Precise infliximab exposure and pharmacodynamic control to achieve deep remission in paediatric Crohn's disease (REMODEL-CD): study protocol for a multicentre, open-label, pragmatic clinical trial in the USA

Phillip Paul Minar, Ruben J Colman, Nanhua Zhang, Tomoyuki Mizuno, Alexander A Vinks

ABSTRACT

Introduction The only biologic therapy currently approved to treat moderate to severe Crohn’s disease in children (<18 years old) are those that antagonise tumour necrosis factor-alpha (anti-TNF). Therefore, it is critically important to develop novel strategies that maximise treatment effectiveness in this population. There is growing evidence that rates of sustained corticosteroid-free remission, endoscopic healing and drug durability considerably improve when patients receive early anti-TNF dose optimisations guided by reactive or proactive therapeutic drug monitoring and pharmacodynamic monitoring. In response, our team has developed a personalised and scalable infliximab dosing intervention that starts with dose selection and continues throughout maintenance to optimise drug exposure. We hypothesise that a precision dosing strategy starting from induction and targeting dose-specific pharmacokinetic and pharmacodynamic endpoints throughout therapy will significantly improve outcomes compared with a conventional dosing strategy.

Methods and analysis Conduct a clinical trial to assess rates of deep remission between Crohn’s disease patients receiving infliximab with precision dosing (n=90) versus conventional care (n=90). Patients (age 6–22 years) will be recruited from 10 medical centres in the USA. Each centre has been selected to provide either precision dosing or conventional care dosing. Precision dosing includes the use of a clinical decision support tool (RoadMAB) from the start of infliximab to achieve specific (personalised) trough concentrations and specific pharmacodynamic targets (at doses 3, 4 and 6). Conventional care includes the use of a modified infliximab starting dose (5 or 7.5 mg/kg based on the pretreatment serum albumin) with a goal to achieve maintenance trough concentrations of 5–10 μg/mL. The primary endpoint is year 1 deep remission defined as a combination of clinical remission (paediatric Crohn’s disease activity index<10 (child) or a Crohn’s disease activity index<150 (adults)), off prednisone>8 weeks and endoscopic remission (simple endoscopic severity-Crohn’s disease≤2).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ One of the first real-world, multicentre, pragmatic clinical trials in children receiving infliximab for Crohn’s disease that includes an objective assessment of intestinal healing (colonoscopy) at the conclusion of the trial.
⇒ Intervention arm includes the use of infliximab dose optimisation from the first dose and continued throughout therapy based on specific pharmacokinetic (proactive therapeutic drug monitoring (TDM)) and pharmacodynamic targets.
⇒ The interventional arm will use a novel precision dosing platform (RoadMAB) throughout the trial that is scalable for use in real-world clinical practice.
⇒ The in-kind drug support (infliximab, from Janssen Scientific Affairs) will assure participants receive the physician specified infliximab dosing and minimise any confounding that may have occurred if the study relied on third-party insurance coverage for the proposed dosing regimen.
⇒ One limitation is the gradual adoption in real-world clinical practice of using infliximab optimisation during induction (doses 5–10 mg/kg) and the routine use of proactive TDM may limit a true control cohort of standard dosing (5 mg/kg) and reactive TDM.

Ethics and dissemination The study protocol has been approved by the Cincinnati Children’s Hospital Medical Centre Institutional Review Board. Study results will be disseminated in peer-reviewed journals and presented at scientific meetings.

Trial registration number NCT05660746.

INTRODUCTION

Crohn’s disease (CD) is a chronic illness that results in intestinal inflammation and unwanted gastrointestinal symptoms. The only biologic (monoclonal antibody) therapy
approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for moderate to severe CD in children (<18 years old) is those that antagonise tumour necrosis factor-alpha (anti-TNF). Initial response rate to labelled infliximab (anti-TNF) dosing ranges from 70% to 80%, however, only about half of infliximab exposed patients will achieve clinical remission and less than 40% will achieve endoscopic healing (EH) after 1 year of therapy. In real-world practice, the probability of remaining on infliximab for 5 years was shown to be 60%. In children, the use of labelled (standard, 5mg/kg at 0, 2, 6 and then every 8 weeks) anti-TNF dosing regimens often leads to significant under-exposure and that a ‘one-size-fits-all’ approach is outdated. In fact, children receiving the standard starting dose during induction has led to a significant rate (36–60%) of infliximab concentrations below the maintenance infliximab trough concentration (cTrough) target (5–10µg/mL) for luminal CD.

Several studies in children and adults have shown that rates of sustained corticosteroid-free clinical remission are improved when patients receive anti-TNF dose (infliximab or adalimumab) optimisations following reactive or proactive therapeutic drug monitoring (TDM). There is growing evidence in adults with CD that anti-TNF (adalimumab) dose optimisations during induction and following pharmacodynamic (PD) monitoring will lead to improved rates of clinical remission, EH and lower rates of immunogenicity. Therefore, given the limited therapeutic options for children with moderate to severe CD, there is a critical unmet need for the development of a personalised and scalable anti-TNF dosing intervention applied from drug start, continued throughout maintenance therapy to optimise drug exposure, reduce immunogenicity and improve rates of EH and drug durability.

In a prior prospective, real-world investigation, our team developed a population pharmacokinetic (PK) model for children and young adults receiving infliximab for moderate to severe CD. In this study, we identified five covariates of infliximab clearance that significantly improved the prediction accuracy of our PK model with less unexplained variability in comparison to previous models. This discovery also led to the development of a clinical-decision support tool (RoadMAB) that performs bedside model-informed precision dosing (MIPD) to optimise drug exposure for the individual patient. The RoadMAB platform performs Bayesian PK estimation to propose up to three treatment regimens using the published population PK model and the five covariates of infliximab clearance. The five biomarkers (covariates) of infliximab clearance are the patient’s weight (kg), serum albumin, erythrocyte sedimentation rate (ESR), neutrophil CD64 (nCD64) and antibodies to infliximab (ATI). In addition to displaying the predicted cTrough throughout induction, RoadMAB incorporates measured infliximab concentrations collected at any timepoint during an interval to further update the platform and guide the future dosing regimen.

As noted, separate randomised controlled trials in adults and children have demonstrated effectiveness of anti-TNF dose (infliximab and adalimumab) optimisation using either PD targets (c-reactive protein (CRP) and/or faecal calprotectin (fCal)), proactive TDM or a clinical decision support tool during maintenance therapy. While these individual strategies improved rates of clinical remission and EH in their respective trials, it is currently unknown if a pragmatic anti-TNF dosing strategy that combines MIPD from induction, proactive TDM and repeated PD assessments to inform dose optimisations as a singular, novel strategy will result in superior clinical and endoscopic outcomes as compared with the current dosing strategy that largely relies on TDM during maintenance and a ‘trial-and-error’ approach to dose optimise infliximab (conventional care). Therefore, our team has designed a pragmatic clinical trial that unifies proven infliximab dosing strategies to increase the rates of deep remission (EH and clinical remission). Furthermore, this study will provide invaluable data regarding whether MIPD of infliximab with a precision dosing platform is feasible, safe and more effective at inducing EH and modernise dosing strategies of other biologics.

The central hypothesis is that the hybrid precision dosing approach (intervention arm) of combining MIPD at the start of infliximab induction with proactive TDM and routine PD monitoring will improve rates of deep remission compared with the current approach to infliximab dose selection and use of proactive TDM prior to the first maintenance dose (control arm). To test this hypothesis, we will conduct a multicentre, pragmatic clinical trial among patients with CD and assess rates of deep remission following 1 year of infliximab therapy between both arms.

**METHODS AND ANALYSIS**

**Study design and population**

The REMODEL-CD study is an open-label, pragmatic clinical trial to assess the superior infliximab dosing strategy to achieve deep remission after 1 year of infliximab. All patients will be recruited from 10 medical centres within the ImproveCareNow learning health network. Five centres will prescribe infliximab using the precision dosing strategy (intervention arm) and five centres will prescribe infliximab according to the conventional dosing strategy (control arm). We will enrol newly diagnosed (<90 days) patients (6–22 years old) with moderate to severe luminal CD who are starting infliximab (additional patient eligibility is listed in table 1). The trial start date is 1 July 2023 with an estimated completion date of 31 March 2027. The specific dosing strategy (treatment arm) has been assigned at the centre level to prevent treatment contamination and assure that all treating physicians have been properly informed and trained on the dosing intervention at their respective centre. Patients meeting...
eligibility criteria will be recruited prior to the start of infliximab.

**Study outcomes**

The primary outcome is deep remission that is defined as clinical remission (an inactive disease activity index and off prednisone>8 weeks) and EH (simplified endoscopic score-CD (SES-CD≥2)) at year 1. As both children and adults will be enrolled, the disease activity index for patients 6–17 years old is assessed with the paediatric CD activity index (PCDAI), while the CD activity index (CDAI) will be used for patients 18 years old. In order to assess for EH, all enrolled patients remaining on infliximab>42 weeks will undergo a standard of care, follow-up ileocolonoscopy with central readers blinded to the patient, treatment arm and centre and the endoscopic report. As noted, EH is assessed by the SES-CD, while the Simplified Endoscopic Mucosal Assessment for CD (SEMA-CD) will be scored as an exploratory measure. Deep remission has been chosen as the primary endpoint as it was identified as a major long-term therapeutic goal by the STRIDE-II consortium. Key secondary endpoints (table 2) will also include assessments of immunogenicity (ATI), patient-reported outcomes (PRO), quality of life assessments and growth restoration in Tanner I–III children consistent with other key STRIDE-II outcome measures.

**Interventions**

All 10 centres participating in the REMODEL-CD trial currently utilise the ImproveCareNow Model IBD Care guidelines (available at www.improvecarenow.org) to manage CD patients starting infliximab. These guidelines recommend physicians use the FDA/EMA approved starting dose of 5 mg/kg (rounding up the nearest 100 mg) but also acknowledge that higher starting doses...
## Table 2  Key secondary outcome measures

<table>
<thead>
<tr>
<th>Name of outcome</th>
<th>Specific measure to be used</th>
<th>Time point(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of steroid-free clinical remission</td>
<td>PCDAI&lt;10 (child) or CDAI&lt;150 (adult) and off prednisone/budesonide for ≥4 weeks</td>
<td>Weeks 14 and 52</td>
</tr>
<tr>
<td>Rate of clinical response</td>
<td>Decrease from baseline PCDAI of at least 12.5 points and total PCDAI&lt;30 or a total PCDAI&lt;10 (child) or a reduction of CDAI&gt;70 from baseline or CDAI&lt;150 (adult)</td>
<td>Weeks 14 and 52</td>
</tr>
<tr>
<td>Rate of primary clinical non-response</td>
<td>On prednisone&gt;16 consecutive weeks from start of infliximab or a PCDAI&gt;30 or CDAI&gt;220 for first four infusions</td>
<td>Week 16</td>
</tr>
<tr>
<td>Rate of primary biologic non-response</td>
<td>Failure to improve baseline faecal calprotectin by &gt;100 µg/g (limited to patients with a baseline faecal calprotectin&gt;250 µg/g) or failure to improve baseline c-reactive protein≥0.5 mg/dL (limited to patients with a baseline c-reactive protein&gt;1.0 mg/dL)</td>
<td>Week 16</td>
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<tr>
<td>Rate of sustained steroid-free clinical remission</td>
<td>PCDAI&lt;10 (child) or CDAI&lt;150 (adult) at dose 5 to week 52 and off prednisone/budesonide from weeks 22–52</td>
<td>Weeks 22–52</td>
</tr>
<tr>
<td>Rate of steroid-free clinical remission—biomarker composite</td>
<td>PCDAI&lt;10 (child) or CDAI&lt;150 (adult), off prednisone/budesonide for ≥4 weeks, CRP≤0.5 mg/dL and faecal calprotectin≤250 µg/g</td>
<td>Weeks 14 and 52</td>
</tr>
<tr>
<td>Rate of endoscopic healing</td>
<td>SES-CD≤2</td>
<td>Week 52</td>
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<tr>
<td>Rate of complete endoscopic healing</td>
<td>SES-CD=0</td>
<td>Week 52</td>
</tr>
<tr>
<td>Rate of endoscopic remission</td>
<td>SES-CD&lt;4</td>
<td>Week 52</td>
</tr>
<tr>
<td>Rate of mucosal healing</td>
<td>SES-CD=2 and Ileal Histologic Activity Score (GHAS)/Colon Global Histologic Activity Score (GHAS)≤2</td>
<td>Week 52</td>
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<tr>
<td>PK model bias</td>
<td>Model predicted vs actual infliximab concentration. Bias: mean predictive error (MPE)</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>PK model precision</td>
<td>Model predicted vs actual infliximab concentration. Precision: root mean squared error (RMSE)</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of IBD-related event—fistula</td>
<td>Occurrence of fistula</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of IBD-related hospitalisation</td>
<td>Occurrence of Crohn's disease-related hospitalisation</td>
<td>Weeks 0–52</td>
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<tr>
<td>Rate of IBD-related surgery</td>
<td>Occurrence of Crohn’s disease-related surgery</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of IBD-related intestinal stricture</td>
<td>Occurrence of Crohn's disease-related intestinal stricture</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of IBD related—starting corticosteroids</td>
<td>Occurrence of patients starting a corticosteroid after week 20</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of IBD-related antibodies to infliximab</td>
<td>Occurrence of antibodies to infliximab defined as &gt;200 ng/mL</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of growth restoration—weight change</td>
<td>In Tanner stage I–III patients: change from baseline weight (kg) by gender and age group</td>
<td>Weeks 14–52</td>
</tr>
<tr>
<td>Rate of growth restoration—height velocity</td>
<td>In Tanner stage I–III patients: change in height velocity (z-score) by gender</td>
<td>Weeks 14–52</td>
</tr>
<tr>
<td>PK of infliximab in paediatric patients</td>
<td>Measured infliximab clearance at baseline and at week 52</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Correlation between infliximab induction exposure and endoscopic remission</td>
<td>The correlation analysis to be performed for the total area under the curve (infliximab exposure, µg*h/mL from week 0–14) and patients achieving endoscopic remission. Endoscopic remission is defined as a SES-CD≤2.</td>
<td>Exposure: weeks 0–14 Efficacy: week 52</td>
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<tr>
<td>Correlation between infliximab induction exposure and deep remission</td>
<td>The correlation analysis to be performed for the total area under the curve (infliximab exposure, µg*h/mL from week 0–14) and patients in deep remission. Deep remission is defined as a PCDAI&lt;10 (child) or CDAI&lt;150 (adult), off prednisone/budesonide for ≥8 weeks and a SES-CD≤2.</td>
<td>Exposure: weeks 0–14 Efficacy: week 52</td>
</tr>
<tr>
<td>Rate of PRO2 response</td>
<td>&gt;50% improvement in total score from baseline</td>
<td>Weeks 6, 14, 26 and 52</td>
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<tr>
<td>Rate of PRO2 remission</td>
<td>Stool frequency≤3.0 and abdominal pain≤1.0 (from baseline)</td>
<td>Weeks 6, 14, 26 and 52</td>
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Continued
can be considered in more severe or extensive disease (including perianal disease). In addition, it is recommended that a cTrough be obtained prior to the first maintenance dose (proactive TDM) and with an acute increase in gastrointestinal symptoms (reactive TDM). The maintenance cTrough target is 5 µg/mL. Once enrolled, all patients will receive infliximab at their centre at no cost from the in-kind (drug-only) support from Janssen Scientific Affairs, LLC. Both treatment arms will receive the standard induction regimen (infusions at 0, 2 and 6 weeks) with maintenance infusions varying between 4 and 8 weeks for both groups. As a pragmatic study, all dosing and management decisions will be made by the patient’s treating physician.

Conventional care (control arm)
The FDA and EMA approved infliximab induction dose is 5 mg/kg occurring at weeks 0, 2 and 6. In order to ensure that the full spectrum of disease severity will be enrolled at these centres, the treating physicians will choose a starting dose between 5 and 7.5 mg/kg based on the patient’s serum albumin (at the time of screening). The patient’s baseline serum albumin was chosen to inform the starting dose as it provides a more objective marker of CD severity and it has been found to be a consistent biomarker of infliximab clearance in multiple paediatric PK studies. The protocol recommends that patients with a serum albumin <3 gm/dL receive 7.5 mg/kg and patients with a serum albumin ≥3 gm/dL receive 5 mg/kg. Once the starting dose has been selected, the patient will receive the same dose (in mg) throughout induction (dose 1, dose 2 and dose 3). As is routine practice, calculated doses of ≥20 mg over a 100 mg increment will be increased up to the nearest 100 mg to minimise drug waste as vials are supplied in 100 mg increments. Rounding to the nearest 100 mg will not be done if the rounding of the induction doses would cause the patient to receive a dose >7.5 mg/kg.

All patients in the conventional care arm will undergo proactive TDM (Esoterix, LabCorp specialty laboratory, Calabasas, CA) prior to receiving dose 4 (~week 14, cTrough). The treating physician will then interpret these results and prescribe future infliximab doses between 5 and 10 mg/kg with a dosing interval between 4 and 8 weeks to achieve or maintain a cTrough target of 5–10 µg/mL. Importantly, the dose will not be rounded to the nearest 100 mg if rounding would result in a maintenance dose >10 mg/kg. As this is a pragmatic dosing study, no dose reductions or intensifications will be study mandated. During the study, the treating physician can obtain one reactive TDM during maintenance if there is a concern for active CD. If ATI are discovered during any TDM, the subsequent dosing regimen (including the possible addition of methotrexate) is at the discretion of the treating physician and will not be considered a treatment failure unless infliximab is discontinued. The use of MIPD programmes, PK software or other commercially available TDM modelling services to inform dosing regimens are not permitted.

Precision care (intervention arm)
The precision care arm includes the use of the RoadMAB platform to inform the first starting dose during induction and assess for opportunities to dose optimise during maintenance based on three strict checkpoints (online supplemental figure 1). Checkpoint 1 (dose 3) includes a cTrough target, while checkpoint 2 (dose 4) and checkpoint 3 (dose 6) include both cTrough and PD targets. Prior to starting infliximab, the treating physician will access the New Start Wizard within the RoadMAB precision dosing software portal (figure 1) and review the dashboard recommended infliximab starting dose. RoadMAB formulates a dosing recommendation based on the predicted infliximab clearance using Bayesian estimation with the Xiong et al population PK model and is guided by a novel method of disease progression modelling. While RoadMAB will display the predicted cTrough at doses 2, 3 and 4, the initial target (checkpoint 1) is a cTrough at dose 3 (week 6) between 18 and 24 µg/mL (target 1).

Table 2 Continued

<table>
<thead>
<tr>
<th>Name of outcome</th>
<th>Specific measure to be used</th>
<th>Time point(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life and disability—IMAPCT-III score</td>
<td>Total IMPACT-III (child) score&lt;sup&gt;19 20&lt;/sup&gt;</td>
<td>Week 52</td>
</tr>
<tr>
<td>Quality of life and disability—IBD disk score</td>
<td>Total IBD disk (without sexual function assessment) score</td>
<td>Week 52</td>
</tr>
<tr>
<td>Quality of life and disability—short IBD score</td>
<td>Total Short IBD Questionnaire (adult) score</td>
<td>Week 52</td>
</tr>
<tr>
<td>Process evaluation—usability of decision support tool</td>
<td>Total System Usability Scare score</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of adverse events</td>
<td>Number of adverse events</td>
<td>Weeks 0–52</td>
</tr>
<tr>
<td>Rate of serious adverse events</td>
<td>Number of serious adverse events</td>
<td>Weeks 0–52</td>
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</table>

CDAI, Crohn’s disease activity index; CRP, c-reactive protein; IBD, inflammatory bowel disease; PCDAI, paediatric Crohn’s disease activity index; PK, pharmacokinetic; SES-CD, simple endoscopic score-Crohn’s disease.
The RoadMAB platform will provide a starting dose (‘Model Informed Dosing’, figure 1B) between 5 and 12.5 mg/kg that will attain the aforementioned dose 3 cTrough target (checkpoint 1).7 Starting doses are rounded up to the nearest 100 mg (as described for the conventional care arm) unless rounding would result in a dose>12.5 mg/kg (max induction dose). The model-informed starting dose is generated by estimating infliximab clearance based on the patient’s weight (kg), serum albumin (g/dL), ESR (mm/h) and nCD64. The treating physician will also have the option of viewing the ‘Standard Dosing’ tab (figure 1C) to preview (as a reference) the predicted cTrough at doses 2–4 for the standard FDA/EMA approved dose (5 mg/kg). Within the ‘Manual Dosing’ tab (figure 1D), the physician is able to interact with RoadMAB to review variable dosing options and the subsequent predicted cTrough. Any deviations from the Model Informed Dosing recommendation will be documented in the case report form.

Prior to dose 3 (week 6), a cTrough will be obtained. The cTrough along with the patient’s weight, albumin, ESR, nCD64 and ATI (ng/mL) will be entered into RoadMAB to further guide a maintenance dosing regimen to achieve a cTrough of 5–10 µg/mL at the next infusion (dose 4). The treating physician will make the final decision for maintenance dosing as there are multiple strategies to maintain the target, including modifying the dose alone, interval alone or changing both dose and interval.

During maintenance, there are two checkpoints that will require additional review. Both checkpoints will assess whether the PK and PD targets were met. As adequate drug exposure has been shown to be a key variable in assessing treatment effectiveness, the cTrough target has been prioritised for both checkpoints and will guide all subsequent dosing recommendations. The PK/PD targets for checkpoints 2 and 3 are listed in table 3. Importantly, if either the CRP or fCal is missing, the missing PD biomarker will default to yes (achieved) with future dosing based on the success or failure of the other PD targets.

Assessing success or failure for checkpoints 2 and 3
During maintenance, the cTrough target concentration (at doses 4 and 6) is dependent on whether the patient is (1) a PK failure only or (2) PK success with PD failure. Following each infusion, vital patient data (weight, albumin, CRP, ESR and nCD64) and dose administration (date and time) will be manually entered into the secure RoadMAB platform. The treating physician will then access the RoadMAB platform to review whether the checkpoint PK and PD targets were achieved to determine the next optimal dose (mg) and dosing interval (weeks). Infliximab maintenance doses will range between 5 and 15 mg/kg (rounded to the nearest 100 mg) and infusion intervals will range between 4 and 8 weeks. As a precaution, rounding up to the nearest 100 mg vial will not be

### Table 3 Pharmacokinetic and pharmacodynamic targets by treatment arm

<table>
<thead>
<tr>
<th>Conventional care arm</th>
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<tbody>
<tr>
<td>Dose 3</td>
<td>Proactive therapeutic drug monitoring is not performed</td>
</tr>
<tr>
<td>Dose 4</td>
<td>Infliximab trough concentration 5–10 µg/mL</td>
</tr>
<tr>
<td>Dose 6</td>
<td>Proactive therapeutic drug monitoring is not performed</td>
</tr>
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<table>
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<tr>
<th>Precision care arm</th>
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<tbody>
<tr>
<td>Dose 3 (checkpoint 1)</td>
<td>Infliximab trough concentration 18–24 µg/mL</td>
</tr>
<tr>
<td>Dose 4 (checkpoint 2)</td>
<td>Infliximab trough concentration 5–10 µg/mL</td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>Infliximab trough concentration 5–15 µg/mL (varies from 5 to 10–15 µg/mL depending on whether target 2 trough concentration was achieved)</td>
</tr>
</tbody>
</table>
| Pharmacodynamic        | 1. Disease activity score+  
Child: PCDAI decrease of at least 12.5 points from baseline and a total PCDAI<10 or a total PCDAI<10  
Adult: Delta CDAI>70 from baseline or a CDAI<150  
2. CRP≥50% change from baseline CRP or a CRP≤0.5 mg/dL+  
3. Faecal calprotectin≥50% change from baseline or a faecal calprotectin<250 µg/g |

CDAI, Crohn’s disease activity index; CRP, c-reactive protein; PCDAI, paediatric Crohn’s disease activity index.

The RoadMAB platform will provide a starting dose (‘Model Informed Dosing’, figure 1B) between 5 and 12.5 mg/kg that will attain the aforementioned dose 3 cTrough target (checkpoint 1).7 Starting doses are rounded up to the nearest 100 mg (as described for the conventional care arm) unless rounding would result in a dose>12.5 mg/kg (max induction dose). The model-informed starting dose is generated by estimating infliximab clearance based on the patient’s weight (kg), serum albumin (g/dL), ESR (mm/h) and nCD64. The treating physician will also have the option of viewing the ‘Standard Dosing’ tab (figure 1C) to preview (as a reference) the predicted cTrough at doses 2–4 for the standard FDA/EMA approved dose (5 mg/kg). Within the ‘Manual Dosing’ tab (figure 1D), the physician is able to interact with RoadMAB to review variable dosing options and the subsequent predicted cTrough. Any deviations from the Model Informed Dosing recommendation will be documented in the case report form.

Prior to dose 3 (week 6), a cTrough will be obtained. The cTrough along with the patient’s weight, albumin, ESR, nCD64 and ATI (ng/mL) will be entered into RoadMAB to further guide a maintenance dosing regimen to achieve a cTrough of 5–10 µg/mL at the next infusion (dose 4). The treating physician will make the final decision for maintenance dosing as there are multiple strategies to maintain the target, including modifying the dose alone, interval alone or changing both dose and interval.

During maintenance, there are two checkpoints that will require additional review. Both checkpoints will assess whether the PK and PD targets were met. As adequate drug exposure has been shown to be a key variable in assessing treatment effectiveness, the cTrough target has been prioritised for both checkpoints and will guide all subsequent dosing recommendations. The PK/PD targets for checkpoints 2 and 3 are listed in table 3. Importantly, if either the CRP or fCal is missing, the missing PD biomarker will default to yes (achieved) with future dosing based on the success or failure of the other PD targets.

Assessing success or failure for checkpoints 2 and 3
During maintenance, the cTrough target concentration (at doses 4 and 6) is dependent on whether the patient is (1) a PK failure only or (2) PK success with PD failure. Following each infusion, vital patient data (weight, albumin, CRP, ESR and nCD64) and dose administration (date and time) will be manually entered into the secure RoadMAB platform. The treating physician will then access the RoadMAB platform to review whether the checkpoint PK and PD targets were achieved to determine the next optimal dose (mg) and dosing interval (weeks). Infliximab maintenance doses will range between 5 and 15 mg/kg (rounded to the nearest 100 mg) and infusion intervals will range between 4 and 8 weeks. As a precaution, rounding up to the nearest 100 mg vial will not be
done if rounding the maintenance dose would result in a single dose >15 mg/kg.

As noted, during maintenance, the PK target takes precedence over the PD assessment. For example, if a cTrough is below target (at dose 4 or 6), RoadMAB will provide a dosing recommendation to achieve the PK target first (irrespective of the result of the PD target). Once a PK target is achieved, the PD targets are assessed by RoadMAB and subsequent dosing recommendations will be presented to the user. Therefore, a PK success with any PD failure (at the two maintenance checkpoints) is then systematically elevated to a new PK tier. PK tiers range from 5 to 10 µg/mL (the starting maintenance cTrough target for all patients), 10–15 µg/mL and up to 15–20 µg/mL depending on the PD outcomes. To achieve PK and PD success, all PD criteria (disease activity index, CRP and fCal) must be achieved. Online supplemental table 1 provides details of the PD failure criteria and the subsequent escalation plan.

**Treatment failure (special circumstances for both arms)**

Primary infliximab failure can be difficult to define in a real-world, pragmatic study as clinicians often dose escalate infliximab to ensure proper exposure prior to drug discontinuation. In this trial, if any of the following criteria are met, the patient will not continue in the study and will be classified as a primary infliximab non-responder. These primary failure criteria include the following: (a) receiving the first two doses of infliximab <7 days apart, (b) receiving >3 doses before week 6, (c) receiving the third dose <2 weeks after dose 2, (d) receiving ≥10 mg/kg during induction (first three doses, in the conventional care arm), (e) receiving >12.5 mg/kg during induction (first three doses, in the precision care arm), (f) continuation of high dose prednisone or prednisolone (at doses >0.5 mg/kg if <40 kg or >20 mg for patients ≥40 kg) beyond week 12, (g) use of oral budesonide beyond week 16 or (f) starting methotrexate, 6-mercaptopurine or azathioprine prior to receiving infliximab dose 4. Criteria for secondary non-response or study withdrawal during maintenance are listed in online supplemental table 2.

The management of ATI (lower limit of detection is 22 ng/mL with the Esoterix, LabCorp assay) will vary by the treatment arm. As a pragmatic trial, infliximab optimisations are determined by the treating physician in the conventional care arm, while dose optimisations in the precision care arm will be informed by RoadMAB. For both arms, the addition of methotrexate (to reduce immunogenicity or improve exposure) is at the discretion of the treating physician. Similarly, the addition of methotrexate during maintenance phase for a cTrough...
persistently below the 5–10 µg/mL is at the discretion of the treating physician and will not be considered a treatment failure.

During the trial, both treatment arms can perform reactive TDM during maintenance. The use of reactive TDM on ≥2 occasions, however, will be recorded as a deviation in both arms. As is standard in clinical care, any patient receiving a dose optimisation will have TDM performed prior to the second new dose. For both treatment arms, dose reduction or interval lengthening is not mandated in the trial but the treating physician is encouraged to discuss the risks and benefits for any patient with a persistently elevated cTrough.

Adverse event monitoring
The trial team at each centre will be responsible for detecting, documenting and reporting events that meet the definition of adverse events including all serious adverse events and adverse events of special interest. Per protocol, the patient will be monitored until the event resolves, stabilises or is reasonably explained. The team will be responsible to determine if the adverse event was related to the study device, a procedure or infliximab while considering pre-existing conditions or concomitant medications. Adverse events will be reported in a timely manner to the medical monitor, the study Data Safety Monitoring Board, the principal investigator, the FDA, the Sponsor and Janssen Scientific Affairs, LLC.

Statistical analysis
Our study design, including the use of a precision dosing platform to optimise infliximab doses during induction in children is novel. Therefore, the expected rates of deep remission with this strategy are currently unknown. In order to develop our sample size calculation, we likened the precision dosing arm (intervention) to patients within the SONIC study that found 63% of adults with CD who received combination of infliximab and azathioprine (within 18 months of diagnosis) achieved deep remission at week 26. The control arm patients would be most similar to the adults with CD who participated in the CALM and TAILORIX clinical trials, where rates of year 1 deep remission were achieved in 23%–36.9% and 27%–33% (variation by treatment arm), respectively. Furthermore, preliminary review of children within the ImproveCareNow learning health network indicated an intra-class correlation (ICC) of 0.02 for clinical remission outcomes. Therefore, based on an anticipated 36.9% deep remission rate in the control arm and 63% deep remission rate in the interventional arm, we determined 140 patients (70 in each arm) would provide 80% power to detect a clinically meaningful absolute difference of at least 25% between the two treatment arms (alpha 0.05), assuming an ICC of 0.02. As study attrition is estimated at 5% and primary non-response is estimated at 12%–15%, the final sample size was increased to 180 patients (90 in each arm).

Generalised linear mixed models with a logit link will be used to compare rates of deep remission between the two arms. Additionally, center-specific random effect will be included to account for dependence of outcomes from the same centre. Our team will individually assess both the intention-to-treat and per protocol populations with the per protocol population to include all enrolled patients who received scheduled infliximab for at least 42 weeks, while the intention-to-treat population will include all enrolled patients who received at least one infliximab infusion (one dose). Fidelity will be assessed to avoid a type III error. We will assess whether core components of each intervention were conducted at the critical timepoints for precision dosing (pretreatment, doses 3, 4 and 6) and for conventional care (dose 4) as noted in the study design. There is a planned interim analysis after the first 40 patients in the precision dosing arm complete 1 year of infliximab.

Ethics and dissemination
The clinical trial has received Institutional Review Board approval at Cincinnati Children’s Hospital Medical Centre. The following participating centres have completed the Reliance agreements to participate in the trial: Nationwide Children’s Hospital, Riley Children’s Hospital San Diego, Medical College of Wisconsin/Children’s of Wisconsin, Riley Hospital for Children, Lucile Packard Children’s Hospital Stanford, Nemours Children’s Health System-Wilmington, Nemours Children’s Health System-Jacksonville, Cleveland Clinic Children’s Hospital and Children’s Hospital of Los Angeles. Parental consent will be required for all children<18 years of age while adults≥18 years of age will provide consent before any study procedures are started (model consent is included in the online supplemental materials).

Patient and public involvement
Prior to submission of this trial for funding, our study team met with parents of children with CD and adult patients with CD to discuss the study hypothesis and study protocol. These individuals were key in refining the inclusion criteria, the interventions, methods to enhance study retention and the plans for dissemination. Following completion of the trial, the results will comply with the Consolidated Standards of Reporting Trials (CONSORT) and results disseminated in peer-reviewed journals and presented at scientific meetings to inform whether precision dosing of infliximab is feasible, safe, and more effective at inducing deep remission then conventional care.

DISCUSSION
Suboptimal inflammatory control of paediatric CD increases the likelihood of irreversible intestinal damage and CD-related complications. Innovative clinical trials using novel approaches to maximise the current FDA/EMA approved biologics in paediatric CD are needed as anti-TNF dose optimisation strategies informed
by proactive TDM in children and PD control in adult CD have been associated with improved outcomes. Dose optimisation in children is particularly important as several studies have shown that anti-TNF clearance is significantly elevated in young patients (<10 years old), those with extensive disease (ileocolonic) or a high inflammatory burden. Therefore, patients enrolled in the precision care arm will receive dose optimisation (based on pretreatment biomarkers of drug clearance) from the start of infliximab with the maintenance regimen (dose and/or frequency) based entirely on achieving specific cTrough and PD targets.

While there is debate whether proactive TDM and PD monitoring will improve near and long-term outcomes, anti-TNF dose optimisation in clinical practice in children and young adults is common. Therefore, our team has designed a clinical trial that is both practical and based on key, objective procedures used in prior clinical trials (CALM, PRECISION and PAILOT). Specifically, in the PAILOT clinical trial, patients were randomised to receive adalimumab dose optimisation using either a reactive or proactive TDM approach (following successful induction). Assa et al found CD patients in the proactive TDM arm (targeting a cTrough>5 µg/mL during maintenance) resulted in higher rates of corticosteroid-free sustained clinical remission. The PRECISION trial randomised adults with IBD receiving maintenance infliximab to model-informed dosing or standard of care dosing. After 1 year, patients receiving model-informed dosing (with a dose calculator similar to RoadMAB) to maintain a minimal cTrough (3 µg/mL) had significantly lower rates of loss of response and a lower median fCal after 1 year.

There are a variety of reasons as to why the prior proactive TDM clinical trials in adults with IBD (TAXIT, TAILORIX or SERENE-CD) failed to demonstrate significant improvement compared with the respective control group. Key limitations to these prior studies include delaying the intervention until maintenance, only including adults with IBD, and use of a low cTarget (3 µg/mL for infliximab or 5 µg/mL for adalimumab). Therefore, we have designed a trial that will enrol children to receive dose optimisation during induction with an intensifying cTrough strategy that starts at 5–10 µg/mL and escalates based on success or failure of key PD biomarkers at specific, early stages of treatment.

While this will be one of the first studies to use a precision dosing support tool to dose optimise infliximab in paediatric CD, several studies in renal transplantation and other chronic conditions have demonstrated superior outcomes using PK software (decision support tools) to guide dose selection and obtain targeted immunosuppressive drug concentrations. Therefore, while the rate of deep remission at year 1 is the primary outcome, we will also be assessing the useability, fidelity, safety and effectiveness of the RoadMAB software platform in real-world clinical practice.

In summary, the current ‘one-size-fits-all’ with labelled anti-TNF dosing often leads to suboptimal drug exposure, poor gut healing and increased burdens on the patient and family. In this trial, our global aim is to conduct the first clinical trial to evaluate the rate of deep remission in children and young adults who have been recently diagnosed with CD and receive infliximab using a combination of MIPD, PD control and proactive TDM throughout induction and maintenance.

Author affiliations
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3Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA
4Division of Biostatistics, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA
5Division of Clinical Pharmacology, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA

Contributors Study concept and design: PPM and AA; initial draft and revising manuscript: PPM, RJ, NC, TM and AA; literature review: RJ, NC and TM; developed both the sample size calculation and statistical analysis plan: NJ, TM and PPM; study protocol review and revision: PPM, NJ, TM and AA. All authors approved the final version of the manuscript including the authorship list.

Funding This work is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK132408) and by Janssen Scientific Affairs, LLC with in-kind, drug-only support (no grant number).

Competing interests PPM and AA are inventors of the RoadMAB dosing platform. Janssen Scientific Affairs, LLC has reviewed and approved the study protocol.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Cincinnati Children’s Hospital Medical Center IRB approval, 2022-0071. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Not applicable.

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ORCID iD Phillip Paul Minar http://orcid.org/0000-0003-4223-4211

REFERENCES


Title of research study: Precise Infliximab Exposure and Pharmacodynamic Control to Achieve Deep Remission in Pediatric Crohn’s Disease

Key Information:

The following is a short summary of this study to help you decide whether to be a participant in it. More detailed information about the study is listed later in this form. This document does not replace the discussion you should have with the research team about this study including having any questions or concerns answered.

If you are 18 years and older: This is a consent form. It explains this research study. If you decide that you want to be in this research study, then you will sign this form to show that you agree to be part of this study. If you sign this form, you will receive a signed copy of it for your records.

Parental Permission: If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required using a separate form. When we say “you” in this form, we mean you or your child; “we” means the study doctor and other staff.

Reason for the study:

Approximately 3 million people in the United States are living with inflammatory bowel disease, which includes Crohn’s Disease. There are limited treatment options approved for use in children and adults with Crohn’s disease. We need better ways to inform decisions on treatment.

We are asking you to be part of this research study because you have been diagnosed with Crohn’s Disease and you are going to start treatment with infliximab as part of your routine clinical care.

Infliximab is a FDA-approved drug to treat Crohn’s Disease. Currently, standard dosing of infliximab is based only on your weight. However, with standard dosing of infliximab, some patients may not have a complete response or may lose response over time. Several research studies have shown that response to infliximab is improved when levels of infliximab are measured more frequently and when drug levels or other blood tests are within the target range.
The main reason for this research study is to determine if a computer program that calculates an individualized dose based on your blood testing results (precision dosing) can better achieve the best possible response to infliximab compared to standard dosing (conventional dosing). This new method of precision dosing is still experimental while the conventional dosing is already approved by the United States Food and Drug Administration.

If you qualify and decide you want to be in the study, you will come to [Site Name] approximately 9 times over the next year. You will receive infliximab prescribed by your regular doctor. Most of these visits will happen when you get your infliximab infusions. You will be asked to provide blood and stool samples at specific infusions.

Your study site has been assigned to one of two groups: the conventional dosing group, which uses standard dosing based on your weight, or the intervention group, which uses the computer program and blood/stool tests to inform your doctor of dosing options. Which group the study site is assigned was chosen by chance, like flipping a coin. You will be told which group your study site has been assigned.

For this study, we will enroll 180 people between 6 and 22 years old with Crohn's Disease.

We expect that you will be in this research study for 12 months.

**Procedures:**

If you decide to participate in the research study, the following tests and procedures will take place.

<table>
<thead>
<tr>
<th><strong>Standard Dosing Group:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>You will receive standard care of infliximab as ordered by your doctor.</td>
</tr>
<tr>
<td>We will:</td>
</tr>
<tr>
<td>• Collect information about you</td>
</tr>
<tr>
<td>• Measure levels of infliximab in your blood</td>
</tr>
<tr>
<td>• Perform other blood and stool tests</td>
</tr>
<tr>
<td>• Compare your results to the other group (intervention group)</td>
</tr>
<tr>
<td>• Your doctor will likely perform a colonoscopy at the end of the study so we can compare the rate of gut healing across both groups.</td>
</tr>
</tbody>
</table>
**Intervention Group:**

We will:
- Collect information about you
- Measure levels of infliximab in your blood
- Perform other blood and stool tests
- Enter the results into the computer program.
- Your doctor will likely perform a colonoscopy at the end of the study so we can compare the rate of gut healing across both groups.

Your doctor will use the computer program to inform their decision on your dose and dosing schedule. Your doctor may need to change your infliximab dose or dosing schedule in order to personalize your dosing plan.

Based on prior studies, your doctor may need to prescribe doses that are higher than the standard dosing.

More detailed information about the study procedures can be found under “(Detailed Procedures)”

**Risks to Participate:**

Like all medicines, infliximab can have side effects. Most side effects are mild to moderate. Some may be serious and may require treatment or additional testing. Side effects may appear up to six months or longer after the last infusion.

The table below shows the most common and most serious side effects that researchers know about. We do not know all of the side effects that may occur.

<table>
<thead>
<tr>
<th>Possible Infections while on Infliximab (some may be serious)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Infections (affects 10% or more)</td>
</tr>
<tr>
<td>o Common cold</td>
</tr>
<tr>
<td>o Bronchitis (coughing up mucus)</td>
</tr>
<tr>
<td>Bacterial Infections (occur between 1-10%)</td>
</tr>
<tr>
<td>o Sinus infection</td>
</tr>
<tr>
<td>o Sore throat</td>
</tr>
<tr>
<td>o Pneumonia Tuberculosis (uncommon)</td>
</tr>
<tr>
<td>Fungal infections (occur between 0.01-0.1%)</td>
</tr>
</tbody>
</table>
Possible Infections while on Infliximab (some may be serious)

Other Side effects of Infliximab
- Infusion Reactions including Allergic Reactions
- Lupus-like reactions
- Antibodies against infliximab
- Cancer (occur between 0.01-0.1%)
- Abnormal liver blood tests or liver problems
- New rash, psoriasis or hair loss
- Blood problems (low white blood cells) or easy bruising

More detailed information about the risks of this study can be found under “(Detailed Risks)”

**Benefits to Participate:**

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include improved control of your Crohn’s Disease and improved drug durability (longer time on the drug). In addition, you will receive infliximab at no cost during the study for up to 365 days.

This study will provide invaluable data regarding future treatment plans for dosing of infliximab.

**Other Options:**

Participation in research is completely voluntary. Your decision to participate or not to participate will not affect the care you receive.

Your alternative to participating in this research study is to not participate.

**Cost to Participate:**

You and your insurance company will be charged for the healthcare services that you would ordinarily be responsible for paying. This includes any additional fees associated with the infusion (such as, but not limited to, facility fees, professional fees and/or laboratory fees). In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay. If your insurance company denies the dose recommended by the computer program, your doctor can appeal.
Payment:

[Sites will alter to conform to their institutions’ policies.]

If you agree to take part in this research study, we will pay you for your time and effort (please see the chart below). You will receive payment for this study in the form of a reloadable debit card (Clincard). We will give you a handout that will explain how to use the card. Because you are being paid for your participation, [Site Name] is required by the Internal Revenue Service (IRS) to collect and use your social security number (SSN) or taxpayer identification number (TIN) to track the amount of money that we pay. You will need to complete a Federal W-9 form for this income tax reporting. This form requires your Social Security number. This form will be given to the [Site Name]’s business office. It will not be kept as part of your study chart. If you move, you will need to complete another W-9 with an updated address.

Your information and samples (both identifiable and de-identified) may be used to create products, including some that could be patented/licensed and sold. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

Payment Chart

<table>
<thead>
<tr>
<th>Study Activity</th>
<th>Doses (infusions)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Questionnaire /Blood sample</td>
<td>$10</td>
<td>$10</td>
</tr>
<tr>
<td>Stool sample</td>
<td>$25</td>
<td>$25</td>
</tr>
<tr>
<td>Optional Pinch biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total for participation</strong> (*dependent on number of infusions in year1)</td>
<td>~$240</td>
<td></td>
</tr>
</tbody>
</table>

*You will receive $10 for each blood sample collected up to 1 year as some patients may require more or less than 9 infliximab doses in one year.
**Additional Study Information:**
The following is more detailed information about this study in addition to the Key Information.

**If I have Questions or would like to know about:**

<table>
<thead>
<tr>
<th>Who to talk to...</th>
<th>You can call ...</th>
<th>At...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergencies</td>
<td>PI Name: [Site PI Name]</td>
<td>Phone: [XXX-XXX-XXXX]</td>
</tr>
<tr>
<td>General study questions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research-related injuries</td>
<td></td>
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<tr>
<td>Any research concerns or complaints</td>
<td></td>
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<th>At...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergencies</td>
<td>Lead Study Coordinator: [Coordinator Name]</td>
<td>Phone: [XXX-XXX-XXXX]</td>
</tr>
<tr>
<td>General study questions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research-related injuries</td>
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<tr>
<th>Who to talk to...</th>
<th>You can call ...</th>
<th>At...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your rights as a research participant</td>
<td>institutional Review Board</td>
<td>Phone:</td>
</tr>
<tr>
<td>This is a group of scientists and community members who make sure research meets legal and ethical standards.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Detailed Procedures:**

- Consent- You will need to read and sign this consent form before doing any study procedures. You will get a copy to keep.
- Demographics – We will collect information including your current age, age of diagnosis, gender, race and ethnicity.
- Medical Record Review- We will review your medical records for information on your health, medical and surgical history, and current medications.
- Physical Exam- We will examine your temperature, heart rate, breathing rate, blood pressure, height, weight, and body mass index. We will also perform an abdomen examination and perianal examination (located around the anus, if needed).
- The study staff will ask you about any symptoms you have had since your last visit.
• Questionnaires- You will answer some questions about your stomach pain, stool frequency, and general well-being.

• You will have up to 20 ml (4 teaspoons) of blood collected for research purposes prior to each infusion. In addition, about 5 ml (1 teaspoon) of blood will be collected 30-60 minutes after infusions 1, 3, 4, and 6. We will try to collect the blood sample from your IV so you do not have to have another needle stick. If we are not able to collect a blood sample at that time, you will be given the option to have another needle stick to collect the blood.

• Stool Collection- You will be asked to collect stool samples. You will be provided the kits for collection and mailing. You may also be given the option to perform additional at-home stool testing. This may include the use of a smartphone and a commercially available application that you would install on your smartphone. The study staff will provide additional information about this.

• Pregnancy Test- If you are female and able to get pregnant, you will be asked to give a small sample of urine for a pregnancy test. We will give the results of this test to the parent. If it is positive, you will not be allowed in the study.

• Drug Infusion (first 3 doses) - As part of your normal infusion visits, you will receive infliximab at 0, 2, and 6 weeks. If you are in the intervention group, you may receive doses that are higher than the FDA approved dose.

• Drug infusion (doses 4 - 9) - As part of your normal infusion visits, you will receive infliximab every 4-8 weeks. The dosing schedule and actual dose is variable and based on your site’s group assignment. You may require more or less than 9 infliximab doses in one year, regardless of your site’s group assignment.

• Drug infusion -You will be monitored for 30 – 60 minutes or longer following your infusion for any infusion-related side effects.

• Approximately 1 year (between 52-84 weeks) after starting treatment, you will likely have a colonoscopy as part of your clinical care.
  - We would like to collect a blood sample and up to 4 intestinal pinch biopsies for this research study. Collection of pinch biopsies is optional. You can indicate your preference on the signature page of this consent.
  - We will capture a video-image of your colonoscopy so the study doctors can review it and give it a score based on the amount of inflammation seen. The video will be labeled with your study ID and stripped of other identifiers.

• The study staff will contact you prior to visits as a reminder of upcoming visits and stool samples.
<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screen</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion dose number</td>
<td>0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 Final</td>
<td></td>
</tr>
<tr>
<td>Weeks (range)</td>
<td>0 2 6 10-14 14-22 18-30 22-38 26-46 30-54 34-62 38-70 42-86 42-90 50-94 52-84</td>
<td></td>
</tr>
</tbody>
</table>

- Ensure you qualify to participate in this study
- Collect Demographic information
- Collect medical and surgical history
- Ask about current and past medications
- Ask about any symptoms you are having or have experienced
- Receive infliximab infusion
- Collect vital signs (temperature, blood pressure, heart rate, weight and height)
- Perform physical exam
- Perform urine pregnancy test (female participants)
- Collect blood sample(s)
- Collect Stool samples
- Complete questionnaires
- Research only pinch biopsies and blood sample at colonoscopy

*Some patients will have a different number of total doses during the one year study. These data are only collected up through the first year of treatment (first 365 days).

**Change of Mind/Study Withdrawal:**

You can leave the research at any time; it will not be held against you.

If you decide to leave the research, contact the investigator so that the investigator can record your reason for withdrawal.

The person in charge of the research study or the sponsor (Cincinnati Children’s) can remove you from the research study without your approval. Possible reasons for removal include significant failure to follow study procedures, if the investigator believes it is not in your best interest, or if your disease gets worse and the investigator believes it is best for you to be removed.

If you stop being in the research, data already collected may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.
If you stop being in the research, you and your insurance company will be responsible for the cost of infliximab.

**Detailed Risks:**

**Infections**

You may have more infections while taking infliximab or if you have an infection it could make it worse. Tell the study doctor if you have a new infection, if an infection keeps coming back, or if you have any signs of infection such as:

- Fever
- Chills
- Night sweats
- Flu-like symptoms
- Weight loss
- Tiredness
- Cold sores
- Headache
- Coughing
- Coughing up blood
- Congestion
- Shortness of breath
- Chest tightness
- Nausea
- Vomiting
- Diarrhea
- Frequency or burning while peeing
- Redness or swelling of limbs, skin or joints
- New or worsening of pain in any location

Infections seen with this treatment are colds, bronchitis (coughing up mucus), sinus infections, sore throat, and pneumonia. Those infections caused by viruses occur “very commonly” while those caused by bacteria occur “commonly.”

Some patients have had serious infections while receiving infliximab. Some of the patients have died from these infections.

Tuberculosis is a serious infection that usually develops in the lungs but can also develop in other areas of your body. Tuberculosis has been reported in patients who have received TNF-blockers, and it has been reported uncommonly in patients treated with infliximab. Tuberculosis requires prolonged treatment with specific medication. You may be more likely to develop tuberculosis while on infliximab. If you or any of your family have ever had tuberculosis you should tell your doctor. While in this study, if you come in contact with anyone who has tuberculosis, you should tell your study doctor.

Your study doctor will do a blood test to see if you have come in contact with tuberculosis.

Fungal infections have been reported in patients taking infliximab. Some of these fungal infections, such as histoplasmosis and coccidioidomycosis, occur rarely and can be serious and involve internal organs. You should find out from your study doctor which fungal infections are common where you live or travel, and what symptoms they cause. Tell your study doctor and family physician right away if you develop symptoms of such illnesses.

You should also tell your doctor if you have ever had chickenpox. If while in the study, you come in contact with someone with chickenpox tell your study doctor.
The use of live virus or bacterial vaccines when you are receiving infliximab may result in an infection. You cannot receive a live virus or bacterial vaccine during this study or for 3 months after your last dose of the infliximab. Other types of vaccines are allowed.

**Congestive Heart Failure**

Patients with congestive heart failure (CHF), a disease where the heart pumping action is weakened, were treated with infliximab in another study. Some of these patients had worsening of their CHF and some died. The risk is unknown. If you have a history of CHF or have received treatment for CHF, you are not allowed to participate in this study.

New cases of heart failure have been reported in patients receiving infliximab. It is not known whether or not these cases are related to infliximab. If you have shortness of breath or swelling in your ankles and/or feet, you must contact your study doctor right away.

Patients treated with infliximab have uncommonly developed worsening CHF or developed CHF for the first time.

**Infusion Reactions including Allergic Reactions and Lupus-Like Reactions**

Your body might have a reaction during or shortly following an infusion of infliximab into a vein. This is called an infusion reaction. These reactions are usually mild to moderate. They are managed by slowing the infusion or by giving you medication. Any drug may cause an allergic reaction in some patients. A life-threatening allergic reaction called anaphylaxis has occurred uncommonly in patients treated with infliximab.

Symptoms of an infusion reaction or an allergic reaction may include 1 or more of the following:

- Fever
- Chills
- Hives
- Rash
- Swelling
- Itching
- Headache
- Flushing
- Nausea
- Light-headedness
- Chest pain or tightness
- Wheezing
- Difficulty breathing or swallowing
- Decrease or increase in blood pressure
- Anaphylaxis (life-threatening allergic reaction)

If the symptoms cannot be managed or become serious or life threatening, the infusion will be stopped and additional treatment will be provided immediately if necessary.

If you have an allergic reaction your regular doctor may give you a medication used to treat allergic symptoms (such as an antihistamine), or to reduce aches, pains, and fever (such as acetaminophen or paracetamol). Antihistamines can make you sleepy, so please use caution when driving a car or operating machinery.
Cases of seizures have also been reported uncommonly. Cases of temporary loss of vision occurring during or within 2 hours of an infliximab infusion have also been reported. Patients have experienced a stroke, heart attack (sometimes resulting in death), or abnormal heart rhythm within 24 hours of the start of their infusion with infliximab.

Another type of reaction is called a delayed hypersensitivity reaction, which as occurred uncommonly in patients treated with infliximab. This reaction can occur 1 to 14 days after the infusion. Symptoms such as fever, rash, muscle aches, and/or joint pain may develop. You should report any of these symptoms to your study doctor right away.

Some patients have developed symptoms or developed abnormal blood tests that look like a disease called lupus. These symptoms may include muscle aches, joint pain, fever, prolonged chest discomfort or pain, rash (including a rash on the cheeks or arms that gets worse in the sun) and shortness of breath. You should report any of these symptoms to your study doctor.

**Antibodies against Infliximab**

Your body may make antibodies against infliximab. These antibodies might cause an allergic reaction if you receive infliximab in the future.

**Cancer**

Cancers have been reported in patients who have received infliximab and other TNF-blockers. Lymphoma (a cancer of lymph nodes) has been reported rarely in patients treated with infliximab (affects between 1 and 10 in 10,000 patients). Cases of leukemia (a cancer of the blood) have also been reported in patients taking TNF-blockers. It has been reported rarely in patients treated with infliximab (affects between 1 and 10 in 10,000 patients).

Rarely (between 0.01-0.1%), patients who received infliximab developed skin cancers, including melanoma.

A very aggressive rare type of lymphoma, called hepatosplenic T-cell lymphoma, has been reported in patients treated with TNF-blockers including infliximab. This type of cancer usually causes death. Almost all patients had received azathioprine or 6-mercaptopurine (6-MP) in combination with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn’s disease or ulcerative colitis, and most were reported in adolescent or young adult males. Cases of hepatosplenic T-cell lymphoma have also occurred in patients with Crohn’s disease and ulcerative colitis receiving azathioprine who were not treated with infliximab. It is unclear what role of infliximab may have in the development of the lymphoma.

Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking infliximab, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.
You should tell your study doctor prior to participating in this study if you have a history of lymphoma or cancer, and if you develop lymphoma or cancer, including skin or cervical cancer, during or after you have participated in this study. You should also regularly discuss cancer screenings with your study doctor, and the impact of life-style choices (for example, smoking) on the risk of developing cancer.

**Central Nervous System**
Some patients, who have a disease of their nervous system, have reported that this disease got worse. You should tell your doctor if you have a disease of your nervous system. Seizures and multiple sclerosis are examples of nervous system diseases. While in this study, if you are diagnosed with a nervous system disease discontinuation of infliximab should be discussed with your doctor.

Rarely, people who did not have a nervous system disease developed one after taking infliximab. Signs of nervous system disease include:

- changes in your vision
- seizures
- numbness or tingling in any part of your body
- weakness in your arms and/or legs

**Lung**
Interstitial lung disease is the name for diseases that inflame or scar the lungs and may cause long term complications. The inflammation and scarring may make it difficult to breathe and get enough oxygen in your blood.

Patients treated with infliximab have rarely developed interstitial lung disease and in some cases, the disease progressed quickly.

**Liver**
If you currently or at any time in the past have had any liver problems, including hepatitis B, you should tell your doctor. Treatment with TNF-blocking agents such as infliximab may result in a reactivation of the hepatitis B virus in people who have been known to carry this virus. Hepatitis B reactivation has been reported rarely in patients treated with infliximab. You will have a blood test to see if you have hepatitis B prior to treatment with infliximab.

Some patients develop abnormal liver blood tests, often without symptoms. If this happens, your doctor may stop your treatments for a period of time or permanently. In most cases the liver tests return to normal after stopping treatment.

There have been cases where people taking infliximab have developed serious liver problems, resulting in liver transplantation or death. Signs that you could be having a problem include:
Skin
Hair loss has commonly occurred in patients treated with infliximab.

Patients treated with infliximab have commonly developed a worsening of psoriasis or new onset psoriasis, including a type called pustular psoriasis. Symptoms may include dry, red skin with yellow blisters, often on the palms of the hands or soles of the feet, although it can occur elsewhere.

Rarely, a type of rash called vasculitis resulting from inflammation of blood vessels in the skin has occurred in patients treated with infliximab.

Stevens-Johnson syndrome and toxic epidermal necrolysis are two forms of a life-threatening skin condition that have been reported rarely in patients treated with infliximab. Another skin condition called erythema multiforme has been reported rarely in patients treated with infliximab.

A skin condition called linear IgA bullous dermatosis has been very rarely reported in patients treated with infliximab. Rarely, another skin condition called acute generalized exanthematous pustulosis has been reported rarely in patients treated with infliximab.

Rarely, lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes) have occurred in patients treated with TNF-blockers, including infliximab.

Blood Problems
With the use of TNF-blockers, including infliximab, sometimes the body fails to make enough white blood cells that help the body fight infection or fails to make enough red blood cells, resulting in anemia. In some instances, the number of white blood cells was severely decreased. In addition, sometimes the body fails to make enough platelets, the cells that help you stop bleeding. Some patients have died from this failure to produce blood cells. Your study doctor will monitor the results of tests done on your blood during the study. If you develop a fever that does not go away or infection, bruise or bleed very easily, look very pale or become tired easily, tell your study doctor right away.

- skin and/or eyes turning yellow
- dark brown urine
- right-sided stomach pain

- nausea
- vomiting
- loss of appetite
- fever
- extreme tiredness

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**Other Risks**

Rarely, people develop sarcoidosis, a multisystem immune disorder which is characterized by the formation of lesions (granulomas) in body organs that could affect the lungs, lymph nodes, skin, and other body systems.

A serious inflammation of the blood vessels called vasculitis may occur and in severe cases may result in permanent damage of the affected internal body organs. Vasculitis has been reported rarely in patients treated with infliximab.

Rarely, patients treated with infliximab have developed a pericardial effusion which is an abnormal amount of fluid between the heart and the sac around the heart. Hemophagocytic lymphohistiocytosis (HLH), a life-threatening condition, has been very rarely reported in patients treated with infliximab. This condition is identified by fever, enlarged liver or spleen, decreased number of blood cells, and neurological abnormalities.

There may be other discomforts or risks to you from this study that we do not yet know about.

Your study doctor and staff will ask you about any side effects you have at every visit. If you have any problems, you should let the doctor know right away.

**Risk of blood collection**

When we collect blood from you for this study, you may experience slight pain at the location of the blood draw. Some bleeding, bruising or discoloration of the skin is common at the site after a blood collection. In rare instances, infection at the site may occur. The study doctor will be able to treat any symptoms you may have.

To reduce risks associated with the blood draw, we will try to take the blood sample at the time the IV is placed so you do not have to have another needle stick.

**Risk of colonoscopy pinch biopsy**

If you agree to additional pinch biopsy samples for research, obtaining the additional intestinal biopsies may not significantly increase the patient’s risk of perforation, bleeding, or infection associated with the colonoscopy. As the colonoscopy will be performed at the discretion of your regular doctor, all potential risks of the procedure, including risks of anesthesia will be discussed with you and separate consent documents will be obtained (separate from this research study).

**Risk of high doses of infliximab**

If you are in the intervention arm, you may receive doses that are higher than the FDA approved dose. These higher doses have been shown to be safe in uncontrolled studies (real world practice).
**Risk of loss of confidentiality**

Your privacy is of great concern to us. There is a minimal risk of loss of confidentiality and we have taken steps to minimize this risk which include removing all identifiable patient information from biospecimens collection tubes, providing a unique study ID number for each participant, using a secure, password protected electronic data collection database (Medidata Rave®) and secure web portal (RoadMAB™), and storing all study related paper materials in a locked cabinet.

**Pregnancy Risks**

The effect of infliximab on the ability to have children is unknown. However, we are not fully aware of the effects of the study drug on unborn babies, on human sperm, or pregnant or breastfeeding women. Pregnant women and women making breast milk to feed infants cannot participate in this study. Female patients (if they have had a first menses) must have a urine or blood test when beginning this study that shows they are not pregnant.

*It is very important that women taking part in this study do not become pregnant while taking part in this study. It is very important that men taking part in this study do not get a woman pregnant while participating in this study.*

During this study and for 6-months after the last dose of infliximab, women of childbearing potential and men must use proven birth control methods (such as avoiding sex, birth control pills or injections, or an intrauterine device). Your study doctor will discuss birth control methods with you.

If you are pregnant, or may become pregnant, treatment with the study drug may lead to new, previously unknown, side effects, and this may involve risks to you and your unborn baby. You will be withdrawn from the study.

If you think that you have become pregnant, have a confirmed pregnancy or may have fathered a child while taking part in the study, you must tell the study doctor immediately. The study doctor will follow your pregnancy to its outcome. You should also notify your childbirth doctor that the mother/father received infliximab.

Infliximab crosses the placenta. If you received infliximab while you were pregnant, your baby may be at a higher risk for getting an infection. It is important that you tell your baby’s doctor and other health care professionals that you have received treatment with a study drug before the baby receives any vaccine. A 12-month waiting period following birth is recommended before the administration of a live vaccine (like BCG and rotavirus) to a baby whose mother received infliximab while she was pregnant. Administration of BCG vaccine within 12 months after birth to the baby whose mother received infliximab while pregnant may result in infection in the newborn with severe complications, including death. For other types of vaccines, discuss with your doctor.
Severely decreased numbers of white blood cells have also been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fever or infections, contact your baby’s doctor immediately.

If you are a female study patient, you must agree to not donate eggs (ova, oocytes) during the study and for 6 months after your last dose of study drug.

If you are a male study patient, you must not donate sperm while you are in the study and for 6 months after your last dose of study drug.

If you are a male study patient, and you father a child during your participation in this study, the study doctor will ask for your partner’s permission to stay in contact with her throughout the length of the pregnancy.

There may be other risks that we do not know about yet.

**Privacy:**

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete privacy. Organizations that may inspect and copy your information include the IRB, the Medical Monitor, your doctor, the Food and Drug Administration, National Institutes of Health (NIH), Janssen Scientific Affairs, LLC, and other representatives of this organization.

As approved by the CCHMC Institutional Review Board, de-identified samples will be stored in the Minar Laboratory. These samples could be used to research the causes of Crohn’s disease, its complications and other conditions for which individuals with Crohn’s disease are at increased risk, and to improve treatment. The Minar laboratory personnel will also be provided with a code-link that will link the biological specimens to each participant, maintaining the blinding.

Samples and/or data collected for or generated from this study could be shared and used for future research. Samples and /or data may be shared with other collaborators at Cincinnati Children’s and possibly with outside collaborators, who may be at another institution or for-profit company.

If information that could identify you is removed from your information or samples collected during this research, that information or those samples could be stored and used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

All future researchers will be given the least amount of information needed to meet the goals of their research project. Researchers that use these samples and information must agree to never try to re-identify a participant from a coded dataset. Researchers will only be allowed to use the provided samples and information for approved research purposes. Any researchers planning to do research with information that may identify you will need to have extra review and approval by the Cincinnati Children’s Institutional
Review Board (IRB). An IRB is a group of scientists and non-scientists who look at research projects like these and make sure research participants’ rights and welfare are protected.

The sponsor (Cincinnati Children's), monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Federal Certificate of Confidentiality:
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

**If injured while in the study:**
If you believe that you have been injured as a result of this research, you should contact [Site PI Name] as soon as possible to discuss the concerns. Treatment for injuries is available at [Site Name]. If you go to the Emergency Room or to another hospital or doctor, it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.
[Site Name] follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

**Return of results:**
Most tests done on samples or images obtained in research studies are only for research and have no clear meaning for healthcare. At certain time points, you and your treating physician will be made aware of select results of your stool and blood testing and amount of infliximab in your blood and may contact you.

**AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH**

Sites may use their own HIPAA language OR use the CCHMC language below

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your “protected health information” (called PHI for short).

**What protected health information will be used and shared during this study?**

[Site Name] will need to use and share your PHI as part of this study. This PHI will come from:

- Your [Site Name] medical records
- Your research records

The types of information that will be used and shared from these records include:

- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- Physician reports and video/photo images of a previous recorded colonoscopy
Who will share, receive and/or use your protected health information in this study?

- Staff at [Site Name] and Cincinnati Children’s
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor (Cincinnati Children’s), Janssen Scientific Affairs, LLC and organizations that the sponsor may use to oversee or conduct the study.
- Government agencies who oversee this study, including the FDA and NIH
- The members of the Cincinnati Children’s Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?

People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?

You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?

Your permission will expire at the end of the study.

Will your other medical care be impacted?

By signing this document, you agree to participate in this research study and give permission to [Site Name] to use and share your PHI for the purpose of this research study. If you refuse to sign this document, you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.
While you/your child are participating in this research study you may not be able to access some of your/your child’s health information that is related to the study. Any request for this information can be fulfilled once the study is completed.

**SIGNATURES**
The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research, you will document your permission by signature below.

You will receive a copy of this signed document for your records.

**Optional procedure:**
Indicate if you **AGREE** or **DO NOT AGREE** to the following optional procedure:

<table>
<thead>
<tr>
<th>Initials:</th>
<th>Yes, I <strong>AGREE</strong> to the collection of extra gastrointestinal biopsies for research.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initials:</td>
<td>No, I <strong>DO NOT AGREE</strong> to the collection of extra gastrointestinal biopsies for research.</td>
</tr>
</tbody>
</table>

__________________________
Printed Name of Research Participant

__________________________
Signature of Research Participant
Indicating Consent  
Date

__________________________
Signature of Parent or Legally Authorized Representative*  
Date

* If signed by a legally authorized representative, a description of such representative’s authority must be provided

__________________________
Signature of Individual Obtaining Consent  
Date
### Supplementary Table 1: Specific Pharmacodynamic (PD) Treatment Failure Criteria and the Target Escalation Plan

<table>
<thead>
<tr>
<th>Specific PD Target</th>
<th>Timing by infusion (~week)</th>
<th>PCDAI/CDAI cut-points</th>
<th>(and/or) CRP cut-points</th>
<th>(and/or) fecal calprotectin cut-points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkpoint 2</td>
<td>Dose4 (~week 10-14)</td>
<td>delta PCDAI &lt; 12.5 or a PCDAI &gt; 30 (child) delta CDAI &lt; 70 (adult)</td>
<td>&lt; 50% change from baseline</td>
<td>&lt; 50% change from baseline</td>
</tr>
<tr>
<td>Checkpoint 3</td>
<td>Dose6 (~week 26)</td>
<td>PCDAI ≥ 10 CDAI ≥ 150</td>
<td>≥ 0.5 g/dL</td>
<td>&gt; 250 µg/g</td>
</tr>
<tr>
<td>PD Target Failure for any 2 consecutive infusions after (dose6)</td>
<td>PCDAI ≥ 30 CDAI ≥ 220</td>
<td>≥ 1 g/dL</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>PD Target Failure for any single infusion after dose 6</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 500 µg/g</td>
</tr>
</tbody>
</table>

| Target Escalation plan* | PD Failure1: New PK target = 10-15 µg/mL | PD Failure2: New PK target = 15-20 µg/mL (max) |

*The trough concentration is the primary target, therefore, pharmacodynamic targets are only instituted if the prior trough concentration was within the target. PCDAI, pediatric Crohn’s disease activity index; CDAI, Crohn’s disease activity index; CRP, c-reactive protein; PK, pharmacokinetic.
Supplementary Table 2. Criteria for Secondary Nonresponse and Study Withdrawal

<table>
<thead>
<tr>
<th>Secondary Nonresponse (may remain in the trial)</th>
<th>Remaining on prednisone/prednisolone or oral budesonide for &gt;14 weeks after week 20 (corticosteroid restarts) or remaining on prednisone/prednisolone or oral budesonide after week 44</th>
</tr>
</thead>
</table>
| Secondary Nonresponse (meet study withdrawal criteria) | Subjects in the conventional care arm receiving >10 mg/kg infliximab and/or <25 days apart between infusions during maintenance.  
Subjects in the precision care arm receiving >12.5 mg/kg infliximab during induction (first 3 doses)  
Subjects in the precision care arm receiving >15 mg/kg infliximab and/or <25 days apart between infusions during maintenance.  
Subjects who have a Crohn’s disease-related surgery  
Subjects who develop an intra-abdominal abscess or inflammatory mass  
Subjects diagnosed with a bacterial infection requiring intravenous antibiotics or hospitalization (related to the infection)  
Subjects who discontinuation of infliximab before week 42 (either initiated by the subject or treating physician)  
Any plan to start another biologic (anti-integrin, anti-cytokine), small molecule (any JAK inhibitor or sphingosine-1-phosphate inhibitor) or 6-mercaptopurine (including Imuran or azathioprine) during the trial  
Anaphylaxis (hypersensitivity reaction) during/after an infusion that is deemed by the provider, medical monitor or principal investigator to be unsafe to attempt a subsequent future infusion |

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**Supplementary Figure 1:** The REMODEL-CD Clinical Trial Overview. The trial includes two arms, the precision care (interventional) and conventional care (control). The conventional care arm will receive starting doses of 5-7.5 mg/kg (based on pre-treatment serum albumin) and one proactive therapeutic drug monitoring (TDM) at dose4. The starting dose in the precision care arm will vary between 5-12.5 mg/kg and is based on predicted (baseline) infliximab clearance and a target trough concentration (cTrough) of 18-24 μg/mL at dose3. Following induction, two additional Checkpoints will be assessed for Pharmacokinetic (PK) and Pharmacodynamic (PD) targets. Infliximab optimization during maintenance is dependent on whether the PK, PD or both PK/PD targets have been met. As noted, the PK target is the first priority before assessing the PD targets and escalating the target concentration to the next tier. ESR, erythrocyte sedimentation rate; nCD64, neutrophil CD64; PCDAI, pediatric Crohn’s disease activity index; CDAI, Crohn’s disease activity index; CRP, c-reactive protein; fCal, fecal calprotectin; MIPD, model-informed precision dosing.