Recommendations to Standardize the Conduct of Clinical Trials Evaluating Novel Therapies for Perianal Fistulizing Crohn's Disease

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BACKGROUND & AIMS: **Perianal fistulizing Crohn's disease (PFCD) is a potentially debilitating condition with few systematically evaluated treatment options. We aimed to develop expert recommendations to standardize study design and conduct of randomized controlled trials of medical therapy for patients with PFCD.**

METHODS: **We utilized a RAND/UCLA appropriateness method to develop a framework for conducting randomized controlled trials of medical therapy in PFCD. An expert international panel of 15 gastroenterologists, radiologists, and colorectal surgeons rated the appropriateness of survey**

*Authors share co-first authorship. §Authors share co-senior authorship.

Abbreviations used in this paper: AGA, American Gastroenterological Association; CAF-QoL, Crohn's Anal Fistula Quality of Life; CD, Crohn's disease; EUA, examination under anesthesia; MAGNIFI-CD, Magnetic Resonance Novel Index for Fistula Imaging in CD; MRI, magnetic resonance imaging; mVAI, modified Van Assche Index; PDAI, Perianal Disease Activity Index; PFCD, perianal fistulizing Crohn's disease; PRO, patient-reported outcome; QoL, quality of life; RAM, RAND/UCLA appropriateness method; RCT, randomized controlled trial; TNF, tumor necrosis factor; VAI, Van Assche Index.

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statements in 2 rounds of voting. Median scores of 1 to ≤3.5, >3.5 to <6.5 and ≥6.5 to 9 on survey statements reflected panel ratings of inappropriate, uncertain, and appropriate, respectively.

RESULTS: **A total of 292 statements were rated in the final survey, of which 156 (53.4%) were considered appropriate and formed the basis for recommendations. Trial eligibility should be decided based on both clinical and radiological criteria and patients should exhibit a minimum degree of clinical disease activity at screening. The primary efficacy outcome should be either a co-primary or composite endpoint of clinical and radiological assessments depending on treatment phase (induction vs maintenance), recognizing that clinical endpoints are meaningful for patients and radiological outcomes are essential to objectively capture the burden of disease. There was uncertainty regarding definition of radiological remission, but presence of a perianal fluid collection of any size was considered inconsistent with radiologic remission.**

CONCLUSIONS: **These recommendations may help to standardize study design and conduct and foster clinical development of much needed therapies for this debilitating manifestation of Crohn's disease.**

Keywords: Fistula; Crohn's Disease; Inflammatory Bowel Disease; Clinical Trial.

Introduction

Perianal fistula is the most common fistulizing complication of Crohn's disease (CD).[1] Anatomically, these fistulas represent a chronic tract of granulation tissue that connects rectal or anal epithelium to perianal skin, which is often preceded by perianal abscess requiring surgical drainage with or without seton placement.[2] Perianal fistulizing Crohn's disease (PFCD) is often challenging to resolve and is associated with considerable morbidity. It impairs social functioning, frequently leads to depression, anxiety, psychological stress, and sexual dysfunction, and exerts an overall substantial negative impact on quality of life (QoL).[3] Approximately 20% of patients with CD develop perianal fistula within the first 10 years of diagnosis.[4,5] Considerably higher direct health care utilization is observed for PFCD compared with CD without perianal involvement.[6]

Successful management of PFCD requires multidisciplinary collaboration between surgeons, radiologists, and gastroenterologists and integration of both medical and surgical interventions. Initial treatment of PFCD typically requires examination under anesthesia (EUA) with seton placement to drain perianal abscess and antibiotics recommended to control infection.[7] Once abscess(es) are adequately drained, advanced therapies can be initiated to control the inflammatory burden. Infliximab, a tumor necrosis factor (TNF) antagonist, is the only pharmacological agent whose efficacy and safety for treatment of fistulizing CD has been systematically evaluated in a phase 3 randomized controlled trial (RCT).[8,9] Evidence for the efficacy of other classes of advanced therapies for PFCD is predominantly derived from observational studies and subgroup analysis of RCTs that were designed to assess the efficacy of these therapies for the treatment of luminal CD.[10] Well-designed studies evaluating the efficacy and safety of existing and novel advanced therapies are a substantial unmet need for PFCD.

Patients with PFCD can exhibit significant variability in their anatomical configuration and involvement of the anal sphincter complex, disease activity, and associated complications. There are several systems for classifying perianal fistula,[11] including the widely used American Gastroenterological Association (AGA) classification,[2] which categorizes perianal fistula as simple or complex. The recently proposed TOpCLASS classification system categorizes patients based on disease severity and treatment outcomes taking into consideration both patient and clinician goals.[12] Similarly, several indices exist for assessing perianal disease and treatment responses, including 3 patient-reported outcome (PRO) measures, 1 clinical index (Perianal Disease Activity Index [PDAI]), 8 magnetic resonance imaging (MRI)–based indices, and 2 ultrasound-based indices.[13] There are no universally accepted standardized criteria for patient eligibility or outcome assessment in PFCD trials, which further challenge both the design and conduct of these studies. Given the unmet need to standardize design and conduct of PFCD trials, we undertook this RAND/UCLA appropriateness method (RAM) study to provide a framework for conducting RCTs of medical therapies for PFCD.

Materials and Methods

RAM Process

An international panel of 15 experts with clinical and research expertise in PFCD (8 gastroenterologists, 4 radiologists specialized in inflammatory bowel disease, and 3 colorectal surgeons) from 8 countries (United States of America, Canada, Spain, Italy, United Kingdom, the Netherlands, Brazil, and Australia) actively leading and/or designing CD clinical trials were chosen to

participate. The final panel was selected by C.M. and V.J. after reviewing a list of eligible experts. All panelists were provided with 2 systematic reviews[10,13] that formed the evidence base for a subsequent modified RAM process that assessed the face validity of statements relevant to clinical trial design and conduct, including patient eligibility, disease activity indices, and definitions of treatment response. One of the two systematic reviews provided up-to-date evidence on clinical trials evaluating the efficacy of pharmacotherapies in PFCD,[10] while the other summarized available disease activity indices for PFCD.[13] RAM employs a widely accepted, iterative, modified Delphi panel approach to combine the best available evidence with expert experience without requiring consensus, recognizing there may be areas of uncertainty. A preliminary list of statements was reviewed by the panelists during an online meeting (September 2023). Statements were subsequently added or revised based on initial panel feedback. Panelists rated the appropriateness of the modified statements on a Likert scale ranging from 1 (extremely inappropriate) to 9 (extremely appropriate) in an online survey. Given the interdisciplinary nature of the panel and survey content, panelists were advised to use their own judgement when rating statements that were potentially outside their expertise.

Results of the first voting round were discussed during a moderated video conference (July 2024), that focused on statements rated as "uncertain" and those for which there was disagreement. Uncertain statements were modified, and new statements were added to a second survey which was subsequently distributed to the panelists. Final survey results were discussed in October 2024. All survey responses were anonymous.

Statistical Analysis

Survey statements were classified as inappropriate, uncertain, or appropriate based on the median panel rating and degree of panel disagreement (inappropriate, median 1–3 without disagreement; uncertain, median 4–6 or any median rating with disagreement; appropriate, median 7–9 without disagreement). Two methods for assessing disagreement were used. The first ("classic") method of defining disagreement was based on at least 3 panelists voting in each extreme range of the Likert scale (1–3 and 7–9). The second method was based on a disagreement index of >1, calculated as the ratio between the interpercentile range and interpercentile range adjusted for symmetry.

Results

Overall Rating of Statements

Of 263 statements in the first survey, 111 were rated appropriate, 142 were uncertain, and 10 were inappropriate. The second-round survey included 292 statements, of which 156 were rated appropriate, 125 were uncertain, and 11 were inappropriate (Supplemental Tables 1–3). Recommendations for the conduct of PFCD trials based on definitively appropriate and inappropriate statements after 2 rounds of voting are summarized in Table 1 and detailed subsequently.

What You Need to Know

Background

Perianal fistulizing Crohn's disease (PFCD) is a potentially debilitating condition with limited treatment options. Drug development is hampered by substantial uncertainty regarding the design and conduct of PFCD clinical trials.

Findings

This study utilized a RAND/UCLA appropriateness method process to provide expert recommendations on study design, eligibility criteria, methods for assessing disease activity, and study endpoints in PFCD clinical trials.

Implications for patient care

Safe and effective therapies are urgently needed for PFCD. These recommendations may encourage and improve the development of treatments and approaches for this indication.

Recommendations on Eligibility of Patients for PFCD Clinical Trials

Patients with at least 1 CD-related perianal fistula actively draining for a minimum of 4 to 12 weeks should be eligible for inclusion in PFCD clinical trials. Simple and complex fistulas are appropriate for inclusion. PFCD may be classified according to either the AGA's Medical Position Statement on Perianal Crohn's Disease[2] or criteria proposed by Geldof et al (TOpCLASS classification).[14] There should be no limit to the number of internal or external openings for patient eligibility, as the number of openings may not correlate with fistula tract(s) anatomical configuration. Radiological and surgical (eg, EUA) assessment is appropriate for evaluating internal openings whereas clinical, radiological, or surgical assessment is appropriate for evaluating external openings, given that they may be difficult to fully appreciate with a single modality. Patients with undrained fluid collections or abscesses measuring >2 cm between inside walls in at least 2 dimensions and excluding solid components should be considered ineligible for study inclusion. Abscess drainage should be conducted during screening (see the following).

Trial eligibility should be based on both clinical and radiological disease activity criteria, rather than either criterion alone. Patients should exhibit a minimum

Table 1. Recommendations for Eligibility, Design, Outcome Measures, and Conduct of Clinical Trials in Perianal Fistulizing Crohn's Disease Based on RAM Outcomes

Inclusion and exclusion criteria
1. To be eligible for inclusion in PFCD trials of medical therapy, patients should have at least 1 perianal fistula that has been actively draining prior to the screening for at least 4-12 weeks
2. Patient eligibility for inclusion in PFCD trials of medical therapy should be based upon a combination of clinical and imaging criteria
3. To be eligible for inclusion in PFCD trials of medical therapy, patients should have a PDAI score >5
4. Patients with concurrent luminal CD irrespective of activity (except for those with Crohn's Disease Activity Index or Harvey-Bradshaw Index scores >450 or >16, respectively) or location should be eligible for inclusion in PFCD trials of medical therapy
5. To be eligible for inclusion in PFCD trials of medical therapy, patients should exhibit at least a minimum degree of disease burden evaluated using the CAF-QoL
6. Endoscopically active proctitis in patients with PFCD should be defined by the presence of rectal ulcers or anal ulcers >0.5 cm or any endoscopic lesion in the anus or rectum that would be included in scoring of the SES-CD (SES-CD ≥ 4)
7. Patients with passable anal or rectal stenosis on digital examination should be eligible for inclusion in PFCD trials of medical therapy
8. Patients with any prior medical therapy including those with demonstrated failure of TNF antagonists or antibiotics or allogeneic stem cells should be eligible for inclusion in PFCD trials of medical therapy
9. Patients should be ineligible for inclusion in PFCD trials of medical therapy if they have an undrained fluid collection or abscess of size >2 cm (measured using the inside walls, only the fluid component, excluding any solid components)
Trial design and conduct
1. Trial participants should be stratified based on prior history of perianal surgery except drainage or seton placement, presence of endoscopically active proctitis, previous failure of TNF antagonists for PFCD, and concomitant TNF antagonist therapy for luminal disease at randomization
2. During screening for inclusion in PFCD trials of medical therapy, patients should undergo abscess drainage, seton placement, and fistula tract curettage prior to randomization as indicated
3. For patients with setons in PFCD trials of medical therapy, timing of seton removal should be determined relative to the timing for administration of investigational treatment administration or assessment of the primary endpoint
4. After investigational treatment administration in PFCD trials of medical therapy, patients should receive permitted antibiotics for no more than 2 weeks
5. In PFCD trials of medical therapy, patients not receiving antibiotics at baseline may receive a rescue course of antibiotics during the clinical trial
Endpoints and outcome measures
1. The primary efficacy outcome in PFCD trials of medical therapy should be assessed at 12–24 weeks for induction trials and 44–66 weeks for maintenance trials with responder re-randomization design
2. The primary efficacy outcome in PFCD induction and maintenance trials of medical therapy should be based on co-primary or composite endpoints comprised of clinical (or patient reported) and radiologic assessments
3. In PFCD trials of medical therapy, treatment failure should be defined as: new onset perianal abscess; requirement for seton drainage; more than 1 rescue antibiotic course; surgical drainage, any surgical intervention for PFCD; rescue biologic therapy for PFCD; new appearance of fluid collection compared with baseline on radiologic imaging; reopening of external openings with active drainage; or development of new fistula on imaging
4. Clinical fistula remission should be defined as absence of fistula drainage with gentle finger compression, or closure of all draining external fistula openings compared with baseline
5. Clinical fistula response should be defined as a 50% reduction in fistula drainage from baseline or 50% reduction in PDAI
6. Radiologic disease activity should be assessed at baseline and follow up in PFCD trials of medical therapy with pelvic magnetic resonance imaging
7. Evaluation of radiologic disease activity should include assessment of the size of the fluid collection, fistula volume, fistula tract fibrosis, and employ the MAGNIFI-CD, the Van Assche, or the modified Van Assche indices
8. Radiological response should be defined as ≥50% improvement in the MAGNIFI-CD, the Van Assche Index, or the modified Van Assche Index
9. A PRO measure should be evaluated at baseline and follow-up in PFCD trials of medical therapy
10. A PRO measure of PFCD should include assessment of severity of fistula drainage and perianal pain; health-related quality of life using the CAF-QoL; and incontinence
11. The presence of a perianal fluid collection of any size is inconsistent with radiologic remission

CAF-QoL, Crohn's Anal Fistula Quality of Life; CD, Crohn's disease; PDAI, Perianal Disease Activity Index; PFCD, perianal fistulizing Crohn's disease; PRO, patient-reported outcome; RAM, RAND/UCLA appropriateness method; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor.

degree of clinical disease activity (PDAI >5) and disease burden (evaluated with the Crohn's Anal Fistula Quality of Life [CAF-QoL]). However, the panelists acknowledged that the evidence to support a specific PDAI threshold for eligibility is lacking. Flexible sigmoidoscopy or ileocolonoscopy should be performed at screening, and luminal disease should generally not preclude patient eligibility. Patients with inactive or concurrently active luminal CD should be eligible for inclusion regardless of disease location, although eligibility should be based on the therapy's anticipated mechanism of action and whether it would also be effective for luminal disease. Endoscopically active proctitis should be defined as the presence of rectal or

anal ulcers >0.5 cm or any endoscopic lesion in the rectum or anus resulting in a Simple Endoscopic Score for Crohn's Disease ≥4 when assessed in rectum and anal canal, and these patients should also be eligible for inclusion in PFCD trials. The presence of severe luminal disease (Crohn's Disease Activity Index >450 or Harvey-Bradshaw Index >16) should be an exclusion criterion. Patients with passable anal or rectal stenosis on digital examination are also eligible; however, those with impassable anal or rectal stenosis should be excluded. There was uncertainty regarding inclusion of patients with anovaginal/rectovaginal fistulas and patients with diverting stoma as these patient groups are considered unique and difficult to evaluate.

Patients with a history of prior medical therapy should be eligible for inclusion, recognizing the high burden of unmet medical needs in patients with prior treatment failure of TNF antagonists, antibiotics, allogeneic stem cells, or attempts at surgical fistula closure.

Recommendations on Design of PFCD Clinical Trials

An induction trial with re-randomization of responders in maintenance or a treat-through design is considered appropriate, whereas the appropriateness of a standalone induction trial is uncertain. The induction phase should range from 12 to 20 weeks, and a duration of at least 40 weeks is appropriate for the maintenance phase in a re-randomization design. A duration of at least 40 weeks is appropriate for treat-through trials.

Appropriate stratification covariables include prior history of perianal surgery (except drainage or seton placement), endoscopically active proctitis, previous failure of TNF antagonist(s) for PFCD, or concomitant TNF antagonist therapy for luminal disease at randomization. Stratification by previous failure of antibiotics for PFCD, the presence of distal rectal or anal canal stenosis, or anal ulceration alone is uncertain.

During screening, patients should undergo abscess drainage, seton placement, and fistula tract curettage if indicated prior to randomization. Timing of seton removal was a topic of considerable discussion. Although evidence for timing for seton removal is lacking, the panel emphasized avoiding removal prematurely and risking perianal complications, or too late when complete tract healing becomes unlikely due to epithelialization. In general, the timing for seton removal should be considered with regard to the timing of investigational treatment administration and primary endpoint assessment. Removal of setons within 4 weeks of investigational treatment administration may be considered appropriate, and there is uncertainty regarding removal of setons after 4 weeks.

Patients should receive permitted antibiotics for no more than 2 weeks after investigational treatment administration. Although the panel was uncertain about administering a mandatory initial course of antibiotics, a rescue course of antibiotics during the trial is appropriate for patients not receiving antibiotics at screening.

Recommendations for Endpoints and Outcomes in PFCD Clinical Trials

In trials with responder re-randomization, the primary efficacy outcomes should be assessed at 12–24 weeks during induction and 44–66 weeks during maintenance, whereas outcomes in a treat-through design trial should be assessed at 52 weeks. Across both induction and maintenance endpoints, therapeutic response should be determined based on (1) a clinical or PRO measure and (2) a radiologic measure in either co-primary or composite configurations.

The PDAI, Crohn's Disease Activity Index, and a PRO should be assessed at baseline and follow-up. PROs for PFCD should include assessment of severity of fistula drainage and perianal pain, incontinence, and health-related QoL (CAF-QoL). Appropriate fistula outcomes may include remission/response, complete/partial healing, and complete/partial closure. Clinical fistula remission and response should be included in the primary endpoint of induction and maintenance trials and be defined as absence of fistula drainage with gentle finger compression or closure of all draining external fistula openings compared with baseline (fistula remission), and at least 50% reduction in fistula drainage compared with baseline or 50% reduction in PDAI (fistula response). Appropriate thresholds for the PDAI score to define fistula remission remain uncertain.

Radiologic endpoints should also be included in the primary outcome of both induction and maintenance trials and should be assessed at baseline and follow-up using pelvic MRI. Computed tomography and endoanal ultrasound are not appropriate for this purpose. Radiologic disease activity assessments should include the size of fluid collection(s), fistula volume, fistula tract fibrosis, and using the Magnetic Resonance Novel Index for Fistula Imaging in CD (MAGNIFI-CD), Van Assche Index (VAI), or modified VAI (mVAI). Although a 50% reduction in the MAGNIFI-CD compared with baseline or either the original or mVAI may be used to define radiologic response, uncertainty exists regarding an appropriate threshold for defining radiologic remission with these indices. However, the presence of a perianal fluid collection of any size is inconsistent with radiologic remission.

The definition of treatment failure should include new onset perianal abscess; requirement for seton drainage, more than 1 rescue antibiotic course, surgical drainage or any surgical intervention for PFCD, rescue biologic therapy; the new appearance of fluid collection compared with baseline on radiologic imaging; reopening of external openings with active drainage; or

development of new fistula on imaging. However, it was acknowledged that not all surgical interventions necessarily represent treatment failure. Procedures such as repeat EUA for repair or seton exchange, in particular, may be part of ongoing management, rather than an indication of medication failure. In our recommendations, treatment failure primarily refers to the need for additional interventions reflecting inadequate response.

Discussion

Perianal fistulas impose significant burdens to both patients with CD and healthcare systems.[3,6] The absence of standardized approaches to clinical trial design and conduct poses a major barrier to the development of new therapies for PFCD. Recommendations developed using a RAM process in this study will provide a conceptual framework for the design, conduct, and assessment of disease activity in PFCD trials.

The considerable variability of perianal fistula tract anatomy and associated complications affects disease evaluation and treatment outcomes.[15] The panel discussed the use of AGA[2] or TOpCLASS classifications[12,14] to define eligibility criteria and describe study populations, although neither system is ideal and serve distinct purposes. For example, the AGA definition of complex perianal fistulas (high-origin fistula or fistula with multiple external openings, or associated features such as perianal abscess, rectovaginal fistula, anorectal stricture, or proctitis) is very broad, lacks specificity, and could result in inclusion of highly heterogeneous PFCD populations. The TOpCLASS classification incorporates patient symptoms and treatment goals and was viewed as more suitable for clinical management of PFCD. Although the Parks[16] and St. James' University Hospital classifications[17] provide surgical- and MRI-derived anatomical descriptions of fistula tracts in relation to the anal sphincter complex, these systems lack utility to estimate disease activity or severity, associated complications, or prognostic outcomes.

Eligibility should be based on both clinical and radiological assessments. Although EUA is considered the reference standard for fistula assessment,[18] it may not fully capture disease features such as tract inflammation or side branching. Similarly, MRI may miss internal openings or underestimate inflammation in patients with setons. Thresholds for collection size on MRI for determining patient eligibility were thoroughly discussed. Although a 2 cm threshold was acknowledged as arbitrary, it was nevertheless viewed as clinically acceptable for determining eligibility and has been used historically in previous PFCD studies.[19] Collections smaller than 2 cm are generally not amenable to drainage and often respond to antibiotic therapy alone. Immunosuppressive therapy was also considered safe for these patients.

PFCD is frequently associated with concurrent active intestinal inflammation.[20] Luminal disease activity and PFCD may not respond similarly to medical therapies, which can interfere with outcome assessments in clinical trials, particularly QoL outcomes. Furthermore, approximately half of patients with PFCD will have associated proctitis.[21] Accordingly, all patients with PFCD were considered appropriate by the panel for inclusion, irrespective of luminal disease activity and location, except in cases of very severe disease. Active luminal disease, particularly proctitis, is associated with lower rates of fistula healing, is associated with increased need for diversion surgery, and may influence fistula response to medical therapy.[22] These factors justified the inclusion of endoscopically active proctitis as a stratification factor. However, the panel was uncertain regarding the inclusion of passable anal or rectal stenosis in the definition of endoscopically active proctitis, and stratifying patients with anal/rectal stenosis at randomization. While the panel acknowledged that a distal stenosis may worsen PFCD outcomes, interobserver reliability for defining a passable stenosis is unclear and clinical practice varies significantly. Practitioners may perform digital dilation on rectal examination, endoscopic balloon dilation, or use smaller diameter colonoscopes.

Both re-randomization and treat-through designs were appropriate, although a treat-through design was considered generally preferable due to slower treatment responses typically observed with PFCD compared with luminal CD. Excluding patients with adequate induction response from the maintenance phase in studies with re-randomization design was deemed inappropriate. In a trial with a re-randomization design, the induction phase should be sufficiently long (ie, at least 12 weeks) to provide a reasonable time for fistula healing based on the half-life of the investigational therapy and seton management.

Surgical curettage and seton placement were appropriate prerandomization procedures especially for patients with drainable perianal abscesses. The indication for surgical intervention prior to medical therapy varies between centers and in clinical practice, and not all patients require surgical curettage or seton insertion prior to initiating medical therapy. However careful surgical curettage may lead to better fistula outcomes in controlled trials, as was observed in the Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's Disease (ADMIRE-CD) and ADMIRE-CD-II clinical trials evaluating allogeneic adipose-derived mesenchymal stem cells vs placebo in patients with PFCD.[19,23] Surgical curettage and seton placement 2–3 weeks prior to treatment in the placebo arms of these trials resulted in high response rates.[19] However, evidence supporting benefit on seton insertion prior to medical therapy is conflicting. A recent systematic review and meta-analysis found superior outcomes with the combination of anti-TNF therapy and surgery (primarily EUA and seton placement).[24] Conversely, a

multicenter observational study involving patients with perianal CD receiving anti-TNF therapy evaluated outcomes in participants stratified by seton placement.[25] The authors found no significant difference in major fistula-related adverse outcomes or fistula remission rates between the 2 groups at 6 and 12 months. However, among patients with a perianal abscess, seton insertion resulted in fewer adverse outcomes, although this difference did not reach statistical significance. Therefore, curettage and seton placement may be considered during the trial screening period and factored into sample size calculations.

The timing for seton removal was also extensively discussed. Although seton removal is essential to fistula closure, the timing for removal should account for the mechanism of action of the investigational therapy, and the timing for therapy administration and outcome assessment, similar to steroid tapering protocols in luminal CD trials. Regrettably, no robust evidence exists to guide these decisions that remain a research priority. In the previously conducted observational studies, the timing varied from 4 to 27 weeks.[26,27] However, in the large multicenter Treatment of Perianal Fistulas in Crohn's Disease, Seton Versus Anti-TNF Versus Surgical Closure Following Anti-TNF (PISA) II trial comparing effectiveness of surgical closure in combination with short term anti-TNF therapy vs anti-TNF therapy alone,[28] setons were removed 6 weeks after insertion in the anti-TNF group. Generally, it is recommended to keep setons in place until completion of induction therapy.[29] Although panelists rated removal of setons within 4 weeks of intervention as appropriate, they acknowledged that this cutoff was arbitrary and not supported by strong evidence. During discussion, it was also noted that seton removal beyond 4 weeks could be reasonable for interventions with slower onsets of action.

Use of antibiotics during induction was another point of discussion. The panel agreed that there are data to support the use of antibiotics for improving induction outcomes in perianal CD. For example, data from the Aadalimumab for the treatment of perianal fistulas in Crohn's disease (ADAFI) trial that demonstrated the combination of adalimumab and ciprofloxacin during induction therapy improved the rate of 50% reduction in fistula drainage at 12 weeks (albeit not at 24 weeks) is supportive for using antibiotics in PFCD.[30] However, it was acknowledged that the context for using antibiotics should be carefully considered because of potential adverse effects due to antibiotic exposure (including but not limited to *Clostridioides difficile* infection in a high-risk inflammatory bowel disease population), and choice of antibiotic therapy might vary based on regional differences in exposures and resistance patterns. The panel discussed that the requirement for antibiotics may vary based on the patient, the presentation, and the phenotype of perianal involvement. Accordingly, there was uncertainty whether every patient in a PFCD trial would require antibiotic induction therapy.

According to the panel, clinical fistula remission may be defined as absence of fistula drainage with gentle finger compression, or closure of all draining external fistula openings compared with baseline. Although the finger compression test for assessment of fistula closure is subjective and has not been validated, it has been widely used for this purpose since it was first described in an RCT of infliximab in PFCD.[8] There was uncertainty regarding the definition of clinical fistula response, as reflected in the variability of the definition of this measure across studies (eg, 50% reduction in fistula drainage vs 50% reduction in the number of draining fistulas). A 50% reduction in fistula drainage was considered acceptable but a 50% reduction in PDAI was regarded as a potentially more objective measure compared with clinical examination alone.

Similarly, there was uncertainty about definitions of radiological outcomes and thresholds for disease activity measured by various MRI indices (VAI, mVAI, and MAGNIFI-CD). There are no validated definitions for radiological fistula outcomes or index thresholds to define radiological remission. In the recent TOpCLASS Delphi consensus, radiological improvement of a fistula was defined by the presence of at least 1 of 6 essential criteria (increasing fibrosis of fistula tract or a reduction in T2-weighted fistula tract hyperintensity, fistula tract diameter, fistula tract length, size of previous abscess, or postcontrast T1 fistula tract hyperintensity). Radiological healing was defined as the absence of a T2-weighted hyperintense signal, and a completely fibrotic fistula tract and/or the absence of contrast enhancement.[31] Definitions based on MRI indices were also proposed where radiological improvement was defined as a 50% index (MAGNIFI-CD, mVAI, VAI, and pediatric MRI–based perianal CD) improvement from baseline and radiological healing was a score of zero on any of these indices. Validation of these definitions in prospective studies to inform design and conduct of future clinical trials is needed.

PROs are recognized as essential measures to capture the patients' perspective. Consequently, regulatory authorities recommend their inclusion in IBD trials. However, validated and universally accepted PROs specific to PFCD are generally lacking. The CAF-QoL is the only PFCD-specific QoL instrument developed with rigorous methodology but needs further validation.[32] Other PRO measures such as the Inflammatory Bowel Disease Questionnaire and the EQ-5D-5L are not specific for PFCD and have not been adequately investigated in this population. Perianal symptoms such as pain, discharge, and incontinence should also be assessed in future studies.

Recommendations from this RAM process provide a standardized framework for trial design and conduct, including eligibility criteria, use of composite endpoints, PROs, and timing of outcome assessment, which have greatly varied across studies to date.[10] Historically, most studies have included endpoints based on clinical

assessment and the PDAI. Large-scale studies dedicated to evaluation of therapies for the treatment of PFCD are limited. Notably, an ongoing phase 3, placebo-controlled randomized clinical trial exploring the efficacy of guselkumab for the treatment of PFCD (NCT05347095) incorporated a composite endpoint of clinical and radiological remission (defined as complete [100%] closure of all external openings without development of new fistulas or abscesses and without drainage by existing external openings [spontaneously or after gentle finger compression], and absence of collections >2 cm of the perianal fistulas in at least 2 of 3 dimensions as confirmed by a blinded central review of MRI images). This trial also incorporated change in MRI-based indices (MAGNIFI-CD) and PROs evaluating quality of life and disability as secondary endpoints. This ongoing trial and the recommendations from the current study represent important progress toward harmonizing outcome measures and improving the methodological quality of clinical trials for this challenging disease phenotype.

Our study has several notable strengths. We involved a diverse group of international experts with a broad range of perspectives and experience. Panel recommendations were derived from the most current and comprehensive evidence to ensure relevance and applicability.

We also acknowledge certain limitations. We did not include patient representatives in the panel to provide additional perspectives on PFCD trial design. Although patients were not part of the voting panel, PROs and QoL aspects were carefully considered in the formulation of the statements. We also specifically considered work from the ENiGMA collaborators[33] when developing statements related to QoL, and this foundational work included extensive feedback from patient participants. Both incontinence and QoL measures identified as important by patients in prior work were incorporated; functional disability from PFCD including outcomes such as sexual dysfunction require further validation as outcome measures for use in RCTs. The appropriateness of several statements remains uncertain especially timing of outcome assessment and seton removal, and definitions of radiological outcomes. Further research is needed to strengthen the evidence base for these important decisions and to explore the role of surgical interventions. Although rigorous methodology is used in the RAM process, panelists are not compelled to vote until a uniform consensus is forced. However, a RAM process allows a more nuanced exploration of expert opinion and can accommodate greater variability in perspectives, which we felt was necessary given existing data gaps in PFCD.

In conclusion, we developed recommendations to standardize study design and conduct, eligibility criteria, outcome measures, and disease activity assessment in PFCD RCTs. Future research should prioritize the validation of disease activity benchmarks using radiological indices for PFCD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.11.005.

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Data Availability

All data relevant to the study are included in the article or uploaded as Supplemental information.