BMJ Open  Prospective randomised controlled trial of adults with perianal fistulising Crohn’s disease and optimised therapeutic infliximab levels: PROACTIVE trial study protocol

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ABSTRACT

Introduction Perianal fistulising Crohn’s disease (pFCD) can be somewhat treatment refractory. Higher infliximab trough levels (TLIs) may improve fistula healing rates; however, it remains unclear whether escalating infliximab therapy to meet higher TLIs targets using proactive, or routine, therapeutic drug monitoring (TDM) improves outcomes. This randomised controlled trial aimed to assess whether infliximab therapy targeting higher TLIs guided by proactive TDM improves outcomes compared with standard therapy.

Methods and analysis Patients with active pFCD will be randomised 1:1 to either the proactive TDM arm or standard dosing arm and followed up for 54 weeks. Patients in the proactive TDM arm will have infliximab dosing optimised to target higher TLIs. The targets will be TLI ≥ 25 µg/mL at week 2, ≥ 20 µg/mL at week 6 and ≥ 10 µg/mL during maintenance therapy. The primary objective will be fistula healing at week 32. Secondary objectives will include fistula healing, fistula closure, radiological fistula healing, patient-reported outcomes and economic costs up to 54 weeks. Patients in the standard dosing arm will receive conventional infliximab dosing not guided by TLIs (5 mg/kg at weeks 0, 2 and 6, and 5 mg/kg 8 weekly thereafter). Patients aged 18–80 years with pFCD with single or multiple externally draining complex perianal fistulas who are relatively new to infliximab treatment will be included. Patients with diverting ileostomies or colostomies and pregnant or breast feeding will be excluded. Fifty-eight patients per arm will be required to detect a 25% difference in the primary outcome measure, with 138 patients needed to account for an estimated 6.1% primary non-response rate and 10% dropout rate.

Ethics and dissemination Results will be presented in peer-reviewed journals and international conferences. Ethics approval has been granted by the South Western Sydney Local Health District Human Research Ethics Committee in Australia.

Strengths and limitations of this study

- This is an investigator-initiated, multicentre, prospective, randomised controlled trial assessing proactive (routine) therapeutic drug monitoring in perianal fistulising Crohn’s disease.
- This is a single blinded study, whereby gastroenterologists evaluating clinical outcomes and radiologists evaluating radiological outcomes will be blinded to study randomisation.
- An advantage of this study is that it includes radiological healing as a secondary outcome, addressing the inherent subjectivity of physical examination for determining clinical outcomes, with all imaging reviewed by centralised radiologists to minimise the risk of interobserver variability.
- Given the nature of the infliximab infusions, it was deemed practically infeasible and cost prohibitive to have sham infusions and thus patients will not be blinded to treatment randomisation. Patients will be instructed not to disclose treatment to reviewing gastroenterologists evaluating clinical outcomes.
- The study’s primary outcome, clinical fistula healing at 32 weeks, will be powered for a difference of 25% or greater.

INTRODUCTION

Perianal fistulising Crohn’s disease (pFCD) is a debilitating phenotype, causing faecal incontinence, perianal pain and sepsis. It is associated with significant morbidity and
increased quality of life, negatively impacting physical, emotional, sexual, and social well-being, and overall productivity. Despite its significant morbidity, there remains a striking paucity of data regarding optimal treatment of pCd, with patients achieving poorer therapeutic outcomes compared with luminal Crohn’s disease.

Tumour necrosis factor-α (TNF) is thought to play a key role in fistula formation by inducing epithelial to mesenchymal transition in intestinal epithelial cells. Anti-TNF agents, specifically infliximab, represent the most effective medical therapy for pCd. While infliximab has been shown to induce and maintain fistula healing, up to 60% of patients lose response within 1 year. This may result from subtherapeutic dosing, with growing evidence that higher infliximab trough levels (TLIs) during induction and maintenance therapy are associated with improved fistula healing and closure.

The advent of quantitative assays for therapeutic drug monitoring (TDM) permits individualisation of infliximab dosing. There is good evidence that reactive TDM, or measuring levels in patients failing treatment, improves outcomes and reduces costs. Proactive TDM is performed in responding patients to optimise therapy and potentially prevent future loss-of-response; however, it is unclear whether proactive TDM improves outcomes. Studies assessing proactive TDM in luminal Crohn’s disease have shown mixed results, although this is possibly due to design issues. The Trough Concentration Adapted Infliximab Treatment (TAXIT) study failed to show a difference in the proportion of patients in clinical remission after 1 year between the proactive TDM and standard care arms, but it did show lower rates of relapse with superior cost-effectiveness in the proactive TDM arm. It is worth noting that all patients had ‘pre-optimised’ dosing, perhaps making a difference between arms during the intervention period less likely. A randomised controlled trial investigating tailored treatment with infliximab for luminal Crohn’s disease (TAILORX) was unable to show a difference in steroid-free remission or mucosal healing between the proactive TDM and standard care arms. However, these results may have been confounded by similar thresholds for and high rates of adjusting infliximab doses across all study arms. The Paediatric Crohn’s Disease Adalimumab Level-based Optimisation Treatment (PAILOT) Trial showed that proactive TDM of adalimumab, another anti-TNF agent, resulted in higher rates of corticosteroid-free clinical remission compared with reactive TDM. Notably, all previous studies on proactive TDM have been in luminal disease and there are no prospective studies evaluating proactive TDM in pCd.

Previous clinical trials involving pCd have measured success using clinical outcomes alone, a subjective measure that may fail to evaluate deeper states of fistula healing. There are also very few studies that assess patient-reported outcome measures and economic burden of pCd. Our study addresses these limitations by including patient-reported outcome measures to provide a more holistic picture as well as MRI, which provides an objective and sensitive means to evaluate deeper states of perianal fistula healing and remission.

This study, a Prospective Randomised Controlled Trial of Adults with Perianal Fistulising Crohn’s Disease and Optimised Therapeutic Infliximab Levels (PROACTIVE) Trial aims to determine whether infliximab therapy guided by proactive TDM with higher target TLIs improves clinical, radiological and patient-reported outcomes and reduces economic costs compared with standard infliximab therapy in pCd. If proactive TDM proves to be beneficial, our results will allow clinicians to optimise infliximab dosage to improve healing rates, symptoms and quality of life. Given the peak incidence of pCd in early adulthood, this will minimise disease burden and will reduce the cumulative burden on patients and the healthcare system.

AIMS AND OBJECTIVES
Primary objective
The primary objective will be to determine the proportion of patients with pCd who achieve fistula healing at week 32 with infliximab therapy targeting a higher TLI guided by proactive TDM compared with patients receiving standard therapy without dose modification. Fistula healing will be defined as cessation in fistula drainage despite gentle finger compression, as determined by physical examination on two consecutive visits.

Secondary objectives
- To determine the proportion of patients with pCd who achieve fistula closure at weeks 32 and 54 in the proactive TDM arm compared with the standard care arm; defined as closure of all external fistula openings on physical examination at two consecutive study visits.
- To determine the proportion of patients with pCd who achieve fistula healing at week 54 in the proactive TDM arm compared with the standard care arm. The Paediatric Crohn’s Disease Adalimumab Level-based Optimisation Treatment (PAILOT) Trial showed that proactive TDM of adalimumab, another anti-TNF agent, resulted in higher rates of corticosteroid-free clinical remission compared with reactive TDM. Notably, all previous studies on proactive TDM have been in luminal disease and there are no prospective studies evaluating proactive TDM in pCd.
- To determine the proportion of patients with pCd who achieve clinical response at weeks 32 and 54 in the proactive TDM arm compared with the standard care arm; defined as reduction of 50% or more from baseline in the number of draining fistulas observed on physical examination at two consecutive study visits.
- To determine the proportion of patients with pCd who achieve radiological fistula healing at weeks 32 and 54 in the proactive TDM arm compared with the standard care arm; evaluated on pelvic MRI and defined as a van Assche Index score of 0 (when scoring the ‘number of fistula tracts’, assigning 0 point to each fistula track with hypointensity on T2-weighted fat suppression images) or Magnetic Resonance Novel Index for Fistula Imaging in Crohn’s Disease (MAGNIFI-CD) score of 0.
- To determine the proportion of patients with pCd who achieve radiological fistula response at weeks 32 and 54 in the proactive TDM arm compared with the standard care arm; defined as closure of all external fistula openings on physical examination at two consecutive study visits.
and patient-outcomes

Secondary outcomes

The primary outcome will be fistula healing at week 32. Economic costs will be assessed at 54 weeks. Time to treatment failure will be evaluated directly and indirectly. Time to treatment failure will be assessed at 54 weeks.

OUTCOMES

Primary outcomes

The primary outcome will be fistula healing at week 32.

Secondary outcomes

The secondary outcomes will include clinical, radiological and patient-reported outcomes, time to treatment failure and economic costs. Clinical outcomes will include fistula healing at week 54, fistula closure at weeks 32 and 54, and objective fistula response at weeks 32 and 54. Radiological fistula healing will be assessed at weeks 32 and 54. Patient-reported outcomes will be measured at baseline, week 32 and week 54. Economic cost-effectiveness will be evaluated directly and indirectly. Time to treatment failure will be assessed at 54 weeks.

METHODS AND ANALYSIS

Study design

The study will be an investigator-initiated prospective multicentre randomised controlled trial. The study will be conducted at 22 tertiary hospitals across Australia, each with a dedicated Inflammatory Bowel Disease (IBD) Service. It is anticipated to run between May 2021 and May 2025.

Study population

Adults aged 18–80 years with pfCD with a single or multiple externally draining complex perianal fistulas will be included. Patients will need to be eligible for induction infliximab therapy as per the Australian Pharmaceutical Benefits Scheme criteria. This incorporates patients with confirmed pfCD treated by a gastroenterologist or consultant physician in internal or general medicine specialising in gastroenterology; with Crohn’s disease confirmed by standard clinical, endoscopic or radiological assessment; and who have an externally draining complex perianal fistula. Patients must not have had exposure to infliximab within 12 months of study inclusion; patients with previous exposure that occurred over 12 months prior will be eligible provided they were infliximab responsive at the time of cessation or non-responsive with below target maintenance TLIs (< 10 µg/mL) and low anti-infliximab antibody titres if present (≤ 60 ng/mL, using Ridascreen assay). Patients previously treated with another anti-TNF agent, adalimumab, will be eligible for inclusion if non-responsive with subtherapeutic trough adalimumab levels (< 5 µg/mL), with or without detectable anti-adalimumab antibody titres. Both patients with pfCD and concurrent luminal disease and patients with isolated pfCD without concurrent luminal disease will be eligible for inclusion. Isolated pfCD will be defined as perianal fistulas with typical histological features of Crohn’s disease. Patients with setons in situ will be eligible for inclusion. Allowed concurrent or previously trialled pharmacological therapies include 5-aminosalicylic acids, thiopurines, methotrexate and corticosteroids. Patients who have previously trialled non-anti-TNF biologic or small molecule agents will be eligible for inclusion. Only patients with controlled perianal sepsis will be included.

Exclusion criteria will include current diverting ileostomies or colostomies, patients planned to undergo faecal stream diversion surgery in the next 3 months, rectovaginal fistulas, rectovesical fistulas, uncontrolled perianal sepsis as determined by colorectal surgeon review, past failure to infliximab therapy with above target maintenance TLIs (≥ 10 µg/mL), conditions interfering with treatment adherence, pregnancy or planning a pregnancy in the next 54 weeks, breast feeding and contraception; anti-TNF agents. Participants who cannot read or understand the Patient Information and Consent Form will not be eligible and may not be enrolled in the study by a guardian or any other individual.

All patients will be reviewed by a gastroenterologist and colorectal surgeon to ensure appropriateness for study inclusion. The study will be based on gastroenterologist and colorectal surgeon review and discussed at an IBD multidisciplinary team (MDT) meeting in the event of uncertainty.

Randomisation

Recruited patients will be randomised 1:1 to either the proactive TDM arm or standard care arm by the research coordinator at the primary site. Randomisation will be performed using the randomisation module on the secured Research Electronic Data Capture (REDCap) platform. Block randomisation will be used with

32 and 54 in the proactive TDM arm compared with the standard care arm; evaluated on pelvic MRI and defined as reduction in van Assche Index score of > 318 or MAGNIFI-CD score of > 4.17

To determine patient-reported outcomes in the proactive TDM arm compared with the standard care arm at baseline, week 32 and week 54. Validated health-related quality of life and sexual dysfunction measuring tools will be used, including the Inflammatory Bowel Disease Questionnaire-32,19 Inflammatory Bowel Disease-Specific Female Sexual Dysfunction Scale and Inflammatory Bowel Disease-Specific Male Sexual Dysfunction Scale.19–22

To determine the time to treatment failure of patients with pfCD in the proactive TDM arm compared with the standard care arm; defined as recurrence of a previously healed draining perianal fistula, development of a new perianal fistula, development of a perianal abscess requiring surgical incision and drainage, or discontinuation of the study due to a perceived lack of efficacy or loss to follow-up.9

To determine the cost-effectiveness in the proactive TDM arm compared with the standard care arm, using the validated measuring tools European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L)23 and Work Productivity and Activity Impairment24 to estimate indirect-economic costs.
randomisation stratified by prior anti-TNF exposure and smoking status.

Blinding
All assessments for clinical fistula outcomes will be made by a reviewing gastroenterologist blinded to study randomisation and TLIs. All other aspects of the trial will be conducted by a different gastroenterologist who is not involved in assessing clinical outcomes. Blinding success will be evaluated by a questionnaire to the reviewing gastroenterologists asking whether they believe the patient has been randomised to the proactive TDM arm or standard care arm. This will be performed at week 0 and at week 30 prior to assessment for the primary endpoint. All pelvic MRI for assessment of radiological fistula healing will be centrally read by two specialised gastrointestinal radiologists blinded to study randomisation and TLIs. Patients will not be blinded to study randomisation; however, patients will be directed not to disclose randomisation to reviewing gastroenterologists. Patients who experience treatment failure or exit the study early will have their TLIs unblinded and will return to the care of their treating gastroenterologist.

Baseline assessment
All patients will have a baseline evaluation of fistula anatomy and evaluation of disease activity including presence of extraintestinal manifestations. This will involve a colorectal surgeon review and pelvic MRI, endoscopy to assess concurrent luminal disease and anal strictures, and if indicated, examination under anaesthesia (EUA) and seton insertion. Temporal requirements for baseline evaluation include pelvic MRI up to 4 weeks prior to or 7 days after study inclusion; EUA and sigmoidoscopy up to 12 weeks prior to inclusion; and colonoscopy up to 6 months prior to inclusion or 4 weeks after study inclusion.

Interventions
The study will consist of two phases relating to infliximab therapy: induction (weeks 0–12) and maintenance (weeks 14–54). Blood will be collected for TLIs and anti-infliximab antibody titres immediately prior to each infliximab infusion. Each infliximab dose will be rounded up to the nearest 100 mg vial.

Induction phase: standard care arm
In the standard care arm, patients will receive infliximab 5 mg/kg at weeks 0, 2 and 6; no additional doses of infliximab will be received (figure 1).

Induction phase: proactive TDM arm
Patients in the proactive TDM arm will receive infliximab 5 mg/kg at weeks 0 and 2. Thereafter, infliximab doses will be modified based on the TLI at the preceding infusion, with dose modification if they have TLIs below the target levels. These targets were chosen based on previous literature and consensus expert opinion.10

If patients have TLIs < 25 µg/mL at week 2, they will receive infliximab 10 mg/kg at week 6. If patients have TLIs ≥ 25 µg/mL at week 2, they will receive infliximab 5 mg/kg at week 6. If patients have TLIs < 20 µg/mL at week 6, they will receive an additional infliximab 5 mg/kg dose at week 10. Patients who have TLIs ≥ 20 µg/mL at week 6 will not receive an additional infliximab dose at week 10 (figure 1). Patients who have TLIs < 20 µg/mL at week 6 will be committed to dose escalation throughout maintenance therapy, as described below.

Transition from induction to maintenance phase
Primary response will be defined as a reduction of 50% or more in the number of draining fistulas from baseline or achieving a marked reduction in fistula drainage from baseline, with improved pain and induration at week 12.25 Only patients who achieve primary response at week 12 will transition to maintenance infliximab therapy, in accordance with current standard of care and Australian Pharmaceutical Benefits Scheme approved prescribing of infliximab. Patients with primary non-response at week 12 will be deemed as treatment failure and exit the study.

Maintenance phase: standard care arm
In the standard care arm, patients will receive infliximab 5 mg/kg every 8 weeks and no additional infliximab doses will be received (figure 2).

Maintenance phase: proactive TDM arm
Patients in the proactive TDM arm will have infliximab doses adjusted every treatment cycle based on the TLIs at the preceding infusion. The target TLI during maintenance will be ≥ 10 µg/mL.10 11

Patients in the proactive TDM arm with TLIs ≥ 20 µg/mL at week 6 will receive infliximab 5 mg/kg at week 14. They will begin infliximab maintenance therapy at 5 mg/kg every 8 weeks, if they have TLIs ≥ 10 µg/mL at week 14 (next infusion to occur at week 22) or 5 mg/kg every 6 weeks if they have TLIs < 10 µg/mL at week 14 (next infusion to occur at week 20) (figure 3).

Patients in the proactive TDM arm with TLIs < 20 µg/mL at week 6 will receive infliximab 5 mg/kg at week 14. They will begin infliximab maintenance therapy at 5 mg/kg every 6 weeks if they have TLIs ≥ 10 µg/mL at week 14 (next infusion to occur at week 20) or 5 mg/kg every 4 weeks if they have TLIs < 10 µg/mL at week 14 (next infusion to occur at week 18) (figure 4).

Thereafter, patients in the proactive TDM arm will have dose modification in a stepwise fashion based on the TLIs at the preceding infusion, with dose modification if TLI < 10 µg/mL. Patients receiving infliximab 5 mg/kg every 8 weeks with TLIs < 10 µg/mL will have future infliximab infusion intervals shortened to 5 mg/kg every 6 weeks. Patients receiving infliximab 5 mg/kg every 6 weeks with TLIs < 10 µg/mL will have future infliximab infusion intervals shortened to 5 mg/kg every 4 weeks. Patients receiving infliximab 5 mg/kg every 4 weeks with TLIs < 10 µg/mL will have a dose increase for future infliximab infusions to 10 mg/kg every 4 weeks (figure 4). As it takes three cycles to reach steady state after doubling a dose.
of infliximab, the subsequent TLI will be performed 12 weeks later. This represents the maximal number of dose adjustments. Patients whose TLIs remain < 10 µg/mL after the maximal dose adjustments will continue to receive 10 mg/kg infusions every 4 weeks and will continue in the arm to which they were randomised until week 54 or early exit due to treatment failure, and the outcomes will be analysed in a sensitivity analysis at week 54.

Treatment failure and exiting the study
In accordance with the Australian Pharmaceutical Benefits Scheme approved prescribing of infliximab, patients with primary non-response at week 12 will exit the study. Primary non-response will be defined as failure to achieve either a reduction of 50% or more from baseline in the number of draining fistulas or a marked reduction in fistula drainage from baseline, with improved pain and induration at week 12.

Patients who experience treatment failure at any point will exit the study, where treatment failure will be defined as recurrence of a previously healed draining perianal fistula, development of a new perianal fistula, development of a perianal abscess requiring surgical incision and drainage, or discontinuation of study due to a perceived lack of efficacy or loss to follow-up. Patients who exit the study early will return to the care of their usual gastroenterologist and will have their TLIs and randomisation unblinded. They will be assessed for clinical response, fistula healing and closure, and have blood tests, faecal calprotectin and a pelvic MRI completed. Their clinical progress and medication history will be followed up until they reach week 54 and data on any major adverse outcomes such as Crohn’s disease-related surgery, hospitalisation and persistence of infliximab use will be collated.
Concurrent medical management

All patients will receive 12 weeks of ciprofloxacin 500 mg orally two times per day from the first infliximab infusion. If not tolerated, metronidazole 400 mg two times per day will be given as an alternative. Patients on corticosteroids will undergo a mandatory dose taper after the first infliximab infusion to achieve corticosteroid cessation by week 14. Combination therapy with immunomodulators will be recommended at conventional dosing from enrolment and maintained throughout the trial, unless contraindicated. Approved immunomodulators include standardised dosing of oral or subcutaneous methotrexate ≥ 10 mg weekly and thiopurine (azathioprine, mercaptopurine or thioguanine) doses titrated to maintain active drug metabolites within therapeutic range; defined as 6-thioguanine nucleotides between 235 and 550 pmol/8×10^8 red blood cells. If a patient develops intolerance or adverse reactions to an immunomodulator, the dose will be reduced or the drug switched to an alternative immunomodulator where possible. If impossible, the immunomodulator will be ceased and the patient will remain in the trial.

Concurrent surgical management

Colorectal surgeon review and surgical interventions will be standardised across sites to minimise heterogeneity and confounding variables. All patients will be reviewed by a colorectal surgeon every 4 weeks to assess sustained sepsis control and adequate fistula drainage, occurring at baseline, weeks 4, 8 and 12 (table 1). For patients with setons in situ, appropriateness for removal of setons and feasibility for definitive surgical intervention will be determined at the week 12 review. This decision will be at the discretion of the colorectal surgeon involved and if unclear will be discussed at an IBD MDT meeting. If deemed appropriate, a repeat EUA and definitive surgical intervention will occur between weeks 12 and 14. If deemed inappropriate, there will be continued colorectal surgeon review every 4 weeks to re-evaluate appropriateness and feasibility until week 24. Patients in whom setons are unable to be removed at week 24 will be deemed to have a perceived lack of efficacy and will exit the trial. Refer to online supplemental appendix for details on surgical management.
Radiological assessment
All MRI will be centrally read by two radiologists with experience with perianal fistula MRI and a van Assche Index score and MAGNIFI-CD score will be calculated. All imaging with discrepant scores will be discussed between the radiologists to obtain a consensus score.

TIMELINE
Clinic visits will be performed at baseline, weeks 2, 6, 12, 22, 30, 32, 38, 46, 52 and 54, or on trial exit if treatment failure. Pathology, MRI, Crohn’s Disease Activity Index (CDAI) and patient-reported outcome measure questionnaires will be performed as outlined in Table 1. Blood will be collected for TLIs and anti-infliximab antibody titres immediately prior to each infliximab infusion and assessed centrally at Liverpool Hospital using a drug-sensitive ELISA, Grifols Promonitor. Anti-infliximab antibody titres will be completed if infliximab concentrations are < 2.0 µg/mL. Anti-infliximab antibodies titres will be performed using Ridascreen ELISA, with high antibodies defined as > 60 ng/mL and low antibodies ≤ 60 ng/mL.

All clinic visits, pathology (excluding TLIs and anti-infliximab antibody titres), MRI and questionnaires can occur within 7 days on either side of the exact date.

Patient and patient advocate involvement
The study team includes patients and a patient advocate from Crohn’s and Colitis Australia. They have been involved in addressing the paucity of patient-focused outcomes in clinical trials, specifically assisting with incorporation of patient-centred endpoints. They have been integral in

Figure 3  Proactive TDM maintenance phase: Patients with target induction TLIs. Patients in the proactive TDM arm with TLIs ≥ 20 µg/mL at week 6 will begin infliximab maintenance therapy at 5 mg/kg every 8 weeks. Thereafter, patients in the proactive TDM arm will have dose modification in a stepwise fashion if the TLI at the preceding infusion is < 10 µg/mL. Patients receiving infliximab 5 mg/kg every 8 weeks will have the following infliximab infusion interval shortened to 5 mg/kg every 6 weeks; patients receiving infliximab 5 mg/kg every 6 weeks will have the following infliximab infusion interval shortened to 5 mg/kg every 4 weeks; and patients receiving infliximab 5 mg/kg every 4 weeks will have an increase in dose to 10 mg/kg every 4 weeks with the next TLI taken 12 weeks later. This represents the maximal number of dose adjustments and patients will continue this dose until week 54.
identifying potential barriers to patient participation, particularly addressing logistical barriers including time demands. This influenced development of a schedule focused on minimising contact time by grouping reviews, testing and treatment where possible.

### Data collection and management

To maintain patient confidentiality and privacy, all data will be entered into REDCap, a secure browser-based, electronic data capture software accessible remotely by approved personnel.26 Data will be collected at each study by trained local research staff, who will be responsible for recording data on hard copy forms and entering it into the site-specific REDCap study site. A central data manager will oversee data entry and ensure timely data entry.

### Statistical analyses

#### Sample size

Fifty-eight patients per arm will be required to detect a difference of 25% in the proportions of patients meeting the primary outcome; assuming 50% of the standard care arm achieve the primary outcome compared with 75% in the proactive TDM arm, with a two-tailed comparison with an alpha of 0.05% and 80% power. The effect size is calculated based on consensus expert opinion and best available evidence limited to retrospective data with no prospective data published11–13; this study represents the first prospective trial of its kind. This sample size will also be sufficient with ≥ 80% power to determine differences between the two groups for the secondary outcomes. The sample size will be inflated to a total of 138 patients to

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Figure 4  Proactive TDM maintenance phase: Patients with below target induction TLIs. Patients in the proactive TDM arm with TLIs < 20 µg/mL at week 6 will be deemed to have a higher clearance of infliximab and will be given dose escalated infliximab maintenance therapy. They will receive infliximab 5 mg/kg at week 14 and then 5 mg/kg every 6 weeks if they have TLIs ≥ 10 µg/mL at week 14 or 5 mg/kg every 4 weeks if they have TLIs < 10 µg/mL at week 14. Thereafter, patients in the proactive TDM arm will have dose modification in a stepwise fashion if the TLI at the preceding infusion is < 10 µg/mL. Patients receiving infliximab 5 mg/kg every 6 weeks will have the following infliximab infusion interval shortened to 5 mg/kg every 4 weeks; and patients receiving infliximab 5 mg/kg every 4 weeks will have an increase in dose to 10 mg/kg every 4 weeks with the next TLI taken 12 weeks later. This represents the maximal number of dose adjustments and patients will continue this dose until week 54.

**IFX,** infliximab; **TDM,** therapeutic drug monitoring; **TLI,** infliximab trough level.
account for an estimated 6.1% failure to meet Australian Pharmaceutical Benefits Scheme criteria for maintenance infliximab therapy and 10% dropout rate during maintenance as based on previous clinical trials.

**Primary objective**

Data will be analysed according to both the intention-to-treat and the per-protocol analyses. Patients who terminate the study early for any reason will be regarded as treatment failures and included in the intention-to-treat analysis but excluded in per-protocol analysis. The primary analysis will assess the effect of the intervention on the clinical healing of perianal fistulas at week 32 by directly calculating relative risks and their 95% CI. Relative risks will be calculated using log binomial regression.

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**Table 1** Assessment schedule study visits, study pathology (excluding TLIs and ATIs) and study imaging can occur within 7 days either side of the exact date

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Induction phase</th>
<th>Maintenance phase</th>
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<tbody>
<tr>
<td></td>
<td>0  2  4  6  8 12</td>
<td>14 22 30 32 38 42 46 52 54*</td>
</tr>
<tr>
<td><strong>Study visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenterologist review</td>
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<td>X X X X X X</td>
</tr>
<tr>
<td>Perianal fistula examination by independent gastroenterologist</td>
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<td>X X X X</td>
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<tr>
<td>IFX infusions†</td>
<td>X X X</td>
<td>X X X X X X</td>
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<tr>
<td>CDAI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IBDQ, IBD-FSDS/MSDS, EQ-5D-5L and WPAI scores</td>
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<tr>
<td>Medication review</td>
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<tr>
<td>AE/SAE assessment</td>
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<td></td>
</tr>
<tr>
<td>Colorectal surgeon review</td>
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<td>X</td>
</tr>
<tr>
<td><strong>Study pathology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFX trough blood tests (TLI±ATI)†</td>
<td>X X X</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Routine blood tests (FBC, UEC, LFT, CRP)†</td>
<td>X X X</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Faecal calprotectin</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Thiopurine metabolites‡</td>
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<td>X X</td>
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<tr>
<td><strong>Study imaging</strong></td>
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<tr>
<td>Pelvic MRI§</td>
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<tr>
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<tr>
<td>Endoscopy**</td>
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</table>

Aside from TLIs and ATIs, visit times for examination, bloods and questionnaires will not change even if dose modification occurs. If patients exit the study early, gastroenterologist review including perianal fistula examination, medication review, blood tests, AE/SAE assessment, TLI±ATI, IBDQ, IBD-FSDS/IBD-MSDS, EQ-5D-5L and WPAI scores, pelvic MRI and faecal calprotectin will be performed at the time of study exit.

†TLI and ATI will be performed prior to each infliximab infusion, which may be more frequent for patients in the proactive TDM arm who have dose escalation. Routine blood tests (FBC, UEC, LFT, CRP) will be performed at baseline and then with infliximab trough blood tests thereafter.

‡Patients on thiopurines will have drug metabolites measured at baseline, weeks 14, 30 and 54; for patients requiring thiopurine dose modification to achieve safe therapeutic levels, drug metabolites will be checked more frequently at the discretion of the reviewing gastroenterologist.

§Baseline pelvic MRI can occur up to 4 weeks prior to or up to 7 days after study inclusion. If deemed appropriate by the reviewing colorectal surgeon, an additional pelvic MRI may be coordinated at week 12.

¶Baseline EUA, if deemed necessary, can occur up to 12 weeks prior to study inclusion. If deemed appropriate for definitive surgical intervention by the reviewing colorectal surgeon, a repeat EUA and definitive surgical intervention will be performed between weeks 12 and 14. If not appropriate, there will be ongoing colorectal review every 4 weeks to re-evaluate appropriateness and feasibility until week 24. If a patient is deemed to be inappropriate for seton removal at week 24, the patient deemed to have perceived lack of efficacy and will exit the trial.

** Baseline endoscopy to assess for proctitis and anal strictures can occur up to 12 weeks prior to study inclusion, at the time of EUA. Baseline complete colonoscopy can occur up to 6 months prior to study inclusion. If a colonoscopy has not occurred prior to inclusion, it will be performed within 4 weeks from the time of study inclusion.
AE, adverse event; ATI, anti-infliximab antibody titre; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; EQ-5D-5L, European Quality of Life Five Dimension Five Level Scale; EUA, examination under anaesthesia; FBC, full blood count; IBDQ, Inflammatory Bowel Disease-specific Female Sexual Dysfunction Scale; IBD-MSDS, Inflammatory Bowel Disease-specific Male Sexual Dysfunction Scale; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; LFT, liver function test; SAE, serious adverse event; TLI, infliximab trough level; UEC, urea and electrolytes; WPAI, Work Productivity and Activity Impairment.
Secondary objectives
For binary secondary outcomes, relative risks will be calculated as above. Continuous secondary outcomes will be analysed by means of analysis of variance if normally distributed and by means of non-parametric tests if distribution is not normal. Secondary outcomes including time-to-event will be analysed by survival analysis. Future modelling will be used to estimate indirect costs using productivity-adjusted life years.

Data monitoring
A Data Safety Monitoring Board will review trial progress, address adverse events and monitor the safety of participants. The Data Safety Monitoring Board members are senior consultants employed at the primary site who are not part of the study team, independent of sponsors and have no competing interests.

Adverse event monitoring
Adverse events are defined as any new or worsening unfavourable and unintended signs, symptoms, physical findings or diseases; whether or not believed to be infliximab related. Serious adverse events result in death, are life-threatening, require hospitalisation or cause significant disability or incapacity. All adverse events will be reported to the site lead investigator and serious adverse events immediately reported to the principal investigator, followed by written reports. Investigators will comply with applicable requirements related to reporting of unexpected serious adverse drug reactions to regulatory authorities.

Ethics and dissemination
This study has been approved by the South Western Sydney Local Health District Human Research Ethics Committee (2020/ETH00492). It is registered through the Australian New Zealand Clinical Trials Registry (ACTRN12621000028353). Results will be published in a peer-reviewed journal.

Contributors
The study design and concept were conceived by BG, MDG, SC, NSD, WN, A-JW, JLP, AG and YW. NVC provided expertise on adjustment of infliximab dosing, BD and RW provided expertise on surgical management. JR and TS provided imaging expertise. SC, NSD, A-JW, WN, JA, JB, WC and GR-S provided expertise on assessment and treatment of perianal Crohn’s disease. ALH provided expertise on quality-of-life assessment. DL provided expertise on cost analysis and assess economic impacts. CT provided expertise on testing of infliximab levels and anti-infliximab titres. WX provided statistical support. BG prepared the first draft of the manuscript. All authors provided edits and critiqued the manuscript for intellectual content.

Funding
The PROACTIVE study is an investigator-initiated study.

Competing interests
NVC reports grants and personal fees from Takeda, grants and personal fees from UCB, grants from R-Biopharm, personal fees from Celltrion, personal fees from Prometheus, outside the submitted work. JA reports lecture fees, grants, Boards, Consultancies for Abbott, AbbVie, Allergan, Anatara, AstraZeneca, Bayer, Celgene, Ferring, Gilead, Hospira, Immunicon, ImmunansT, Janssen, MSD, Nestle, Progenity, Pfizer, Shire, Takeda and Vifor, grants from the Royal Adelaide Hospital Research Fund, outside the submitted work. JB reports grants from AbbVie, personal fees from Pfizer, personal fees from BMS, grants and personal fees from Janssen, personal fees from Takeda, personal fees from Gilead, personal fees from Microba, grants and personal fees from Ferring, outside the submitted work. ALH has served as consultant, advisory board member or speaker for AbbVie, Arena, Atlantic, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda and serves on the Global Steering Committee for Genentech, outside the submitted work. DL reports consultancy fees from AbbVie, Asterias, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer and Sanofi, grants from AbbVie, Asterias, AstraZeneca, Bristol-Myers Squibb, CSL-Behring, Novartis, Pfizer, Sanofi and Shire, and travel expenses from AstraZeneca and Bayer; outside the submitted work. GR-S reports fees to his institute from Ferring Australia, grants and fees to his institute from Janssen, fees to his institute from Takeda, fees to his institute from Pfizer, fees to his institute from AbbVie, outside the submitted work. JR reports grants from AbbVie, personal fees from Takeda, personal fees from Gilead, grants from Genentech, personal fees from Alimentiv, personal fees from Janssen, during the conduct of the study. TS reports personal fees from Seimens Workshop, personal fees from Bayer, outside the submitted work. CT reports grants from Janssen, grants from Pfizer, grants from MSD, outside the submitted work; and is a director of laboratory that performs therapeutic drug monitoring for infliximab. A-JW reports grants and personal fees from Ferring, personal fees and non-financial support from AbbVie, personal fees from Janssen, personal fees and non-financial support from Takeda, outside the submitted work. WN received grants from Janssen and Pfizer, during the conduct of the study; grants and personal and speaker fees from AbbVie, Takeda, Grants from Ferring and Shire unrelated to the submitted work. NSD reports personal fees from AbbVie, personal fees from Pfizer, personal fees from BMS, personal fees from Janssen, outside the submitted work. SC reports grants from Janssen, grants from Pfizer, during the conduct of the study; grants and personal fees from AbbVie, educational support from Aspen/Orphan Australia; grants and personal fees from Ferring, personal fees from Gilead, grants and personal fees from Janssen, personal fees from Novartis, grants, personal fees and educational support from Pfizer, grants, personal fees and educational support from Shire/Takeda, outside the submitted work.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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REFERENCES

Appendix – Protocol for Surgical Management

To minimise heterogeneity and potential confounding variables, it is preferred that all patients have standardised definitive surgical intervention where appropriate and feasible (Figure A1). Initial surgical management is directed towards sepsis control, with adequate drainage of abscesses, followed by the placement of setons where appropriate and concomitant antibiotics to ensure continued adequate drainage and assist tract maturation and healing. However, fistulas and abscesses frequently reoccur following seton removal and therefore setons represent a temporary bridging measure to definitive surgical interventions. Improved long-term healing rates of complex perianal fistulas have been achieved with closure of the internal opening as the definitive surgical intervention with comparatively reduced observed surgical complications.

All patients will have a baseline evaluation of fistula anatomy and disease activity, involving a colorectal surgeon review and pelvic magnetic resonance imaging (MRI), endoscopy to assess concurrent luminal disease and anal strictures, and if indicated, examination under anaesthesia (EUA) and seton insertion. Temporal requirements for baseline evaluation include pelvic MRI within four weeks of inclusion, EUA and sigmoidoscopy, within twelve weeks of inclusion and colonoscopy within six months of inclusion. If a colonoscopy has not occurred, it will be performed within four weeks from the time of study inclusion. Colorectal surgeon review and, where feasible, surgical interventions, will be standardised across sites to minimise heterogeneity and confounding variables.

All patients will be reviewed by a colorectal surgeon every four weeks to assess sustained sepsis control and adequate fistula drainage, occurring at baseline, weeks 4, 8 and 12 (Table 1). Appropriateness for definitive surgical intervention will be determined by the colorectal surgeon or fellow review at week 12, incorporating a combination of sepsis control, absence of active proctitis, absence of significantly obstructing anal strictures, and decreased fistula drainage. The decision of appropriateness and feasibility will be at the discretion of the colorectal surgeon or fellow involved and if unclear will be discussed at an IBD MDT meeting. An additional pelvic MRI may be requested if clinically warranted to guide planning and ensure absence of contraindications, specifically uncontrolled sepsis and active proctitis.

If deemed appropriate, a repeat EUA and definitive surgical intervention will occur between weeks 12 and 14. The preferred definitive surgical intervention will involve removal of setons if in situ, curettage of the fistula tract, debridement of the internal opening with cut-diathermy or blade, and closure of the internal opening with simple interrupted 2-0 vicryl absorbable sutures. Post definitive closure, the patients should be placed on ciprofloxacin or metronidazole for a total of four weeks.

If deemed inappropriate, there will be continued colorectal surgeon review every four weeks to re-evaluate appropriateness and feasibility. until week 24. If a patients is deemed to be inappropriate for seton removal at week 24, patients deemed to have perceived lack of efficacy and will exit the trial.

In the setting of multiple fistula tracts, it is recommended that definitive surgical intervention only be attempted if all tracts are healing. If deemed appropriate for definitive surgical intervention, it is recommended that all tracts are closed if feasible; whether closure be
attempted on a single or multiple tracts during a single procedure will be at the discretion of the colorectal surgeon or fellow involved.

At any point throughout the study, if deemed clinically warranted by the colorectal surgeon or fellow, a repeat examination under anaesthesia with tract curettage and replacement or adjustment of setons if present may occur. Additionally, if significantly obstructing anal strictures are present, dilatations after commencement of infliximab therapy may also occur if warranted. These interventions will not represent treatment failure.

This aspect of the study and implementation of a set surgical protocol was developed with expert colorectal surgeons at St Vincent’s Hospital Melbourne and Liverpool Hospital. This is a simple technique that can be easily completed at all centres involved in the study and can be completed by any member of the surgical team provided a colorectal surgeon is present in theatre.

Figure A1. Standardised Surgical Management