- 6 wks)	W 91 (+/- 6 wks)	W 104 (+/- 6 wks)	W 117 (+/- 6 wks)	W 130 (+/- 6 wks)	W 143 (+/- 6 wks)	W 156 (+/- 6 wks)		
Study Procedures																	
Informed Consent, Parental Permission, Assent	x																
Demographics	x																
Inclusion / Exclusion Criteria	x	x															
Medical History (incl. pre-existing conditions and perianal history at screening)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Prior IBD medications	x																
Concomitant medications (incl. anti-TNF and steroid use)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exam (incl. abdominal, height and weight, perianal, if done)	X[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
sPCDAI	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Physician Global Assessment	x		x	x	x	x	x	x	x	x	x	x	x	x	X	x	
Confirm negative TB within the past year	x																
Pregnancy Test (age ≥ 12 or younger if post-menstrual)	x																
WBC, Platelets, HCT, HGB	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CRP (w/ULN)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ESR	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Study Period	Screening	Randomization and Treatment Initiation	Blinded Treatment Phase												End of Study[g]	Additional Visits	Early Termination [d]
Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	AV	ET
Study Week	W-3 to W0	W0[a]	W4 (+/- 4 wks)	W 14 (wk 9 to wk 22)[b]	W26 (wk 22 to wk 32)	W 39 (+/- 6 wks)	W 52 (+/- 6 wks)	W 65 (+/- 6 wks)	W 78 (+/- 6 wks)	W 91 (+/- 6 wks)	W 104 (+/- 6 wks)	W 117 (+/- 6 wks)	W 130 (+/- 6 wks)	W 143 (+/- 6 wks)	W 156 (+/- 6 wks)		
Study Procedures																	
Albumin	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ALT (w/ULN)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AST (w/ULN)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Creatinine	x																
Document fecal calprotectin (if performed)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Document colonoscopy (if performed)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reproductive counseling (age ≥ 12 or younger if post-menstrual) [f]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Document / verify mailing address and email address(es) [f]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PRO collection	x	x (if not done at visit 1)		x	x	x (if not done at visit 4)	x	x (if not done at visit 6			x				x	x (if skipped at prior scheduled visit)	
Provider assessment of study drug dosage and continuation [f]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization and initial study drug shipment to patient (13-week supply)		x															
Follow-up Contact [f]		x		x	x	x	x	x	x	x	x	x	x	x			
Non-Serious Adverse Event Reporting [f] (including 14 days post last study dose)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serious Adverse Event Reporting (including 14 days post last study dose)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Study Period	Screening	Randomization and Treatment Initiation	Blinded Treatment Phase												End of Study[g]	Additional Visits	Early Termination [d]
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**AV**	**ET**
Study Week	W-3 to W0	W0[a]	W4 (+/- 4 wks)	W 14 (wk 9 to wk 22)[b]	W26 (wk 22 to wk 32)	W 39 (+/- 6 wks)	W 52 (+/- 6 wks)	W 65 (+/- 6 wks)	W 78 (+/- 6 wks)	W 91 (+/- 6 wks)	W 104 (+/- 6 wks)	W 117 (+/- 6 wks)	W 130 (+/- 6 wks)	W 143 (+/- 6 wks)	W 156 (+/- 6 wks)		
Study Procedures																	
Review patient diary information (if completed) [f]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Document date of first anti-TNF treatment[c]			x														
Anti-TNF level and antibody (if performed for clinical purposes)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Document Non-IBD reason for SPCDAI ≥15 (if applicable)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Provider assessment of outcomes (treatment failure) [f]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug refill shipments (13 week supply) [f]				x	x	x	x	x	x	x	x	x	x	x			
Collect unused study medication				x	x	x	x	x	x	x	x	x	x	x	x		x
Bio sample collection (if consent provided)				x	x (if not done at visit 3)					x	x (if not done at visit 9)					x (if skipped at prior scheduled visit)	
Unblinding															x		
Document patient withdrawals, lost to follow-up (incl. date of last contact & study drug dose)																	x

[a]Week 0 is the week patient is randomized
[b]End of anti-TNF Induction--Must be at least 2 weeks after 3rd anti-TNF dose
[c]Anti TNF start occurs ± 42 days from randomization date
[d]Collect if known
[e]Screening exam may occur up to 30 days prior to randomization date
[f] Not applicable to patients OFF study drug but in follow-up. Reference section 6.9 for details.
[g]Visit 14 End of Study is either Week 156 or the patient's last visit if the study is closing