

Treat-to-target of endoscopic remission in patients with inflammatory bowel disease in symptomatic remission on advanced therapies (QUOTIENT): rationale, design and protocol for an open-label, multicentre, pragmatic, randomised controlled trial

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ABSTRACT

Introduction Targeted immunomodulators (eg, advanced therapies) effectively achieve symptomatic remission in patients with inflammatory bowel disease (IBD). However, ~25%–50% of patients with IBD achieving symptomatic remission with an advanced therapy may have continued endoscopically/radiologically active bowel inflammation, and it is uncertain whether changing alternative advanced therapies in asymptomatic patients with IBD will reduce bowel inflammation and achieve durable deep remission.

Methods and analysis The Quality Outcomes Treating IBD to Target (QUOTIENT) study is an open-label, multicentre, pragmatic, randomised, controlled trial that aims to compare the efficacy and safety of switching to an alternative advanced therapy targeting endoscopic/radiological remission (treat-to-target) versus continuing the initial, or index, advanced therapy, in asymptomatic patients with IBD with moderate-to-severe endoscopic/radiological bowel inflammation. Enrolment is planned for ~250 participants in Canada/USA, randomised 1:1 to switching to alternative advanced therapy or continuing index advanced therapy, and then followed 104 weeks within routine clinical practice. Patient-reported outcomes measure efficacy and quality of life/treatment burden/safety. Primary endpoint is the time from randomisation to treatment failure.

Ethics and dissemination The study is conducted in compliance with the protocol, ICH Good Clinical Practice, applicable regulatory requirements and appropriate

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treat-to-target endoscopic and/or radiological remission is a potential therapeutic strategy that may improve patient outcomes in patients with inflammatory bowel disease (IBD). However, whether treatment should be switched in asymptomatic patients with active inflammation in pursuit of a treatment target of endoscopic and/or radiological remission presents clinical equipoise.

review boards/independent ethics committees (approval numbers: Pro00077486; Pro00061437; STUDY00002062; 22-004171; i22-01269; IRB22-0890; IRB_00154397; 2000032384; SHIRB#2022.095-2; STUDY00007146; MMC#2024-18; REB#125290; 17784; Pro00142214; 20240660-01H), with documented written informed consent. Findings will be disseminated through peer-reviewed journals, scientific presentations, and publicly available Patient-Centered Outcomes Research Institute (PCORI) websites, including lay summaries. The Crohn's & Colitis Foundation Education, Support, and Advocacy Department, and our patient advocacy stakeholder, will develop educational and marketing resources to communicate findings to a broad audience (>250 000 patients/caregivers/healthcare professionals).

Trial registration number NCT05230173.

WHAT THIS STUDY ADDS

⇒ The QQuality Outcomes Treating IBD to Target (QUOTIENT) study is an open-label, multicentre, pragmatic, randomised, controlled trial designed to address this knowledge gap by comparing two treatment strategies of treat-to-target in patients with IBD in symptomatic remission but with significant ongoing bowel inflammation detectable by endoscopy and/or radiology, to determine if a targeted immunomodulator (advanced therapy) switch will reduce bowel inflammation and achieve remission. With a primary endpoint of time from randomisation to treatment failure during 104 weeks of follow-up within routine clinical practice, the trial focuses on comparing two advanced therapy treatment strategies rather than different medications, since the primary question for treat-to-target is treatment modification, not specifically treatment sequencing. We will capture quality of life, treatment burden, and patient satisfaction to discern how patients view two competing advanced therapy treatment strategies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This pragmatic clinical trial represents a real-world approach for treating patients with IBD and comparing two distinct, yet valid, advanced therapy treatment approaches. This trial focuses on patient-centred outcomes and will directly impact clinical guidelines and practice.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD), affect approximately 2.4 million and >320 000 individuals in the USA¹ and Canada,² respectively, cost >\$25 billion annually, and cause substantial patient morbidity, diminished quality of life and decreased work productivity.^{3–5} As a chronic relapsing-remitting disease, treatment goals for patients with IBD involve resolving symptoms, minimising relapses and unplanned healthcare utilisation, and reducing disease-related complications.

Standard treatment of IBD often involves long-term use of potent targeted immunomodulator therapies, referred to herein as advanced therapies, including biologic agents such as tumour necrosis factor- α antagonists, anti-integrins, interleukin (IL)-12/IL-23 and IL-23 antagonists, and small molecule drugs (eg, Janus kinase inhibitors and sphingosine-1 phosphate receptor modulators). These agents have revolutionised the management of IBD; approximately 40%–60% of patients achieve symptomatic remission with these agents and avoid disease-related complications. However, these medications can be associated with side effects increasing the risk of serious infections and certain cancers, including non-melanoma skin cancers and lymphoma.^{6–8} Advanced therapies are also very expensive and contribute substantially to the rising cost of managing IBD.

While advanced therapies are effective in achieving symptomatic remission, approximately 25%–50% of patients with IBD achieving symptomatic remission with an index advanced therapy (defined as the initial advanced therapy the participants are receiving at the

start of the study) have persistent endoscopic evidence of inflammation.^{9–12} Cohort studies and post-hoc analyses of clinical trials have demonstrated that persistent endoscopic inflammation can substantially increase the risk of clinical relapse, disease-related complications, unplanned healthcare utilisation, and lead to inferior quality of life compared with patients achieving endoscopic remission by resolving bowel inflammation,^{13–17} which may contribute to patients' worries and fears about the disease.^{18 19}

Cohort studies suggest 20%–38% of patients with IBD treated with advanced therapies require dose optimisation, with approximately 30%–54% of these patients achieving clinical and/or endoscopic remission.^{20–22} Consequently, clinical guidelines and expert consensus statements recommend optimisation of index therapy, if feasible, in patients not achieving symptomatic and endoscopic remission targets.^{23–25} However, despite iterative optimisation of advanced therapy (online supplemental figure 1), approximately 35% of patients with CD and 15% of patients with UC who are in symptomatic remission could be estimated to continue to have significant bowel inflammation.^{26–29} The Effect of Tight Management on Crohn's Disease (CALM) trial demonstrated that a treat-to-target strategy, involving treatment escalation when symptomatic and/or objective biochemical targets were not achieved, resulted in improved clinical outcomes compared with symptom-based escalations in therapy only.³⁰ However, it was designed around optimising the index treatment rather than switching to an alternative therapy and did not use endoscopy/radiology as a treatment target. Therefore, patients and providers are often faced with a dilemma as to whether switching to an alternative advanced therapy in asymptomatic patients with ongoing bowel inflammation would be beneficial. With limited evidence on the comparative efficacy of advanced therapies and a lack of predictive biomarkers to personalise the choice of advanced therapies, this empiric treatment switch may inadvertently be a less effective therapy, increasing the risk of relapse and complications, and may still not achieve endoscopic remission. This equipoise represents a key evidence gap in the management of patients with IBD.

While treat-to-target strategies (figure 1)³¹ are recommended over a non-targeted treatment approach in other chronic diseases such as rheumatoid arthritis, optimal treatment targets are set at clinical and biochemical remission rather than aiming for complete radiological resolution of inflammation.³² There is considerable variability in IBD guidelines and recommendations, and consequently, practice patterns for treat-to-target in IBD. Some clinical guidelines and expert consensus statements recommend symptomatic and endoscopic remission as preferred treatment targets in patients with IBD, and suggest changing treatment iteratively in order to achieve a target of endoscopic remission.^{23 25 33} In contrast, other guidelines identify risk-benefit synthesis of targeting symptomatic remission versus incrementally

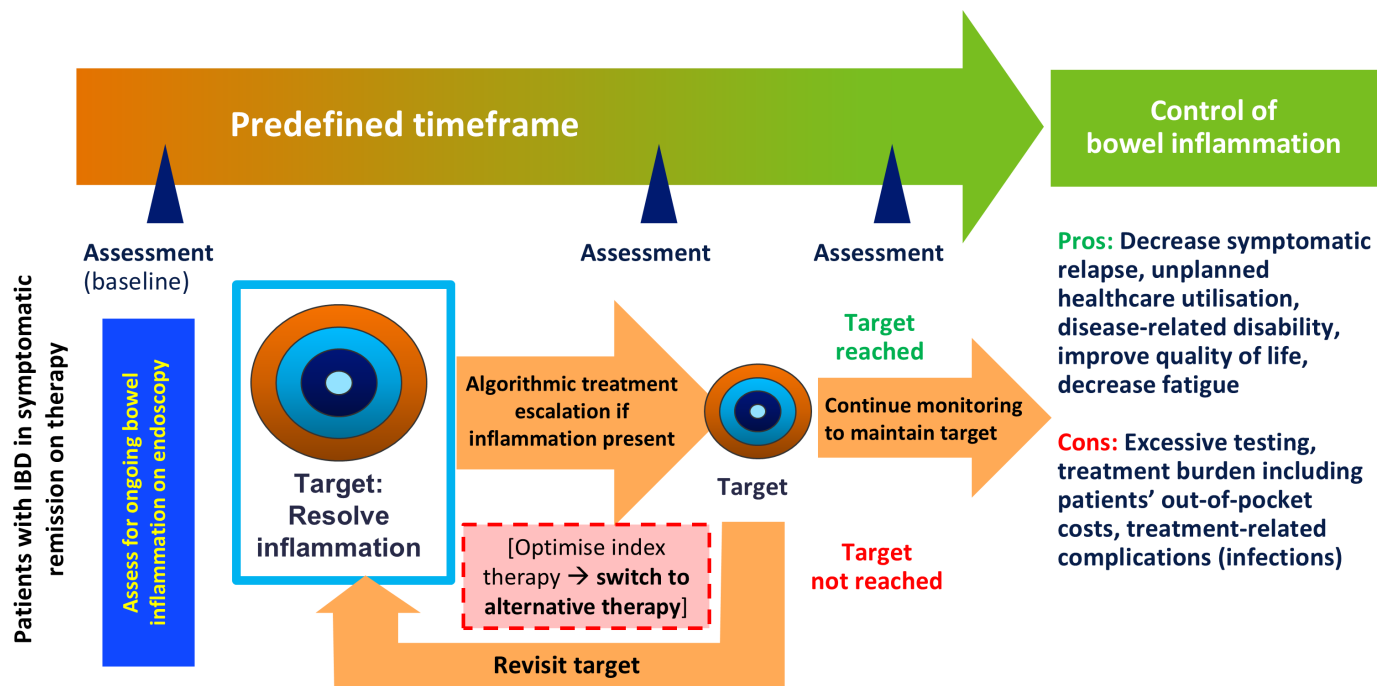


Figure 1 Core concept of treat-to-target of endoscopic remission in patients with IBD. IBD, inflammatory bowel disease. Source: adapted from Bouguen *et al.*³¹

treating to endoscopic remission as a key knowledge gap.^{24 34–36} Furthermore, there is considerable variability in practice patterns for treat-to-target strategies in the real world.³⁷ Since five classes of advanced therapies are currently approved for managing IBD, switching to an alternative advanced therapy within a treat-to-target paradigm may achieve endoscopic remission in patients with persistent bowel inflammation.^{38 39} However, the benefits and advisability of switching treatments in asymptomatic patients in real-world practice are unknown. There is a risk that an asymptomatic participant may deteriorate on new therapy when switching advanced therapies, as well as the potential risk of running out of other advanced therapies to switch to if a participant continues to not achieve endoscopic/radiological remission with different advanced therapies.

There is a critical unmet need for a real-world, patient-centred evaluation of the efficacy and safety of treat-to-target strategies in patients with IBD. This study protocol describes an open-label, multicentre, pragmatic, patient-centred, randomised controlled trial comparing a strategy of switching advanced therapies to treat to a target of endoscopic/radiological remission versus continuing the index advanced therapy, in asymptomatic patients with IBD with persistent moderate-to-severe bowel inflammation, to assess which approach improves outcomes without increasing treatment burden or adverse events (AEs).

METHODS AND ANALYSIS

Study objectives

The objectives of this study are to compare (1) the efficacy and (2) quality of life and the burden and safety

of switching to an alternative advanced therapy to treat to a target of endoscopic/radiological remission versus continuing the index advanced therapy in asymptomatic patients with IBD with ongoing significant bowel inflammation, detectable on endoscopy/radiology. Advanced therapies approved for IBD treatment include biologic agents (eg, tumour necrosis factor- α antagonists; ustekinumab; vedolizumab) and small molecule inhibitors (eg, Janus kinase inhibitors such as tofacitinib; ozanimod), and future advanced therapies that become commercially available during the conduct of the trial.

Study design and population

The Quality Outcomes Treating IBD to Target (QUOTIENT) study is an open-label, multicentre study conducted in asymptomatic patients with IBD who have persistent moderate-to-severe endoscopic or radiological inflammation, and has been designed as a pragmatic trial, using the PRECIS-2 framework (online supplemental figure 2).⁴⁰ This study plans to enrol approximately 250 participants in the USA and Canada. Patients who meet the inclusion criteria without exhibiting exclusion criteria are eligible to be enrolled in the study (table 1; online supplemental table 1). Participants' written informed consent is obtained and documented (online supplemental table 2).

After randomisation, participants in both treatment arms are followed prospectively within routine clinical care for up to 104 weeks with their treating physician and are scheduled for routine clinical follow-up, either in-person or using telemedicine (eg, phone call/video conference), as per local site practice, at the discretion of their treating physician. A period of 104 weeks was

Table 1 Inclusion and exclusion criteria

Inclusion criteria	<ol style="list-style-type: none"> 1. Male or non-pregnant, non-lactating females, ≥ 18 years of age 2. Diagnosis of CD or UC for ≥ 6 months, based on standard clinical criteria 3. Current treatment with an approved advanced therapy for IBD treatment, including biologic agents and small molecule inhibitors. Optimisation of index advanced therapy, particularly TNF antagonists, will be encouraged but not mandated due to significant variability in real-world practice patterns 4. Experiencing no other IBD-related symptoms and in corticosteroid-free symptomatic remission 5. Evidence of moderate-to-severe bowel inflammation on the local reading of colonoscopy, flexible sigmoidoscopy, balloon-assisted enteroscopy, capsule endoscopy, MRE, CTE or IUS*, performed ≤ 6 months prior to screening on a stable dose of advanced therapy
Exclusion criteria	<ol style="list-style-type: none"> 1. Presence of ostomy or ileoanal pouches 2. Mild endoscopic disease activity where treating providers would not consider switching advanced therapy 3. Taking prednisone or equivalent at the time of qualifying endoscopy or imaging study, and any time between qualifying procedure and enrolment

*Since there are no clear criteria for differentiating inflammation from fibrosis using IUS, strict IUS criteria are not mandated. CD, Crohn's disease; CTE, computed tomography enterography; IBD, inflammatory bowel disease; IUS, intestinal ultrasound; MRE, magnetic resonance enterography; TNF, tumour necrosis factor; UC, ulcerative colitis.

chosen to provide sufficient time for asymptomatic participants to potentially experience an IBD flare or symptomatic relapse. There is no study-mandated visit schedule; however, participant visit schedules will follow local standard of care (SOC) with additional visits at the treating physician's discretion, and participants are required to complete the patient-reported outcome (PRO) questionnaires at predefined timepoints (table 2). An overview of the study design and schedule of events is provided in figure 2 and table 2. The baseline qualifying endoscopy (or imaging study) can occur within 6 months prior to enrolment, and if multiple endoscopy/imaging procedures were performed in the preceding months, then the most recent qualifying procedure will be captured. The dose of advanced therapy must be stable for at least 3 months prior to the qualifying endoscopy/radiology, and will remain stable between the qualifying procedure and randomisation. No treatment escalation of advanced therapy or addition of immunomodulators, corticosteroids or mesalamines after the qualifying endoscopy/radiology procedure up to randomisation is permitted. The Standard Protocol Items: Recommendations for Interventional Trials checklist is provided in online supplemental table 3.

This study is patient-centred, with patient-prioritised outcomes. A patient advisory board (the IBD Qorus Patient Advisory Council), which meets quarterly, helped design this study and prioritised clinical status (eg, risk of symptomatic relapse and need for corticosteroids; IBD- or treatment-related hospitalisation, surgery and complications), quality of life (eg, overall quality of life; physical, social, and emotional well-being; fatigue; IBD-related disability), the burden of treatment (eg, financial burden; burden of monitoring; treatment side effects), and treatment satisfaction as outcomes of interest. During the planning of this study, the Patient Advisory Board expressed decisional conflict related to switching advanced therapies, which highlighted their fears about

weighing trade-offs of switching therapy with hope of avoiding future complications. Potential risks associated with switching to a new advanced therapy may include worsening of underlying disease activity, potential progression to disease-related complications and/or side effects related to the new advanced therapy. In addition, treatment interruption of an index advanced therapy, while trying an alternative advanced therapy in the treat-to-target paradigm, may render the index therapy ineffective if retreatment is warranted due to the potential development of antidrug antibodies. In contrast, continuing treatment with index advanced therapy in participants with ongoing inflammation may result in ongoing or worsening bowel inflammation that leads to a higher risk of relapse, unplanned healthcare utilisation due to disease-related complications, and inferior quality of life that can lead to other complications. However, all treatment scenarios proposed in this protocol are part of routine clinical care and therefore, the risks and benefits are not different from what would be observed in routine clinical care. Patient-prioritised treatment goals were to (1) achieve remission off corticosteroids while maintaining good quality of life, (2) avoid unpredictable relapses and disability, (3) decrease the risk of hospitalisation and surgery, while (4) minimising treatment burden and (5) avoiding treatment complications.

Recruitment

A total of 29 sites are planned, with currently 6 in Canada (members of the Canadian IBD Research Consortium) and 23 USA sites within IBD Qorus, which is a learning health system built on a collaboration between patients and providers that aims to improve healthcare value for patients with IBD.⁴¹ The participating sites are a mixture of academic, single-specialty gastroenterology, and multi-specialty gastroenterology practice centres. Study enrolment began on 5 October 2022; as of 19 December 2024,

Table 2 Schedule of events*

Week	Baseline		Follow-up observation period (weeks)								EOS/ED	UNS
	Screen (-8 to 0)	Randomisation	12	24	36	48	60	72	84	96	104	N/A
EDC (site data collection) (± 4 weeks)	x	x		x		x		x			x	x
Eligibility screen	x											
Written informed consent	x											
Assess inclusion/exclusion criteria	x											
SOC assessments												
Lower endoscopy/imaging	t						t				t	t
Demographics		t										
Medical, disease, and surgical history (IBD-related), and comorbidities		t										
Prior and concomitant IBD-related medications and advanced therapy treatment details		t					t				t	t
Clinical laboratory tests (FC, CRP)		t					t				t	t
Safety information		t					t				t	t
Study-related activities												
Confirm inclusion/exclusion criteria		x										
Randomisation (continuing index advanced therapy or switching to alternative advanced therapy)		x										
Local outcome assessment		x					x				x	x
Central adjudication of outcomes							x				x	x
Protocol/treatment strategy compliance		x					x					x
Patient-reported outcomes												
PRO2 (3-day recall)	x		x	x	x	x	x	x	x	x	x	x
SIBDQ		x		x		x					x	
IBD-Control		x		x		x					x	
PROMIS-7		x		x		x					x	
IBD-DI-SR		x		x		x					x	
TBQ		x		x		x					x	
TSQM		x		x		x					x	
CoPaQ		x		x		x					x	
Patient survey		x	x	x	x	x	x	x	x	x	x	x

*As a pragmatic trial being conducted within usual clinical practice, comparing two commonly accepted treatment strategies, no trial-related endoscopies, medications or laboratory assessments are mandated. 'x' denotes trial-mandated activities and 't' denotes timing of tests and endoscopies performed within typical clinical practice which will be used for the study when and as performed. No trial-mandated endoscopies will be performed. If a participant experiences a symptomatic relapse in between the 12-week collection schedule, the patient survey and PRO2 questionnaire will be administered, and SOC clinical data will be collected if available. Patient confidentiality will be maintained. All confidential information will be kept in strict confidence and restricted to the study personnel involved in conducting the study, except if the information is required by the institutional review board/independent ethics committee or similar committees. The participant's information will be made available only to the extent permitted by the applicable laws and regulations. Study records will identify participants by initials, where permitted, and the assigned participant identification number. Reasons for participant drop-out and missing data will be recorded. For the primary composite outcome, time-to-event analysis will be performed, and participants lost to follow-up will be censored. For secondary continuous outcomes, mixed-effects model analyses will be conducted to allow for data missing at random. CoPaQ, Costs for Patients Questionnaire; CRP, C reactive protein; ED, early discontinuation; EDC, electronic data capture; EOS, end of study; FC, faecal calprotectin; IBD, inflammatory bowel disease; IBD-DI-SR, IBD Disability Index for Self-Report; N/A, not applicable; PRO2, 2-item patient-reported outcome; PROMIS 7, Patient-Reported Outcomes Measurement Information System (Fatigue-Short Form 7a); SIBDQ, Short Inflammatory Bowel Disease Questionnaire; SOC, standard of care; TBQ, Treatment Burden Questionnaire; TSQM, Treatment Satisfaction Questionnaire for Medicine; UNS, unscheduled.

88 participants are enrolled and 22 sites are currently recruiting. The expected study completion date is 1 June 2028. During the prescreening process, providers evaluate clinical data related to treat-to-target,

including endoscopic remission status, current IBD medications, and plan for treat-to-target of endoscopic/radiological remission. Monthly reports are collected from all sites, and include lists of eligible

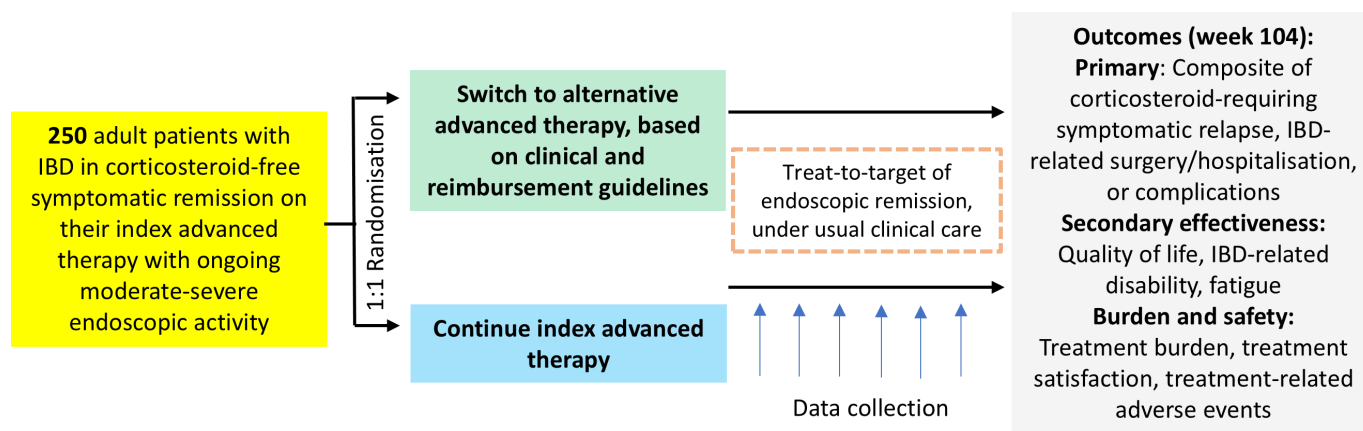


Figure 2 Overview of Quality Outcomes Treating IBD to Target (QUOTIENT) study: open-label, multicentre, pragmatic, randomised, controlled trial of treat-to-target strategies in IBD. IBD, inflammatory bowel disease.

patients, the number consented/randomised, and of those not consented, why they were excluded including patients' and/or providers' preference for making a decision to switch or not to switch.

Randomisation and blinding

Eligible participants are randomly assigned in a 1:1 allocation ratio to one of two treatment strategies, that is, either continuing index advanced therapy or switching to an alternative advanced therapy. Randomisation occurs through a computer-generated, centralised randomisation service with permuted block randomisation of alternating sizes to ensure allocation concealment. Randomisation is stratified by disease phenotype (eg, CD vs UC).

Since this is an open-label study, participants and site investigators are not blinded to treatment allocation. To minimise bias related to open-label design, outcome is adjudicated by blinded outcome assessors.

Study outcomes

The specific objectives and endpoints of the QUOTIENT study are described in [table 3](#).

Treatment

Participants in both treatment arms continue routine clinical care with their treating provider, including testing and continuation or discontinuation of any concomitant therapies. Participants randomised to a strategy of switching advanced therapy discontinue their existing advanced therapy and are switched to an alternative advanced therapy approved for management of IBD and covered by the participants' insurance formulary as part of routine care. Participants may be switched to another medication in the same drug class. Addition of another advanced therapy (ie, dual biologic or biologic combined with advanced oral molecule drug) to an existing advanced therapy does not constitute a switch, since adding another advanced therapy while maintaining treatment with the current advanced therapy is less likely to put the participants at risk of flare. However, for participants on advanced combination therapy, switching one

of the advanced therapies with a new advanced therapy, while keeping the other advanced therapy unchanged, is considered a switch. No study-related medications are provided. The selection of an alternative agent is determined at the discretion of the local site physician in accordance with clinical guidelines on management of moderate-to-severe UC and CD^{23–25} and any updates during the course of the trial. These guidelines include recommendations on the positioning of advanced therapies for first-line use in patients who are advanced therapy-naïve and second-line use in patients with prior advanced therapy exposure.

Participants (and their providers) in either treatment arm are allowed to stop or start new advanced therapies and other IBD-directed therapies in case of symptomatic relapse or intolerance to therapies, at the discretion of the treating provider-patient team.

Medication records of randomised participants are used to assess adherence to the selected treatment strategy, and a medical log is used to document any advanced therapy switches or if the criteria were not met. Fidelity measures are analysed by measuring adherence and non-adherence to the study protocol using a physician-reported survey to assess whether participants were switched to an alternative advanced therapy when randomised to continue the index advanced therapy, and vice versa. Given potential heterogeneity in the advanced therapy switching arm, survey questions include the type of medication switch and reasons for choosing specific medications: (1) participant preference, (2) provider preference, (3) access/cost, and (4) other (with a brief explanation).

Participants are permitted to continue taking, starting or stopping mesalamine, thiopurines, or methotrexate, or adding other advanced therapies to the existing index advanced therapy after randomisation, at the discretion of the treating provider-patient team. If IBD-related medications are added/modified in response to a symptomatic flare (eg, adding corticosteroids/budesonide, immunomodulators, another advanced therapy or dose-escalating existing advanced therapy), the participant will have met

Table 3 Planned outcomes and measures

Primary or secondary	Outcome	Specific measure to be used	Timepoints	Powered? Yes/no
Effectiveness				
Primary	Clinical status	Time to treatment failure, as a composite of: (1) moderate-to-severe symptomatic relapse based on PRO2*, with objective confirmation of inflammation within 2 months of event (FC>150 µg/g, or CRP>5 mg/L, or endoscopy showing moderate-to-severe inflammation, or MRE/CTE/IUS showing active inflammation) with need for escalation of therapy†; (2) need for rescue therapy with corticosteroids‡ for a documented symptomatic IBD flare; (3) IBD-related hospitalisation§; (4) IBD-related surgery; (5) IBD-related structural complications (CD: symptomatic stricture, fistula or abscess; UC: symptomatic stricture¶); (6) TEAE requiring drug discontinuation	From randomisation up to 104 weeks	Yes
Secondary	Clinical status	Treatment failure as defined in the composite primary outcome	Binary, 104 weeks	Yes
Secondary	Clinical status	Time to each individual component of the composite primary outcome	From randomisation up to 104 weeks	Yes
Secondary	Quality of life	<ul style="list-style-type: none"> ▶ Scores of the SIBDQ ▶ Scores of the PROMIS-7 ▶ Scores of the IBD-DI-SR ▶ Scores of the IBD-Control 	Continuous, EOS (104 weeks) or ED	Yes
Treatment burden/safety				
Secondary	Treatment burden	Scores of the Treatment Burden Questionnaire, including medication, time and administrative burden, lifestyle change, social life and financial burden	Continuous, EOS (104 weeks) or ED	Yes
Secondary	Treatment satisfaction	Scores of the Treatment Satisfaction Questionnaire for Medication, measuring treatment satisfaction across domains of effectiveness, side effects, convenience, and global satisfaction	Continuous, EOS (104 weeks) or ED	Yes
Secondary	Patient cost	Scores of the CoPaQ, including out-of-pocket costs, for management of IBD, including treatment, monitoring, outpatient visits, and any unplanned healthcare utilisation	Continuous, EOS (104 weeks) or ED	Yes
Secondary	Safety	<ul style="list-style-type: none"> ▶ Treatment-related SAEs or unexpected SAEs (including death) ▶ Serious infections, defined as infections requiring hospitalisation and/or intravenous antibiotics 	From randomisation up to 104 weeks	No

*Moderate-to-severe symptomatic relapse based on PRO2 is defined as stool frequency score >4 and/or abdominal pain score ≥2 (CD), or rectal bleeding score ≥2 and with stool frequency score ≥2 (UC).

†Need for escalation of therapy includes adding corticosteroids/budesonide, adding immunomodulator, adding another advanced therapy, or dose-escalating existing advanced therapy.

‡Corticosteroid requirement is ≥30 mg/day prednisone equivalent (or 9 mg/day budesonide) being planned taper over ≥4 weeks. After randomisation, initiation of corticosteroids is deemed treatment failure only if used for treating an IBD flare with an intended duration of treatment >4 weeks. Cases where steroids are used for other indications will be recorded but not deemed treatment failure.

§IBD-related hospitalisation for a flare requiring initiation of corticosteroids with intention of treating for ≥4 weeks and/or need for escalation of index therapy, or hospitalisation for symptomatic structural complication of IBD.

¶Structural complications can be new or already present, but now causing moderate-to-severe symptoms in the opinion of the investigator. This includes new or relapse of perianal/intra-abdominal abscess, symptomatic intra-abdominal phlegmon or significant increase in fistula drainage or new obstructive symptoms in the setting of stricture.

CD, Crohn's disease; CoPaQ, Costs for Patients Questionnaire; CRP, C reactive protein; CTE, computed tomography enterography; ED, early discontinuation (ie, discontinuation due to investigator/sponsor or participant decision or lost to follow-up); EOS, end of study; FC, faecal calprotectin; IBD, inflammatory bowel disease; IBD-DI-SR, IBD Disability Index for Self-Report; IUS, intestinal ultrasound; MRE, magnetic resonance enterography; PRO2, 2-item patient-reported outcome; PROMIS-7, Patient-Reported Outcomes Measurement Information System (Fatigue-Short Form 7a); SAE, serious adverse event; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TEAE, treatment-emergent adverse event (defined as one or both of the following: adverse event onset date ≥1st study treatment date; or adverse event onset date <1st study treatment date and either the severity worsened on or after the 1st study treatment date or the event became serious on or after the 1st study treatment date; to qualify as an outcome, this TEAE should lead to discontinuation of therapy); UC, ulcerative colitis.

the primary outcome. At enrolment, participants cannot be on prednisone (or equivalent); initiation of corticosteroids as rescue therapy for a documented symptomatic IBD flare during the study is considered treatment failure (ie, deemed to have met the primary outcome, as defined

in table 3). All participating sites have a standard practice of confirming active inflammation prior to initiation of prolonged courses of corticosteroids, and all oral and/or rectal IBD-related medications (eg, mesalamine, corticosteroids, thiopurines, methotrexate, advanced therapies,

etc) received by the participant following randomisation are recorded.

Assessments

Baseline data are collected for the most recent SOC assessments that occurred within 6 months prior to informed consent. Demographic, medical, disease, and surgical history variables are collected at baseline, including age, sex, race and ethnicity, body mass index, smoking status, IBD diagnosis with date of onset, disease location, Montreal classification, major comorbidities, medication history, laboratory and imaging assessments, and prior IBD surgeries.

Participants complete PRO measures electronically, which are used to determine primary (efficacy) and secondary (quality of life, treatment burden and satisfaction) outcomes to determine how participants perceive their condition and its impact on their life. Participants complete the validated 2-item PRO (PRO2) questionnaires at baseline and approximately every 12 weeks during the 104-week follow-up period, which commences after randomisation. The PRO2 UC consists of stool frequency and rectal bleeding subscores of the Mayo Clinic Score, and the PRO2 CD consists of daily stool frequency and abdominal pain score. Additional questionnaires (eg, IBD-Control, Patient-Reported Outcomes Measurement Information System (Fatigue-Short Form 7a), Short Inflammatory Bowel Disease Questionnaire, IBD Disability Index for Self-Report, Treatment Burden Questionnaire, Treatment Satisfaction Questionnaire for Medication, and the Costs for Patients Questionnaire) are completed at baseline following randomisation, and three additional times (at 6, 12 and 24 months) during the 104-week follow-up period (table 2).

Endoscopic disease activity

Endoscopy results are collected if/when performed in the context of routine clinical care; no study-mandated endoscopies will be performed. The baseline qualifying endoscopy must be within 6 months prior to screening without interval treatment change. All endoscopy results are assessed by local readers, including confirmation of eligibility; all site investigators are trained to standardise endoscopy reading.

Participants randomised to switching advanced therapy to pursue a target of endoscopic/radiological remission typically undergo SOC endoscopy to assess resolution of inflammation approximately 6–9 months after the treatment switch, followed by optimisation of switched advanced therapy in case of failure to achieve endoscopic remission. Participants randomised to continuation of index advanced therapy undergo testing for resolution of inflammation at the discretion of the treating provider-participant team.

Completion of endoscopic disease activity assessments are at the discretion of the treating physician and are completed as per local SOC. The endoscopic/radiological remission target is typically assessed in both treatment

arms at approximately 26 weeks following study enrolment, with endoscopic remission defined for CD using the Simple Endoscopic Score for Crohn's Disease score <3 or Simplified Endoscopic Mucosal Assessment for Crohn's Disease score <2, or resolution of ulcers; and for UC using Mayo Endoscopic Score=0/1. Endoscopic response for CD is also measured, defined as >50% reduction from baseline.

Data collection and management

Data on effectiveness, treatment burden, and safety outcomes, including advanced therapy treatment details, use of IBD-related concomitant medications, laboratory and imaging disease-monitoring assessments, PRO assessments, safety assessments, and health-resource utilisation assessments, are collected from sites by trained site personnel and entered into the electronic data capture system (REDCap)⁴² database hosted at the Crohn's & Colitis Foundation. Routine clinical data are collected by the sites at baseline and then approximately every 6 months thereafter, up to a 104-week follow-up period.

In addition, self-reported data from the participants on primary effectiveness outcomes are captured in-between visits every 12 weeks in the patient-facing REDCap survey, through a short five-question survey eliciting clinical, functional status and healthcare utilisation (online supplemental table 4); additionally, at predetermined intervals, more detailed PRO questionnaires are also administered electronically through an email with a link. Paper versions of the questionnaires are available for participants who are unable to use the online versions.

A Data and Safety Monitoring Board has been established for the study and reviews the interim unblinded data every 6 months to monitor safety and effectiveness, and provides recommendations to ensure that participants are not exposed to undue risks. The investigators permit study-related monitoring and audits of the data collection process.

Statistical analyses

Sample size determination

The sample size estimation is based on a primary analysis of time to the first occurrence of a composite event, using methods described by Lachin.⁴³ Based on information from American Gastroenterological Association guidelines, the estimated 1- to 2-year risk of relapse and complications in asymptomatic patients with IBD with significant bowel inflammation is approximately 50%–60%.^{44 45}

The Patient Advisory Board deemed that to overcome their decisional conflict to justify switching advanced therapies, the expected benefit with treatment switching should be a 25%–50% lower risk of relapse and unplanned healthcare utilisation. Hence, with a 104-week control event rate and 5% dropout rate every 6 months, to detect a 36% (eg, the mid-point of the 25%–50% interval) lower risk of experiencing composite outcome measure with intervention for 80% power and two-sided significance level of 5%, assuming a recruitment period of 54 weeks

and a total study time of 104 weeks, a total sample size of ~250 participants (randomised 1:1 to intervention and control) would be required. This sample size will provide >80% power to detect a moderate effect size (mean difference divided by SD) of 0.30 in continuous effectiveness outcome measures, which is above the minimal clinically important difference for these outcomes.

Medication switch is assessed to evaluate if the switch is concordant with clinical guidelines, and sensitivity analyses are conducted per protocol, such that no adjustments are made to, after initial randomisation, exclude participants who were switched to an alternative advanced therapy from the continuation arm at their providers' discretion in the absence of patient-related symptoms, as well as exclude patients in whom a second advanced therapy is added after initial randomisation in either arm. Descriptive analyses of reasons for medication switching that are not concordant with clinical guidelines are performed.

Analyses

The primary analysis is based on all participants who are randomised to a strategy of switching to an alternative advanced therapy to treat to a target of endoscopic remission versus continuing index therapy (full analysis set), in an intention-to-treat (ITT) principle. Participants randomised to switching advanced therapies who are unable to switch due to insurance denial will be analysed in the treatment group they were assigned to, in ITT analysis.

Secondary analyses will be conducted based on the modified ITT (mITT) analysis set (participants randomised to switching who receive ≥ 1 dose of the alternative advanced therapy). In both the primary and secondary datasets, participants who drop out after randomisation (in 'full analysis/ITT set') and receipt of the first dose of alternative advanced therapy (in 'mITT analysis set') will be considered censored. Participants randomised to switching advanced therapies who are unable to switch will also be considered censored, in mITT analysis.

Participants will also be analysed in a per-protocol analysis (participants who continue in the group they were allocated to after randomisation, throughout the study until the study end or until they meet the primary outcome, whichever comes first). The per-protocol analysis will exclude participants who were switched to an alternative advanced therapy from the continuation arm at their providers' discretion in the absence of patient-related symptoms.

Outcome analysis

For the primary composite outcome, time to treatment failure, between-group comparisons will use the Mantel log-rank test, with magnitudes of treatment quantified by HRs (95% CI) obtained from Cox proportional hazard regression analysis. Alternatively, win probability by treatment will also be estimated to account for outcome hierarchy of surgery, hospitalisation, structural complication,

severe symptoms and AEs, using methods similar to those in cardiovascular research literature, which have applicability for randomised trials in other therapeutic areas.⁴⁶ Win probability quantifies the effect size as the probability that a participant in the switching arm will have a better change score (or win) over a participant in the continuation arm. For secondary outcomes, time-to-event outcomes will be analysed with Cox proportional hazard regression, binary outcomes will be analysed with the modified Poisson regression,⁴⁷ and continuous outcomes will be analysed with linear mixed effects model for repeated measures.⁴⁸ These analyses will be repeated in the per-protocol analysis set. All analyses will be adjusted for stratification factors used in the randomisation. Non-parametric methods will also be used to estimate win probabilities by treatment for binary, ordinal and continuous data.⁴⁹

Safety analysis

Safety data for this study includes serious infections, defined as infections requiring hospitalisation and/or intravenous antibiotics. The primary safety outcome variable is the number of serious infections (eg, infections requiring hospitalisation and/or intravenous antibiotics) over 104 weeks of follow-up, analysed using the negative binomial regression. Hospitalisation due to complications of testing/monitoring and incidental cancer on advanced therapies will also be captured. Comparison of treatment effects will be conducted using the extended modified Poisson regression.⁵⁰ Data on serious AEs (SAEs) will be presented by treatment group. Descriptive statistics will be presented, and no formal statistical tests will be performed because of data sparsity. SAEs will be summarised by the number and percentage of participants experiencing any SAEs, and any AEs leading to study drug discontinuation. Safety data will be presented by the treatment group.

ETHICS AND DISSEMINATION

The ethical considerations for such a study are important.⁵¹ The risks of treatments as identified in pivotal trials and in real-world experience are weighed against the risks of disease that is inadequately controlled, either because of subclinical inflammation that results in progressive complications of relapse or tissue damage, or if a switched therapy results in less efficacy than the index treatment or if it results in a drug-related or disease-related AE. Given that the risks of 'silent' inflammation and the benefits of mucosal healing which are associated with improved short- and longer-term outcomes, QUOTIENT was designed with this in mind, and with confidence that there is indeed clinical equipoise in this approach. The separate issue of patient autonomy and the discussions with patients about why a treatment change when they are feeling well may be warranted. As the field of IBD has moved to disease

monitoring strategies that are available and visible to patients, the acceptability of treatment changes based on objective measures of disease activity is evolving. This study will add significantly to that conversation and inform patient educational materials as well. Results will be disseminated at scientific congresses and in peer-reviewed journals.

As of 19 December 2024, the current Institutional Review Board (IRB) approvals are Pro00077486; Pro00061437; STUDY00002062; 22-004171; i22-01269; IRB22-0890; IRB_00154397; 2000032384; SHIRB#2022.095-2; STUDY00007146; MMC#2024-18; REB#125290; 17784; Pro00142214; and 20240660-01H. Additional IRB approval information is available in online supplemental table 5.

DISCUSSION

There is increasing emphasis on using the treat-to-target strategy to improve bowel healing and patient outcomes. Most providers and patients are comfortable with optimisation of an existing advanced therapy in efforts to treat-to-target; however, whether treatment should be switched to an alternative advanced therapy in pursuit of a treatment target of endoscopic/radiological remission presents clinical equipoise. The QUOTIENT study is designed to address this knowledge gap comparing two treatment strategies of treat-to-target in patients with IBD in symptomatic remission who have significant ongoing bowel inflammation, detectable by endoscopy/radiology.

No prior studies have addressed this specific clinical dilemma. In a cluster randomised trial, the Randomised Evaluation of an Algorithm for Crohn's Treatment Study-2 (REACT-2), Jairath and colleagues compared the effectiveness of an enhanced-care algorithm incorporating early combination therapy and treatment intensification targeting absence of ulcers, to a step-care approach targeting clinical remission.⁵² In REACT-2, the investigators observed no difference in the risk of CD-related complications between treating to target of symptomatic remission versus treating to target of endoscopic remission. However, in a subset of patients with known active disease (known ulcers or elevated C reactive protein), treat-to-target of endoscopic remission decreased the risk of complications by 25%–30%, compared with a step-care approach. In contrast to prior trials like CALM and REACT-2, the patient population in QUOTIENT is asymptomatic with evidence of active inflammation on an advanced therapy. Moreover, the treatment strategy in QUOTIENT involves a potential 'high-risk' intervention, with switching to an alternative advanced therapy in patients who are feeling well (asymptomatic) on their existing advanced therapy.

Since QUOTIENT is a pragmatic trial being conducted in usual clinical practice, there are inherent differences from an explanatory trial. First, the primary and secondary outcomes are focused on patient-centred outcomes such as symptomatic remission, quality of

life, treatment burden, and satisfaction. Achievement of endoscopic/radiological remission is not an outcome of the study, though this will be captured if endoscopy/radiology is being performed in routine care. Second, as a treatment strategy study, there is no mandate for a strict treatment algorithm regarding which patients receiving advanced therapies (who are randomised to switching) should be switched.⁵³ In real-world settings, these decisions are variable, highly individual, and driven by the providers' interpretation of evidence and experience on comparative effectiveness of different advanced therapies, patients' preference for specific advanced therapies, and insurance coverage of different alternative advanced therapies. A limitation of this study is being underpowered for subgroup analyses, and several of those findings may be hypothesis-generating. In addition, medication adherence is measured using the participants' medical records, which may not be as reliable as using a self-report adherence scale for self-administered therapies.

In summary, this pragmatic trial compares two treatment strategies of treat-to-target in patients with IBD who are asymptomatic but have evidence of ongoing significant bowel inflammation despite being optimised on their current therapy.

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