BMJ Open

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 ,[1,2] Ruben J Colman,[3] Nanhua Zhang,[4] Tomoyuki Mizuno,[2,5] Alexander A Vinks[2,5]

To cite: Minar PP, Colman RJ, Zhang N, *et al*. 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. *BMJ Open* 2024;**14**:e077193. doi:10.1136/bmjopen-2023-077193

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-077193).

Received 27 June 2023
Accepted 04 March 2024

For numbered affiliations see end of article.

Correspondence to
Phillip Paul Minar;
phillip.minar@cchmc.org

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 clinical 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).

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.

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.

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.[1–3] In real-world practice, the probability of remaining on infliximab for 5 years was shown to be 60%.[4 5]

In children, the use of labelled (standard, 5 mg/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.[6] 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 (5–10 µg/mL) for luminal CD.[2 7 8]

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).[9–12] 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.[6 13] 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.[2] 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.[2] 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.[2 14] 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.[11 13 15] 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

Table 1 REMODEL-CD eligibility criteria

Inclusion criteria	► Written informed consent from the patient (≥18 years old) or from parent/legal guardian if patient is <18 years old ► Written informed assent from patient when age appropriate ► Diagnosis of Crohn's disease within the last 90 days (luminal-only or luminal with a perianal fistula or abscess treated with antibiotics for at least 7 days) ► ≥6 years to ≤22 years of age, anti-TNF naïve and starting infliximab ► Clinical activity and luminal inflammation, defined by *both* (1) and (2) ► (1) PCDAI>10 (<18 years old) or CDAI>150 (≥18 years old) in last 60 days before the decision to start infliximab ► (2) SES-CD>6 or SES-CD>3 for isolated ileal disease (or a report of large intestinal ulcerations) within the last 60 days or a faecal calprotectin>250 µg/g within last 75 days prior to screening ► C-reactive protein>1.0 mg/dL in last 30 days and/or faecal calprotectin>250 µg/g within last 75 days prior to screening ► Negative TB (tuberculosis) interferon-gamma release test *and* a negative urine pregnancy test for female patients (if menstruation has started)
Exclusion criteria	► Diagnosis of ulcerative colitis or inflammatory bowel disease-unspecified ► Prior use of anti-TNF therapy (*infliximab, adalimumab, certolizumab pegol or golimumab*) ► Internal (abdominal/pelvic) penetrating fistula(e) in last 180 days ► Intra-abdominal abscess/phlegmon/inflammatory mass in the last 180 days ► Active perianal abscess (receiving oral antibiotics for <7 days) ► Intestinal stricture (luminal narrowing with prestenotic dilation>3 cm) and surgery planned in next 90 days ► Have tested positive for Clostridium difficile toxin (stool assay) or other intestinal pathogens within 14 days of screening unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen ► Current hospitalisation for complications of severe Crohn's disease ► Planned use of methotrexate or 6-mercaptopurine (azathioprine) during the induction (first 3 doses of infliximab) phase ► Current ileostomy, colostomy, ileoanal pouch and/or previous extensive small bowel resection (>35 cm) or any Crohn's disease surgery planned within the next 90 days ► History of autoimmune hepatitis, primary sclerosing cholangitis, thyroiditis or juvenile idiopathic arthritis ► Treatment with another investigational drug in last 4 weeks ► History of malignancy (including lymphoma or leukaemia) ► Currently receiving treatment for histoplasmosis ► History of TB, HIV, an immunodeficiency syndrome, a central nervous system demyelinating disease, history of heart failure or receiving intravenous antibiotics in last 14 days for any infection ► Currently pregnant, breast feeding or plans to become pregnant in the next 1 year ► Inability or failure to provide informed assent/consent ► Any developmental disabilities that would impede providing assent/consent

CD, Crohn's disease ; CDAI, CD activity index; PCDAI, paediatric CD activity index; SES, simplified endoscopic score; TNF, tumour necrosis factor.

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.[3 13] 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.[16 17] 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.[18] Key secondary endpoints (table 2) will also include assessments of immunogenicity (ATI), patient-reported outcomes (PRO), quality of life assessments[19–21] and growth restoration in Tanner I–III children consistent with other key STRIDE-II outcome measures.[18]

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

Name of outcome	Specific measure to be used	Time point(s)
Rate of steroid-free clinical remission	PCDAI<10 (child) or CDAI<150 (adult) and off prednisone/budesonide for ≥4 weeks	Weeks 14 and 52
Rate of clinical response	Decrease from baseline PCDAI of at least 12.5 points and total PCDAI<30 or a total PCDAI<10 (child)[1] or a reduction of CDAI>70 from baseline or CDAI<150 (adult)[31]	Weeks 14 and 52
Rate of primary clinical non-response	On prednisone>16 consecutive weeks from start of infliximab or a PCDAI>30 or CDAI>220 for first four infusions	Week 16
Rate of primary biologic non-response	Failure to improve baseline faecal calprotectin by >100 µg/g (limited to patients with a baseline faecal calprotectin>250 µg/g) or failure to improve baseline c-reactive protein≥0.5 mg/dL (limited to patients with a baseline c-reactive protein>1.0 mg/dL)	Week 16
Rate of sustained steroid-free clinical remission	PCDAI<10 (child) or CDAI<150 (adult) at dose 5 to week 52 and off prednisone/budesonide from weeks 22–52	Weeks 22–52
Rate of steroid-free clinical remission—biomarker composite	PCDAI<10 (child) or CDAI<150 (adult), off prednisone/budesonide for ≥4 weeks, CRP≤0.5 mg/dL and faecal calprotectin≤250 µg/g[13]	Weeks 14 and 52
Rate of endoscopic healing	SES-CD≤2[23]	Week 52
Rate of complete endoscopic healing	SES-CD=0	Week 52
Rate of endoscopic remission	SES-CD<4	Week 52
Rate of mucosal healing	SES-CD≤2 and Ileal Global Histologic Activity Score (GHAS)/Colon Global Histologic Activity Score (CGHAS)≤2	Week 52
PK model bias	Model predicted vs actual infliximab concentration. Bias: mean predictive error (MPE)	Weeks 0–52
PK model precision	Model predicted vs actual infliximab concentration. Precision: root mean squared error (RMSE)	Weeks 0–52
Rate of IBD-related event—fistula	Occurrence of fistula	Weeks 0–52
Rate of IBD-related hospitalisation	Occurrence of Crohn's disease-related hospitalisation	Weeks 0–52
Rate of IBD-related surgery	Occurrence of Crohn's disease-related surgery	Weeks 0–52
Rate of IBD-related intestinal stricture	Occurrence of Crohn's disease-related intestinal stricture	Weeks 0–52
Rate of IBD related—starting corticosteroids	Occurrence of patients starting a corticosteroid after week 20	Weeks 0–52
Rate of IBD-related antibodies to infliximab	Occurrence of antibodies to infliximab defined as >200 ng/mL	Weeks 0–52
Rate of growth restoration—weight change	In Tanner stage I–III patients: change from baseline weight (kg) by gender and age group[18]	Weeks 14–52
Rate of growth restoration—height velocity	In Tanner stage I–III patients: change in height velocity (z-score) by gender[18]	Weeks 14–52
PK of infliximab in paediatric patients	Measured infliximab clearance at baseline and at week 52	Weeks 0–52
Correlation between infliximab induction exposure and endoscopic remission	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.	Exposure: weeks 0–14 Efficacy: week 52
Correlation between infliximab induction exposure and deep remission	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<10 (child) or CDAI<150 (adult), off prednisone/budesonide for >8 weeks and a SES-CD≤2.	Exposure: weeks 0–14 Efficacy: week 52
Rate of PRO2 response	>50% improvement in total score from baseline[18]	Weeks 6, 14, 26 and 52
Rate of PRO2 remission	Stool frequency≤3.0 and abdominal pain≤1.0 (from baseline)[32]	Weeks 6, 14, 26 and 52

Continued

Table 2 Continued

Name of outcome	Specific measure to be used	Time point(s)
Quality of life and disability— IMAPCT-III score	Total IMPACT-III (child) score[19 20]	Week 52
Quality of life and disability—IBD disk score	Total IBD disk (without sexual function assessment) score	Week 52
Quality of life and disability—short IBD score	Total Short IBD Questionnaire (adult) score	Week 52
Process evaluation—usability of decision support tool	Total System Usability Scare score	Weeks 0–52
Rate of adverse events	Number of adverse events	Weeks 0–52
Rate of serious adverse events	Number of serious adverse events	Weeks 0–52

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.

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.[2 7 22] 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 (3). 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[2] 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).[7]

Table 3 Pharmacokinetic and pharmacodynamic targets by treatment arm

Conventional care arm	
Dose 3	Proactive therapeutic drug monitoring is not performed
Dose 4	Infliximab trough concentration 5–10 µg/mL
Dose 6	Proactive therapeutic drug monitoring is not performed
Precision care arm	
Dose 3 (checkpoint 1)	Infliximab trough concentration 18–24 µg/mL
Dose 4 (checkpoint 2)	
Pharmacokinetic	Infliximab trough concentration 5–10 µg/mL
Pharmacodynamic	1. Disease activity score+ Child: PCDAI decrease of at least 12.5 points from baseline and a total PCDAI<30 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
Dose 6 (checkpoint 3)	
Pharmacokinetic	Infliximab trough concentration 5–15 µg/mL (varies from 5 to 10 or 10–15 µg/mL depending on whether target 2 trough concentration was achieved)
Pharmacodynamic	1. Disease activity score+ Child: PCDAI<10 Adult: CDAI<150 2. CRP≤0.5 mg/dL (or CRP≤5 g/dL)+ 3. 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

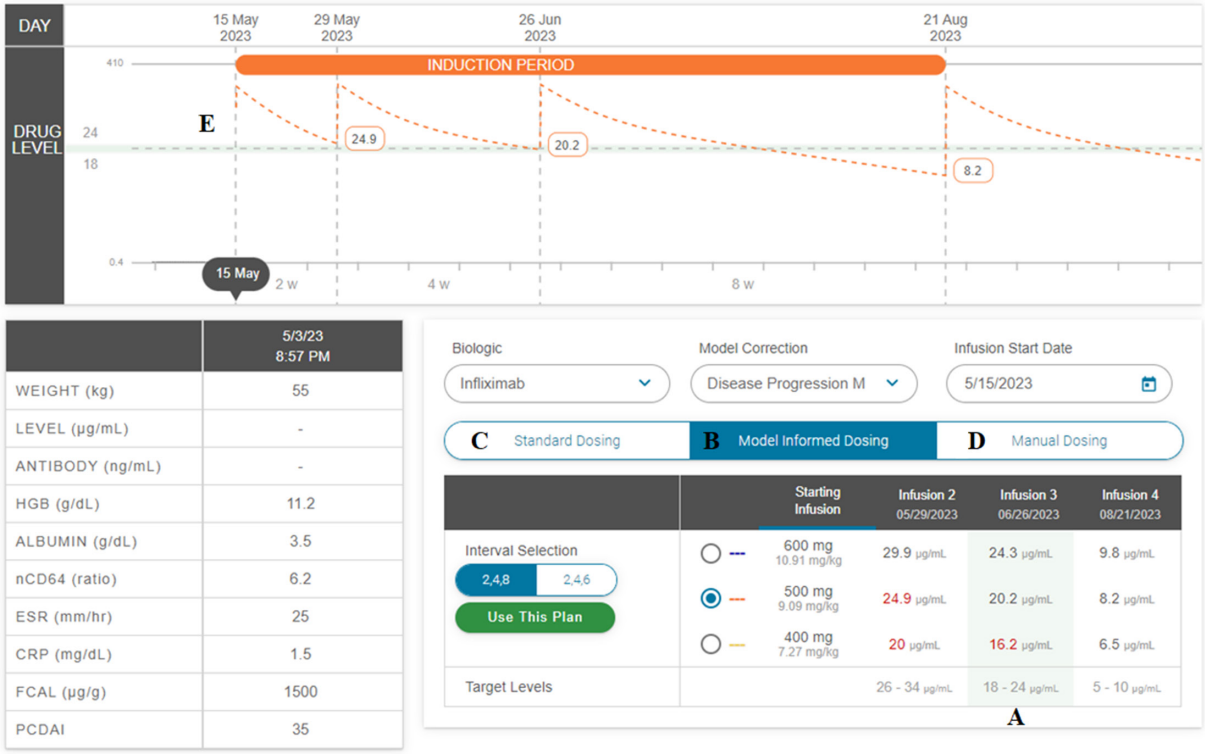

Figure 1 RoadMAB precision dosing platform. The RoadMAB New Start Wizard will launch prior to the first dose. Pretreatment biomarkers, including weight, albumin, erythrocyte sedimentation rate and neutrophil CD64, are manually entered into the table prior to launching the platform. The Wizard uses dynamic disease progression modelling along with the population pharmacokinetic model to simulate a dosing regimen to achieve the (A) dose 3 (week 6) target concentration of 18–24 µg/mL. The default tab is (B) model-informed dosing, however, the user can also toggle through (C) standard dosing and (D) manual dosing to inform the dosing decision. (E) The predicted concentration over time curve is shown and based on the selected starting dose.

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.[23] 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.[13 24] 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%,[1] 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, Rady 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.[25 26] 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[9 11] and PD control in adult CD[13] 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.[2 6 11] 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).[11 13 15] 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).[11] 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.[11] The PRECISION trial randomised adults with IBD receiving maintenance infliximab to model-informed dosing or standard of care dosing.[15] 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.[15]

There are a variety of reasons as to why the prior proactive TDM clinical trials in adults with IBD (TAXIT,[27] TAILORIX[24] or SERENE-CD[28]) 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.[15 29 30] 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
[1]Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[2]Department of Pediatrics, University of Cincinnati School of Medicine, Cincinnati, Ohio, USA
[3]Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA
[4]Division of Biostatistics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[5]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Contributors Study concept and design: PPM and AAV; initial draft and revising manuscript: PPM, RJC, NZ, TM and AAV; literature review: RJC, NZ and TM; developed both the sample size calculation and statistical analysis plan; NZ, TM and PPM; study protocol review and revision: PPM, NZ, TM and AAV. 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 AAV 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.

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

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