



# 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 TLI 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  $\geq 25$   $\mu\text{g/mL}$  at week 2,  $\geq 20$   $\mu\text{g/mL}$  at week 6 and  $\geq 10$   $\mu\text{g/mL}$  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 naïve 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.

**Trial registration number** Australian New Zealand Clinical Trials Registry (ACTRN12621000023853); Pre-results.

## 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

decreased quality of life, negatively impacting physical, emotional, sexual, and social well-being, and overall productivity.<sup>1-4</sup> Despite its significant morbidity, there remains a striking paucity of data regarding optimal treatment of pfCD, with patients achieving poorer therapeutic outcomes compared with luminal Crohn's disease.<sup>2,5,6</sup>

Tumour necrosis factor- $\alpha$  (TNF) is thought to play a key role in fistula formation by inducing epithelial to mesenchymal transition in intestinal epithelial cells.<sup>7</sup> Anti-TNF agents, specifically infliximab, represent the most effective medical therapy for pfCD. While infliximab has been shown to induce and maintain fistula healing, up to 60% of patients lose response within 1 year.<sup>8,9</sup> 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.<sup>10-13</sup>

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.<sup>14</sup> 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.<sup>15</sup> 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 (TAILORIX) was unable to show a difference in steroid-free remission or mucosal healing between the proactive TDM and standard care arms.<sup>14</sup> 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 pfCD.

Previous clinical trials involving pfCD have measured success using clinical outcomes alone, a subjective measure that may fail to evaluate deeper stats of fistula healing. There are also very few studies that assess patient-reported outcome measures and economic burden of pfCD. 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 pfCD. 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 pfCD 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 pfCD 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.<sup>8,9</sup>

### Secondary objectives

- To determine the proportion of patients with pfCD who achieve fistula healing at week 54 in the proactive TDM arm compared with the standard care arm.
- To determine the proportion of patients with pfCD 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.<sup>8,9</sup>
- To determine the proportion of patients with pfCD 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.<sup>8</sup>
- To determine the proportion of patients with pfCD 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)<sup>16</sup> or Magnetic Resonance Novel Index for Fistula Imaging in Crohn's Disease (MAGNIFI-CD) score of 0.<sup>17</sup>
- To determine the proportion of patients with pfCD who achieve radiological fistula response at weeks

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  $> 3$ <sup>18</sup> or MAGNIFI-CD score of  $> 4$ .<sup>17</sup>

- 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,<sup>19</sup> Inflammatory Bowel Disease-Specific Female Sexual Dysfunction Scale and Inflammatory Bowel Disease-Specific Male Sexual Dysfunction Scale.<sup>19–22</sup>
- 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.<sup>9</sup>
- 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)<sup>23</sup> and Work Productivity and Activity Impairment<sup>24</sup> to estimate indirect-economic costs.

## 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.<sup>25</sup> 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 ( $< 10 \mu\text{g/mL}$ ) and low anti-infliximab antibody titres if present ( $\leq 60 \text{ ng/mL}$ , 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 ( $< 5 \mu\text{g/mL}$ ), 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 ( $\geq 10 \mu\text{g/mL}$ ), conditions interfering with treatment adherence, pregnancy or planning a pregnancy in the next 54 weeks, breast feeding and contraindications to 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. This evaluation 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.<sup>26</sup> Block randomisation will be used with



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 to not 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.<sup>10</sup>

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.<sup>8 25</sup> 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).

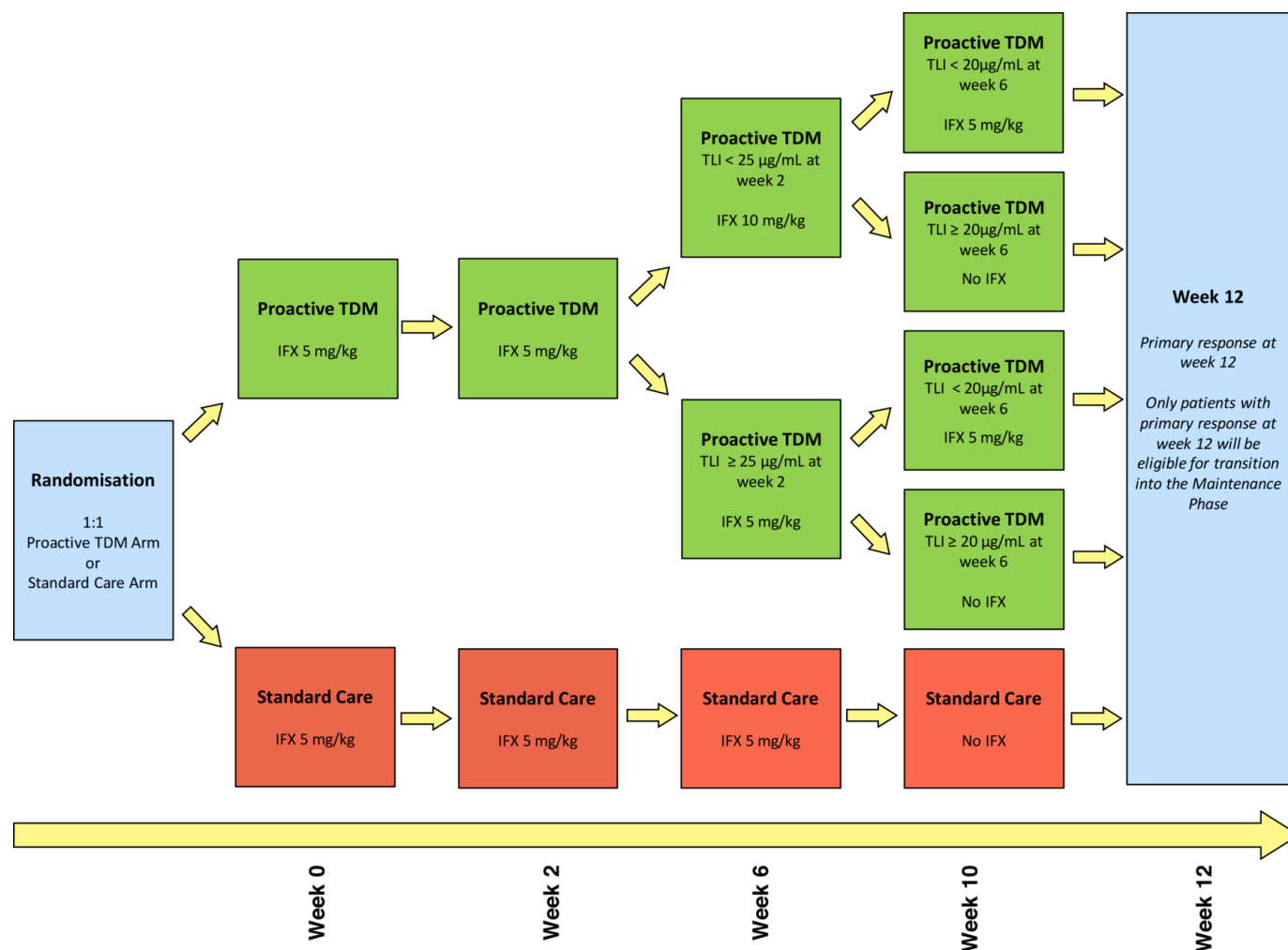
#### Maintenance phase: proactive TDM arm

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.<sup>10 11</sup>

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



**Figure 1** Induction phase. Patients in the standard care arm will receive infliximab 5 mg/kg at weeks 0, 2 and 6, with no additional infliximab doses. Patients in the proactive TDM arm will receive infliximab 5 mg/kg at weeks 0 and 2. If patients have TLIs < 25 µg/mL at week 2, they will be given 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. **IFX, infliximab; TDM, therapeutic drug monitoring; TLI, infliximab trough level.**

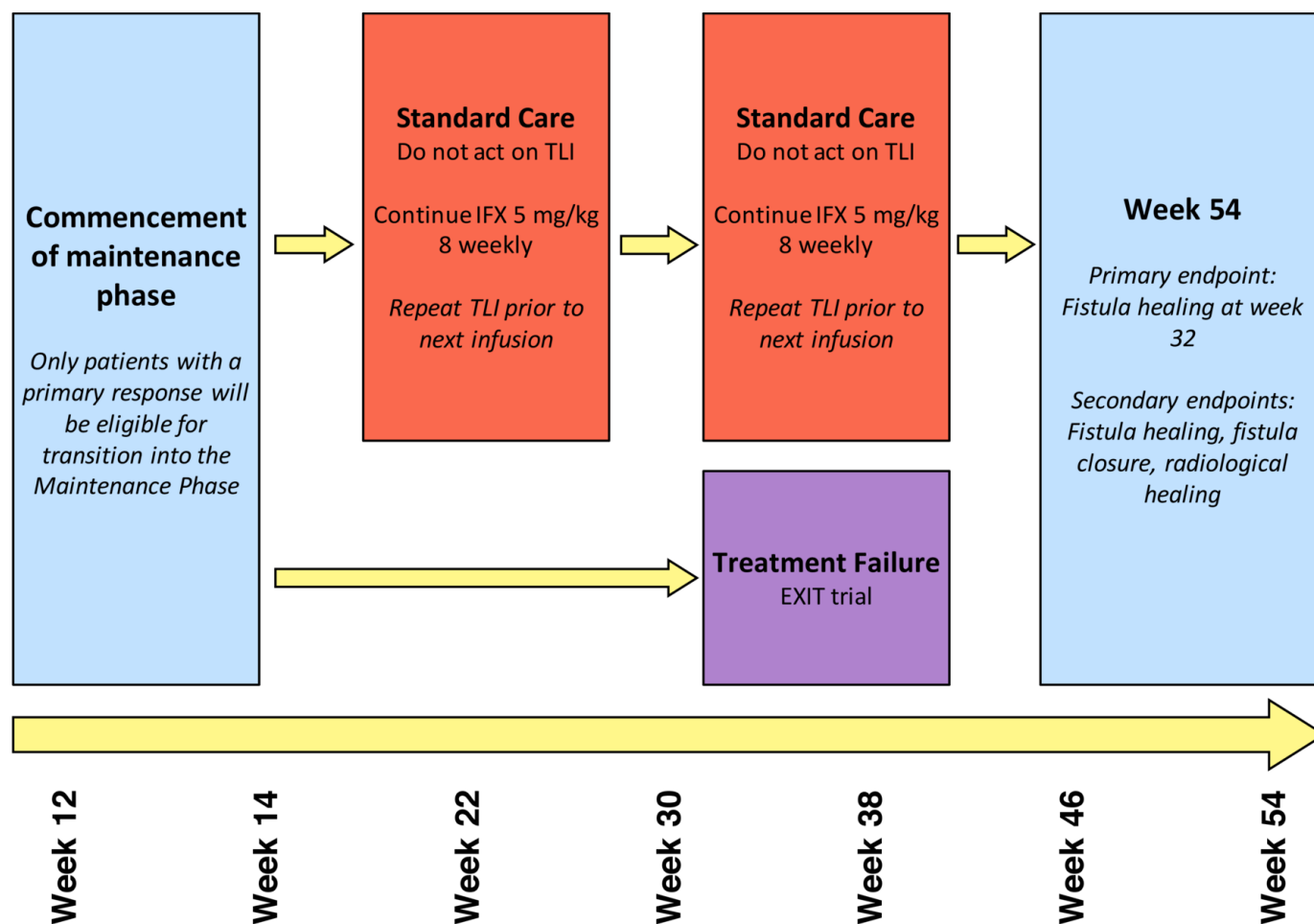
of infliximab, the subsequent TLI will be performed 12 weeks later.<sup>27</sup> This represents the maximal number of dose adjustments. Patients whose TLIs remain < 10 µg/mL after the maximal dose adjustments will continue to receive 10 mg/kg infusions every 4 weeks and will continue in the arm to which 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.<sup>8 25</sup>

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.<sup>9</sup>

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.



**Figure 2** Standard care maintenance phase. The standard care arm will receive infliximab 5 mg/kg every 8 weeks with TLIs measured prior to each infusion. No dose modification will occur in the standard care arm.

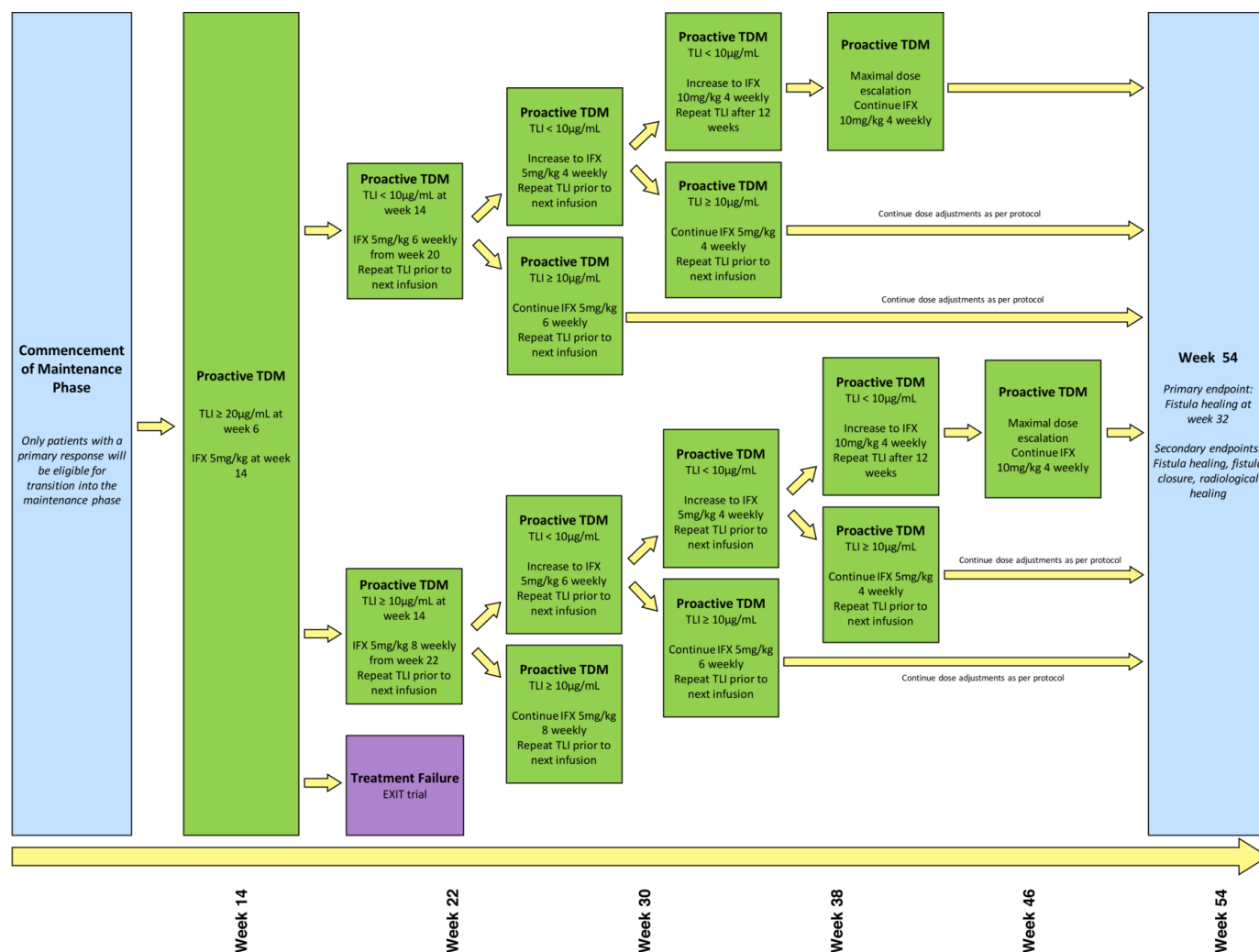
IFX, infliximab; TLI, infliximab trough level.

### 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  $\geq 10$  mg weekly<sup>28</sup> 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/ $8 \times 10^8$  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 immunomodulators 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.



**Figure 3** Proactive TDM maintenance phase: Patients with target induction TLIs. Patients in the proactive TDM arm with TLIs  $\geq 20$   $\mu\text{g/mL}$  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  $< 10$   $\mu\text{g/mL}$ . 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.

**IFX, infliximab; TDM, therapeutic drug monitoring; TLI, infliximab trough level.**

## Radiological assessment

All MRI will be centrally read by two radiologists with experience with perianal fistula MRI and a van Assche Index score<sup>16</sup> and MAGNIFI-CD score<sup>17</sup> will be calculated. All imaging with discrepant scores will be discussed between the radiologists to obtain a consensus score.

## TIMELINE

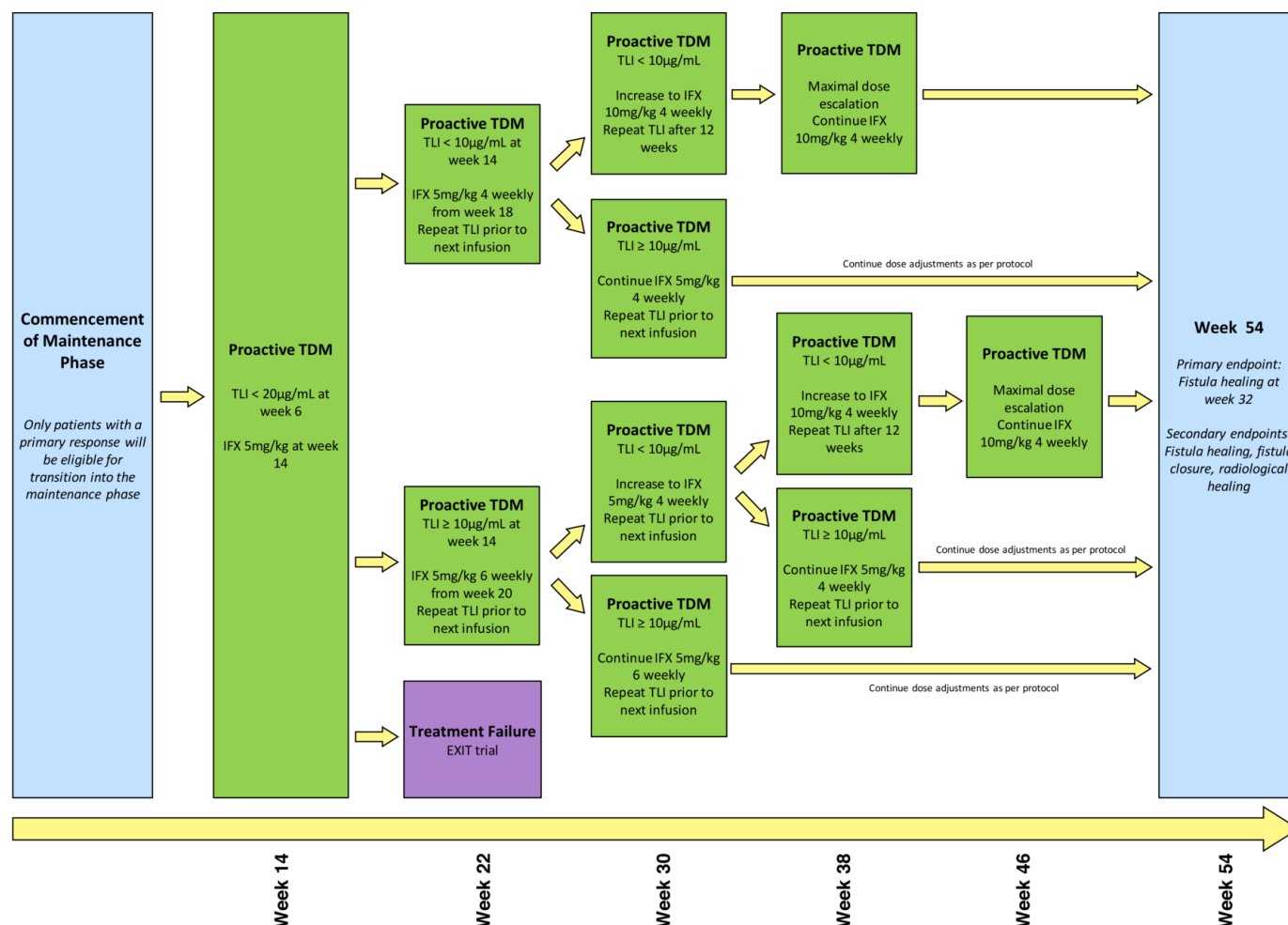
Clinic visits will be performed at baseline, weeks 2, 6, 12, 22, 30, 32, 38, 46, 52 and 54, or on trial exit if treatment failure. Pathology, MRI, Crohn's Disease Activity Index (CDAI) and patient-reported outcome measure questionnaires will be performed as outlined in [table 1](#). Blood will be collected 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  $< 2.0 \mu\text{g/mL}$ . Anti-infliximab antibodies titres will be performed using Ridascreen ELISA, with high antibodies defined as  $> 60 \text{ ng/mL}$  and low antibodies  $\leq 60 \text{ ng/mL}$ .

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 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.

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.<sup>26</sup> 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 published<sup>11–13</sup>; 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



**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

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

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; IBD-FSDS, 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.

account for an estimated 6.1% failure to meet Australian Pharmaceutical Benefits Scheme criteria for maintenance infliximab therapy<sup>25</sup> and 10% dropout rate during maintenance as based on previous clinical trials.<sup>15</sup>

### 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.

## 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 (ACTRN12621000023853). Results will be published in a peer-reviewed journal.

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