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Developing a core outcome set for fistulising perianal Crohn's disease

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ABSTRACT

Objective Lack of standardised outcomes hampers effective analysis and comparison of data when comparing treatments in fistulising perianal Crohn's disease (pCD). Development of a standardised set of outcomes would resolve these issues. This study provides the definitive core outcome set (COS) for fistulising pCD.

Design Candidate outcomes were generated through a systematic review and patient interviews. Consensus was established via a three-round Delphi process using a 9-point Likert scale based on how important they felt it was in determining treatment success culminating in a final consensus meeting. Stakeholders were recruited nationally and grouped into three panels (surgeons and radiologists, gastroenterologists and IBD specialist nurses, and patients). Participants received feedback from *their panel* (in the second round) and *all participants* (in the third round) to allow refinement of their scores.

Results A total of 295 outcomes were identified from systematic reviews and interviews that were categorised into 92 domains. 187 stakeholders (response rate 78.5%) prioritised 49 outcomes through a three-round Delphi study. The final consensus meeting of 41 experts and patients generated agreement on an eight domain COS. The COS comprised three patient-reported outcome domains (quality of life, incontinence and a combined score of patient priorities) and five clinician-reported outcome domains (perianal disease activity, development of new perianal abscess/sepsis, new/recurrent fistula, unplanned surgery and faecal diversion).

Conclusion A fistulising pCD COS has been produced by all key stakeholders. Application of the COS will reduce heterogeneity in outcome reporting, thereby facilitating more meaningful comparisons between treatments, data synthesis and ultimately benefit patient care.

INTRODUCTION

The management of fistulising perianal Crohn's disease (pCD) remains challenging. Fistulas are often complex in nature, and recurrence after treatment is common. Perianal manifestations of Crohn's disease are recognised in the Montreal classification as a distinct phenotype¹ from luminal disease. Fistulising pCD is associated with significant morbidity and reduced quality of life.² The

Significance of this study

What is already known on this subject?

► There is heterogeneity in the outcome measures used in interventional studies in fistulising perianal Crohn's disease. This limits meta-analysis and other methods for comparing treatment options in this disease.

What are the new findings?

► The generation of a patient-centred core outcome set (COS) based on the principles set out by the Core Outcome Measures in Effectiveness Trials (COMET) initiative and using a Delphi consensus of stakeholders including patients and clinicians who regularly manage fistulising perianal Crohn's disease.

How might it impact on clinical practice in the foreseeable future?

► This COS will form the basis of outcome measurement in future interventional studies of fistulising perianal Crohn's disease.

established treatment pathway is multidisciplinary³ and involves management of proctitis and drainage of sepsis, prior to optimisation of medical treatment, usually with a combination of thiopurine and antitumour necrosis factor (TNF) therapies.⁴ Initial drainage of sepsis and placement of loose setons are the mainstay of surgical treatment, although reparative surgery aimed at fistula closure may be offered in selected patients, and defunctioning stoma or proctectomy may sometimes be required. Undrained ongoing perianal sepsis, injudicious surgery and recurrent perianal sepsis may all result in a poor functional outcome for the patient.

There has been significant recent innovation in managing fistulising pCD both in biological therapy with trials studying fistula healing as a primary outcome measure⁵ and in the introduction of novel, sphincter preserving techniques⁶⁻⁸ as well as modification of existing operations, such as the BioLIFT⁹ or LIFT-Plug.¹⁰ There are restrictions in the current literature that impair evidence synthesis and meta-analysis. One limitation is a lack of standardised outcome measurement, which hampers

effective analysis and comparison of techniques and leads to a high risk of reporting bias.¹¹ Most importantly, the currently used outcomes lack relevance to patients.

Measuring success or failure should not be determined by researchers alone, and the views of patients and other healthcare professionals involved in the care of patients with perianal Crohn's fistula must be considered. The Core Outcome Measures in Effectiveness Trials (COMET; www.comet-initiative.org/initiative) initiative has improved understanding of outcome reporting and standardised outcome reporting through the development of core outcome sets (COS). COSs are the minimum outcomes that should be reported in every study of a given condition.¹² They have usually been informed by a systematic review and developed through a Delphi consensus process with key stakeholders.

COS are not restrictive; triallists may choose to investigate other outcomes but should always include the COS as a minimum within their study design. New COS are increasingly being developed,¹³ and they are widely recognised in a number of specialties, such as rheumatology,¹⁴ paediatric surgery¹⁵ and colorectal surgery.¹⁶ Increasingly, funding bodies advocate the inclusion of COS within proposed trial methodology¹⁶ and uptake among triallists is increasing.¹⁷

The aim of this study was to develop a COS for fistulising pCD using Delphi methodology.

METHODS

Protocol registry

The development of this COS is based on the principles advised by the COMET initiative¹⁸ and reported in accordance with the Core Outcome Set-STAndards for Reporting (COS-STAR) Statement.¹⁹ This study has been registered with the COMET initiative (www.comet-initiative.org).

Scope

The scope of the COS is to include all medical treatments and surgical interventions used alone or in combination for adult patients with fistulising pCD. Most patients with Crohn's fistula will undergo both medical and surgical interventions and studies usually follow a combined multidisciplinary stepwise approach, even when this is not explicit. The multimodal approach is used irrespective of whether the treatment intention is to induce fistula healing or palliate symptoms. A COS describes *what* outcomes should be measured but does not stipulate *how* they should be measured. It can be used for all types of study design, including audit.

Overview

In phase 1, a long list of candidate outcomes that could be measured in fistulising pCD trials was identified, and outcomes were categorised into domains.

In phase 2, outcome domains were presented via a web-based Delphi system that was used to assess key stakeholders' views on the importance of each domain.

In phase 3, a consensus meeting with all stakeholders was used to finalise and ratify the COS.

Participants

Stakeholder representation was chosen to correlate with the clinical scenario since patients with perianal Crohn's fistulas are managed by multidisciplinary teams, including surgeons, gastroenterologists, radiologists and IBD specialist nurses. Inclusion

Box 1 Stakeholder groups demonstrating the three panels

Panel SuRa

- ▶ Colorectal surgeons (Su)
 - Association of Coloproctology of Great Britain and Ireland with a declared specialist interest in managing IBD.
- ▶ Radiologists (Ra)
 - British Society of Gastrointestinal and Abdominal Radiology.

Panel GaNu

- ▶ Gastroenterologists (Ga)
 - British Society of Gastroenterology IBD section.
- ▶ IBD specialist nurses (Nu)
 - Royal College of Nursing regional and national network group of IBD nurses.

Panel Pa

- ▶ Patients (Pa)
 - Crohn's and Colitis United Kingdom, for Crohns, 'St Mark's Patient panel', and Ileostomy Association (IA) (The ileostomy and internal pouch Support Group).

was limited to holding a consultant position or being on the IBD specialist nurse register.

All stakeholders were recruited through national organisations (and their subcommittees), and the study management group agreed that this should be limited to the UK to facilitate the process of ensuring equal though broad representation. The stakeholders were divided into three panels. Patients were given a panel to themselves as they were considered essential stakeholders (box 1).

A participant information sheet was available on the webpage of the organisations and charities. On registration, participants were again provided with information about the survey and invited to complete an initial registration survey to capture demographic data. One reminder was sent if no response was received after 2 weeks. A purposive sampling technique was used to ensure variation based on geographical regions.

There are limited data to inform severity stratification or prognostic classification of patients with Crohn's fistula, an 'unmet need' recognised internationally.²⁰ After discussion within the study management group, it was decided that 'health states' would be a more useful way of categorising patients.

Four groups were determined by the study management group to reflect the various health states patients with fistulising pCD patients may be in.

1. 'This is my first anal fistula causing me symptoms'.
2. 'I've had at least one anal fistula before which got better but now I've got a new or newly symptomatic anal fistula'.
3. 'I have had anal fistula in the past and currently. They never completely settle and always give me symptoms'.
4. 'My fistula has healed following intervention'.

We aimed to invite 180 experts to ensure 70 experts with a 40% response rate. To maximise ongoing commitment to the process, we offered acknowledgement of participants completing all three rounds on publication of the study and sent newsletters after each of the Delphi rounds.

Information sources

A list of candidate outcomes were generated from a systematic literature review, interviews with patients, a dedicated patient

Table 1 Demographics of stakeholders

Participants characteristics	Registered participants (n=238)			Consensus meeting (n=47)		
	Clinicians	Patients	Total	Clinicians	Patients	Total
Gender						
Male	108	18	126	23	2	25
Female	45	65	110	10	12	22
Did not answer	2	0	2	0	0	0
Region						
Northern England	37	18	55	8	2	10
Midland	22	8	30	5	1	6
Southeast England	58	33	91	13	9	22
Southwest England	20	8	28	3	2	5
Wales	6	6	12	1	0	1
Scotland	7	6	13	1	0	1
Northern Ireland	2	3	5	2	0	2
Did not answer	3	1	4	0	0	0
Type of hospital						
DGH	56	64	120	10	7	17
Tertiary unit	97	17	114	23	7	30
Private		1	1	0	0	0
Other		1	1	0	0	0
Did not answer	2	0	0	0	0	0
Other clinicians characteristics						
Length of consultant appointment (years)						
0–5	46			8		
6–10	34			4		
11–20	53			16		
>20	20			5		
Other patient characteristics						
Age (years)						
20–29		32			3	
30–39		27			4	
40–49		17			5	
50–59		5			2	
Years with Crohn's disease (years)						
0–5		25			4	
6–10		19			2	
11–20		24			6	
>20		15			2	
Years with anal fistula (years)						
0–5		52			2	
6–10		18			8	
11–20		11			2	
>20		1			0	
Did not answer					2	
Fistula status						
First anal fistula		24			2	
Previously healed anal fistula, now new fistula		12			2	
Recurrent anal fistula		32			4	
Fistula healed following intervention		12			1	
Did not answer		0			5	

and public involvement (PPI) meeting²¹ and the study management group.

A systematic review of studies assessing medical, surgical and combined (medical/surgical) treatment of fistulising pCD was performed in accordance with a prospectively registered protocol (PROSPERO CRD42016039019).

The OVID SP version of MEDLINE (1950–2016) and Embase (1980–2016) were searched using validated terms for ‘Crohn's disease’, ‘anorectal fistula’ and ‘randomized controlled trials or prospective studies’ separated by the Boolean operator ‘AND’ (online supplementary file 1). This was supplemented with a free-text search of the same databases, using relevant keywords/

terms (including synonyms and variants), also separated by the Boolean operator 'AND'. The search was limited to studies conducted in human adults aged ≥18 years old and to papers published between 1 January 2010 and 12 July 2016, in order to ensure that identified outcomes were contemporary and currently applicable.

Prospective studies (including cohort comparisons, case controls and case series) that reported on outcomes on an intervention (medical, surgical and combination) for patients with fistulising pCD and recruited ≥10 patients were included. Systematic reviews were included, and the individual studies reviewed were searched to ensure complete capture. Evaluation of luminal studies not primarily targeted at perianal fistulas were included where a subgroup analysis was presented for patients with fistula. Excluded were studies where the fistulas were of a non-Crohn's aetiology, were not perianal or were not published in the English language.

Five independent reviewers (KS, SOA, PJT, MJL and NH) used predefined selection criteria to screen the studies, using Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Each study was reviewed by at least two independent reviewers. Studies were initially screened in abstract format before full-text review. Conflicts were resolved by discussion with recourse to senior investigators (AH and NSF) where necessary.

Reported outcomes were extracted verbatim and listed in preparation for categorisation into domains.

Domain categorisation

Three members of the study team, two researchers (KS and PJT) and a patient representative (AV), categorised similar outcomes identified from the systematic review into domains by consensus. Four members of the study team (KS, PJT, SOA and AV) assessed and categorised the transcripts from the patient interviews and from the PPI meeting to supplement the list generated from the systematic review. All the included outcomes were categorised into themes and presented as such throughout the rest of the process.

Discrepancies were resolved through discussion with the senior authors (NF and AH). Overlapping domains between data sources were condensed, producing a final list of candidate outcomes. The study management group, consisting of all stakeholder groups, methodologists and patient representatives, then reviewed and finalised the domains. Outcomes that were felt to be solely applicable to luminal disease were excluded if all members of the study management group were in agreement.

The patient representatives (SB, AV) created plain English definitions for all outcomes under consideration. The long list of all possible outcomes was presented to the stakeholders through a web-based system purposefully designed to conduct a three-phase Delphi process.

Consensus process

A three-round online Delphi process was used to prioritise outcomes. In each round, participants scored outcomes using the numerical scale suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group (<http://www.gradeworkinggroup.org>). Scale 1–3 signified an outcome of limited importance (categorised as 'not important'), 4–6 signified important but not critical (categorised as 'fairly important') and 7–9 signified an outcome of critical importance (categorised as 'really important'). In addition, a free-text space was provided for stakeholders to comment on the outcome definitions.

In round 1, participants were asked to score each outcome based on how important they felt it was in *deciding whether the overall treatment of [their/their patient's] pCD was successful* and to suggest additional outcomes they felt were important but which had not previously been scored. All newly suggested outcomes were reviewed by the study management group and taken forward for assessment in the second round if within the scope of the COS.

In round 2, participants were asked to score the outcomes again having been shown numerical and graphical representations demonstrating how others in *their* panel scored each outcome in the first round. They were also shown their own response from the first round. In round 3, participants rescored the outcomes having been shown numerical and graphical representations of how *all* panels scored outcomes in the previous round. They were also shown their response from the second round.

Each round was open for 4 weeks. A reminder email was sent to participants who had not completed the round after 2 weeks and then again at 3 weeks. The final reminder asked if participants were experiencing difficulties in completing the questionnaire or if they had decided not to participate further in the study. Participants who completed round 1 were invited to complete both round 2 and round 3. A newsletter was sent to all participants in between all rounds to update them on progress and modifications.

Outcomes that were prioritised during the Delphi process were discussed and voted on at a face-to-face consensus meeting. Electronic voting was used to maintain anonymity (ResponseCard, Turning Technologies, Belfast, UK). An initial vote, 'In,' 'Out' or 'unsure,' was followed by debate among participants, refinement of the wording of the consensus statement and then a second vote of 'in', 'out' or 'unsure'.

Outcome scoring and consensus definition

Outcomes were carried forward between rounds if more than >70% of all participants scored them as 'really important' (7–9). Each outcome was assessed for heterogeneity between the panels using a histogram depicting median scores. In

Table 2 Voting across rounds

Voting demographics		Round 1	Round 2	Round 3	Consensus meeting (n)
SuRa (n/N (%))	Surgeons	39/47 (83)	39/39 (100)	39/39 (100)	12
	Radiologists	21/27 (78)	21/21 (100)	21/21 (100)	4
GaNu (n/N (%))	Gastroenterologists	44/59 (75)	44/45 (98)	44/44 (100)	12
	Nurses	17/22 (77)	15/17 (88)	15/15 (100)	5
Pa (n/N (%))	Patients	66/83 (80)	57/66 (86)	59/64 (92)	14

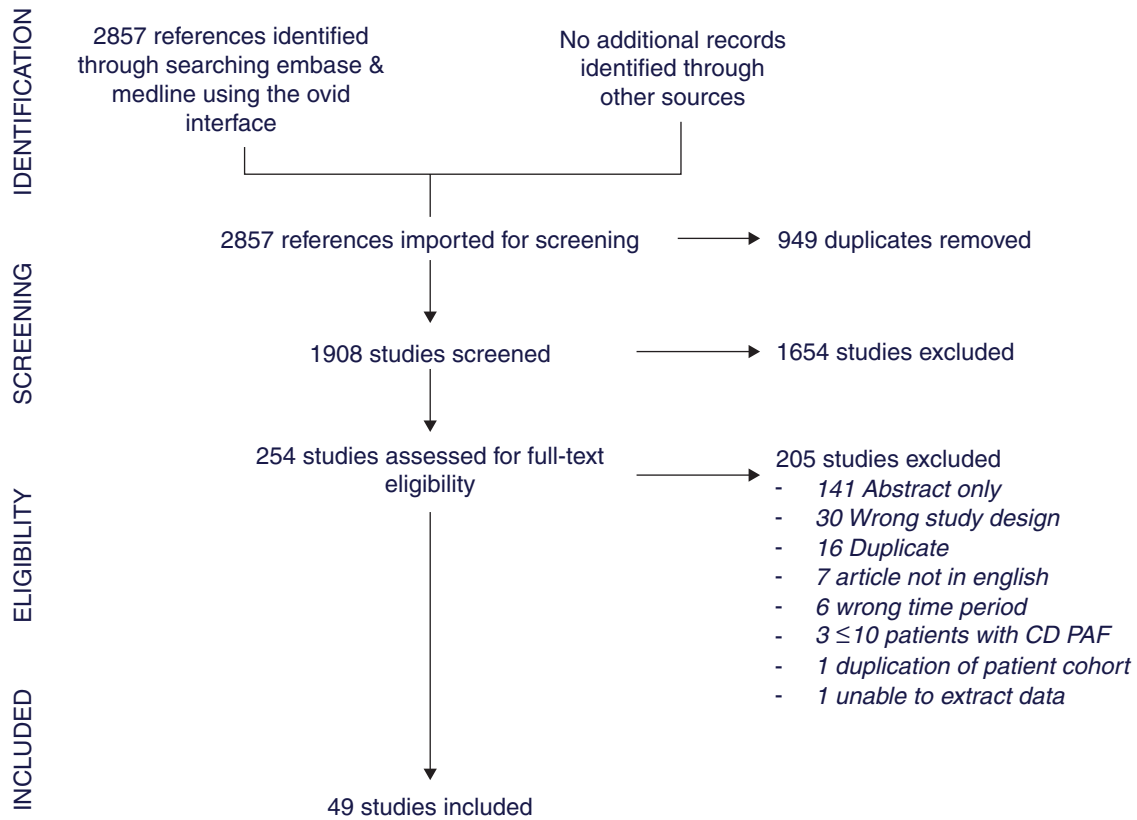


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of studies considered for the systematic review. CD, Crohn’s disease; PAF, perianal fistula.

addition, during each round, participants were given the opportunity to comment on the clarity and appropriateness of each outcome. All comments were reviewed by the study management group, and outcomes were modified to improve clarity if necessary.

At the end of each round, the study management group discussed all outcomes below the threshold for inclusion. The discussion was based on heterogeneity and any comments that had been recorded by the participants. Modification and frequently asked comments were sent to all participants using a newsletter in between rounds.

At the consensus meeting, participants were presented with the round 3 results and asked to vote prediscussion on whether they believed an outcome should be ‘included in the COS’, ‘not included in the COS’ or whether they were unsure. Participants were then asked to advocate either for inclusion or exclusion of an outcome, before repeating the voting. Those where 70% of participants voted for their inclusion were retained in the COS.

Ethical considerations

The local research and development department deemed the project to be service evaluation and therefore review by a National Health Service Research Ethics Committee was not necessary. The stakeholders were provided with information prior to registering to participate and throughout the process via newsletters. Consent to participate in the study was implied through completion of demographic questionnaires and voluntary attendance at the final meeting. Stakeholders were able to withdraw from the study at any time either by contacting the study team or by simply not responding to any of the questionnaires.

RESULTS

Protocol modifications

Following the analysis of the round 2 of the Delphi process, it

Table 3 Number of outcome measures reported and completeness of outcome reporting in perianal Crohn’s fistula studies

	Randomised studies (n=10)	Non-randomised studies (n=39)
Year		
2010–2011	2	15
2012–2013	2	11
2014–2016	6	13
Intervention		
Medical	5	18
Surgical	4	14
Combination	1	7
Number of patients with fistula		
<50	3	22
50–100	5	4
>100	1	3
NR	1	9
Number of outcomes measures		
<5	3	18
5–10	6	20
>10	1	1
Meets all core criteria for completeness of outcome reporting (%)	50.0	12.80

NR, not recorded.

Table 4 The most commonly outcome measures reported

Outcome measures in the included studies	Number of studies
≥50% tracts not draining on clinical examination	22
Perianal Disease Activity Index	20
Crohn's Disease Activity Index	19
Closure of external opening	17
No drainage either spontaneously or on gentle finger pressure	12

was identified that that panel colorectal surgeons and radiologists (SuRa) were the most discriminatory and the panel patient was the least discriminatory. Using the prespecified criteria, only 6/79 (7.6%) outcomes were below the threshold for exclusion for the patient panel compared with 45/79 (57.0%) from the most discriminatory panel (SuRa) (online supplementary file 2).

The criteria for retention in the second round of the Delphi process were therefore modified, so that not only were outcomes where >70% participants overall scored them 7–9 retained but also those which >90% of the patient panel had scored them 7–9 were carried forward to phase 3. In addition, four outcomes (online supplementary file 2) were retained by the study management group as they were felt to be of key importance and would benefit from further evaluation and discussion.

High patient scoring and a change to the protocol in round 2 meant the study management group decided that no outcomes were to be excluded in round 3. Analysis of round 3 confirmed the decision as again the 70% cut-off was deemed insufficiently discriminatory (online supplementary file 3). This allowed for the participants in the consensus meeting to be given the opportunity to see all the remaining outcomes.

Participants

A total of 238 participants registered their interest. Of these, 187/238 participants (78.5%) registered their demographics and completed round 1 of the Delphi survey. One hundred and seventy-six out of 187 participants (94.1%) completed round 2 and 183/187 participants (97.9%) completed round 3. In total, 47 participants attended the face-to-face meeting across the panels (16 from *panel SuRa*, 17 from *panel gastroenterologists and IBD specialist nurses (GaNu)* and 14 from *panel patients (Pa)*). Demographic details for each stakeholder group are summarised in tables 1 and 2.

Information sources and domain categorisation

A total of 2857 titles were identified, of which 949 were duplicates and the remaining 1908 were screened. Of these, a further 1654 studies were excluded based on title and abstract review. Following full-text review, a further 205 papers were excluded for the following reasons: only the abstract could be found, non-prospective study design, non-English language publications or not having a sufficient number of patients with Crohn's fistula receiving treatment. This resulted in 49 included studies (figure 1). No additional papers were identified from systematic reviews or other trials. In total, 18 of the studies (37%) were prospective cohort studies (including two studies where data were retrospectively analysed from a prospectively collected database), 18 (37%) were systematic reviews and meta-analyses, 9 (18%) were randomised controlled trials and the remainder were non-randomised studies. The median number of study participants with Crohn's perianal fistula who received treatment was 29 (IQR 17–68).

There were 295 different clinical outcomes reported, with studies reporting a median of six (IQR 3–7) outcomes; these are summarised in table 3. The three most commonly reported outcome measures in the studies were: ≥50% of tracts not draining on clinical examination (22 studies; 45%), Perianal Disease Activity Index (20 studies; 41%) and Crohn's Disease Activity Index (CDAI) (table 4). No single outcome was reported in every study. The individual studies and the quality of outcome reporting were assessed using the five core questions proposed by Harman's criteria²² in online supplementary file 4. Duplicate and analogous terms were merged to form 89 unique outcome domains. Eleven further outcomes were generated through a combination of patient interviews and the PPI day. The study management group added a further six. The resultant 106 outcomes were reviewed by the study management group, and 14 were excluded as they were felt to be applicable only to luminal disease, resulting in 92 unique outcomes that entered round 1 of the Delphi process. A summary of outcomes used in the online Delphi process with their lay definitions, organised according to themes, is presented in table 5.

Outcome prioritisation

The 92 outcomes were reviewed by participants in round 1, which generated 201 individual comments. The study management group retained nine outcomes having altered the name (or lay description), due to polarising views/heterogeneity or comments by participants, implying a lack of clarity (online supplementary file 5). Five de novo outcomes were added, and 18 outcomes were excluded according to the preset criteria. At the end of round 1, interim analysis demonstrated that the top 10 outcomes rated by the panels were similar and are seen in table 6.

Of the 79 outcomes that entered round 2, 41 were below the preset threshold for exclusion. After a modification to the protocol, 12 of these were retained (eight due to high patient scoring and four by the study management group, as described above), which resulted in 29 (36.7%) being dropped from round 2 (online supplementary file 2). The resultant 49 outcomes entered into the third round, and all were taken forward to the face-to-face consensus meeting (table 7). The process is described in figure 2, and individual scores for each round are in online supplementary files 2–4.

Consensus meeting

Following scoring at the consensus meeting, eight outcomes were retained in the COS. This constituted three patient-reported and five clinician-reported outcome domains (box 2).

The outcome *radiological outcome* was felt to be important by the attendees at the consensus meeting but did not meet criteria for retention in the COS after consensus discussion. Attendees' main reason for excluding the outcome was that the cost associated with MRI was likely to prohibit its use in research across both low-income and high-income countries and that it was therefore not appropriate for inclusion in a COS.

The meeting attendees did however note that it should be recommended for use as an outcome in all studies where it was feasible to do so.

At the consensus meeting, the individual outcomes in the 'impact on life' theme did not meet universal consensus but were scored very highly by the patients and advocated for by them. Members of other panels felt the inclusion was important but were unable to differentiate the importance between them. As such, after a unanimous decision, it was decided that an

Table 5 Outcome domains identified through phase 1 with lay definitions

Themes	Outcome	Lay definitions
Fistula response to treatment (symptoms)	<p>≥50% tracts not draining on clinical examination</p> <p>Closure of internal opening</p> <p>Rectal mucosal healing</p> <p>Complete fistula healing assessed clinically</p> <p>Partial fistula healing assessed clinically</p> <p>Closure of all the external openings on clinical examination</p> <p>Clinical assessment of drainage either spontaneously or on gentle finger pressure</p>	<p>More than half the openings on the bottom are dry and not oozing anything.</p> <p>The hole inside the bottom (as opposed to on the buttock skin surface) closes. This must be assessed by a doctor.</p> <p>An assessment of the last part of your intestine in clinic assessed by inserting a small probe into your bottom.</p> <p>An assessment of the bottom in clinic where all the opening/holes on the skin have closed on ≥2 consecutive clinic appointments (ie, assessed more than once).</p> <p>An assessment of the bottom in clinic where there is a decrease in the size/number of fistula and a reduction in drainage.</p> <p>An assessment of the bottom in clinic where all the opening/holes on the skin have closed on a single examination (ie, assessed once).</p> <p>An assessment of the bottom in clinic where the doctors press around the openings on the bottom to look for discharge and also ask the patient about the drainage from their fistulae.</p> <p>An assessment of the bottom looking for acute inflammation around the fistula (swelling and redness) and chronic inflammation (scarring and shrinking of the anal opening).</p>
Direct impact of fistula on the patient	<p>Incontinence to wind</p> <p>Mucus leakage</p> <p>Recurrence of fistula</p> <p>Development of a new fistula</p> <p>Perianal abscess on clinical assessment after intervention</p> <p>Wound infection</p> <p>An incontinence score</p> <p>Incontinence to liquid stool</p> <p>Incontinence to solid stool</p> <p>Pads for continence/leakage</p> <p>Plug for continence/leakage</p> <p>#Discrimination between passing stool and gas</p> <p>Tenesmus or incomplete evacuation</p> <p>Anal bleeding</p> <p>Anal pain</p> <p>Increased frequency of loose stool</p> <p>Perianal related hospitalisation</p> <p>Surgical reintervention</p> <p>Faecal diversion or proctectomy</p> <p>Faecal urgency</p>	<p>A scoring system used to assess whether the perianal disease is active and flaring up or stable.</p> <p>Developing skin tags, anal stenosis (narrowing), anal fissures, ulcers or cancer.</p> <p>The patient saying there has been a decrease in the oozing/drainage from the openings on the bottom.</p> <p>Unable to stop wind/flatulence/gas escaping from your bottom.</p> <p>Unable to stop mucus coming out from your bottom.</p> <p>The same fistula hole that closed opens up again (the hole inside the bottom or the hole on the buttock skin surface).</p> <p>A new perianal fistula develops in another place; that is, a new hole forms on the buttock skin surface or deeper inside the bottom after the intervention.</p> <p>An abscess (collection of pus/infection) or lumps in the bottom area that forms after treatment.</p> <p>Increasing pain, redness, swelling in the wound requiring antibiotics (without an abscess).</p> <p>A scoring system used over time to assess change in continence/bowel motion (consistency/frequency).</p> <p>Unable to stop liquid stool escaping from your bottom.</p> <p>Unable to stop stool/faeces escaping from your bottom.</p> <p>Needing to use pads inside underwear to soak up liquid discharge/oozing from the fistula.</p> <p>Needing to use anal plug to soak up liquid discharge/oozing from the fistula.</p> <p>Unable to know whether you have passed wind/flatulence/gas or whether you have passed faeces/stool.</p> <p>Feeling like you need to go to the toilet all the time (even if just been).</p> <p>Blood coming out of the bottom area (either from the fistula or the bowel).</p> <p>Pain around the bottom.</p> <p>Runnier bowel motion and having to empty bowels more often than before.</p> <p>Being admitted to hospital because of your perianal Crohn's disease, such as an abscess.</p> <p>Another operation is needed after the first treatment.</p> <p>Operation to remove the rectum (last part of the bowel) and/or having a stoma bag fitted.</p> <p>Inability to delay going to the toilet/defecation for 15 min.</p>

Continued

Table 5 Continued

Themes	Outcome	Lay definitions
Impact on the patient as a person	<p>Lifestyle alterations (pain/restriction of activities)</p> <p>Limitation to moderate activities</p> <p>Limitation to vigorous activities (eg, running, lifting heavy objects, participating in strenuous sports)</p> <p>Change in general health—physical</p> <p>#A quality of life score, for example, Short Form Survey 36</p> <p>Change in general health—psychological</p> <p>Lethargy and fatigue</p> <p>Social interaction avoidance</p> <p>Anxiety and worries</p> <p>Feeling depressed and down, and hopelessness</p> <p>Irritable, frustrated and angry</p> <p>Concern over further intervention</p> <p>Sleep disturbance</p> <p>Modifying how you walk, sit or stand because of your fistula*</p> <p>Modifying travel*</p> <p>Body detachment*</p> <p>A feeling of being unhygienic*</p> <p>Concerns about and impact on fertility, birth, parenthood and family*</p> <p>Restriction of sexual activity</p> <p>Physically restricted in self care</p> <p>Patient perception of continence compared with others or baseline</p> <p>Tolerability of treatment</p> <p>Decisional regret of treatment choice</p> <p>Avoidance of intimacy*</p> <p>Unable attend school/work</p> <p>Change in lifestyle based on toileting needs</p> <p>Restricted in what you wear*</p> <p>Embarrassment and feeling isolated*</p>	<p>Change in lifestyle because of the fistula.</p> <p>Difficulty performing tasks such as light housework.</p> <p>Unable to run, lift heavy objects, participate in strenuous sports.</p> <p>Change in physical ability to do things.</p> <p>A scoring system that patients fill out to assess the various aspects of a person's life.</p> <p>Change in thought and feelings.</p> <p>Exhausted, tired because of the fistula.</p> <p>Stop leaving the house unless you have to (going to work and medical appointments but not going to see friends or going to parties/celebrations).</p> <p>Anxious or worried about impact of the fistula.</p> <p>Feeling depressed and down, and hopelessness.</p> <p>Feeling irritable, frustrated and angry.</p> <p>Concerns over needing more treatment (having just had one type of treatment).</p> <p>Having to get up at night due to toileting needs, soiling sheets, underwear change and so on.</p> <p>Sitting on one buttock rather than both, standing as sitting is too painful or having to walking with your legs wider apart.</p> <p>Choosing modes of transport depending on access to the toilet (eg, train) or planning car journeys around toilet stop-offs.</p> <p>Feeling 'medicalised' and that rather than yourself you are a 'body' on which medical treatment is performed.</p> <p>Feeling unclean, dirty and unhygienic (rather than actual being unclean, dirty and unhygienic).</p> <p>Worried about getting pregnant in the first place, about actually going through labour, keeping up with busy children and inability to give them everything because of limitation of the disease (eg, not being able to go for long walks).</p> <p>Unable to have sex or be physically close to someone.</p> <p>Unable to wash, get dressed or look after yourself without help from someone else because of the fistula.</p> <p>A difference/change in continence compared with other people or how you used to be before the fistula.</p> <p>An overall assessment of how 'acceptable' a treatment is; for example, does it have so many side effects that you want to stop it?</p> <p>A measure of regret of choosing a specific treatment option whether (medical or surgical).</p> <p>Avoiding getting too close with another person (hugging, sitting next to each other and so on) due to fears that you smell or they might know that you have a fistula. This includes getting into new relationships.</p> <p>Cannot go to school/college/university or do your usual job because of perianal fistula due to need to be off at short notice.</p> <p>Go out less or only go to places where you know there is a clean toilet and washing facilities because of perianal fistula. Or take spare clean underwear and wipes with you when you go out.</p> <p>Being unable to wear tight clothing and wearing baggy clothes to reduce pain, conceal bulging pads or bulky gauze inside underwear. Also wearing dark clothing to conceal stains.</p> <p>Feeling conscious of the fistula, which subsequently affects the way I walk/behave/interact with the world, which is obvious to others and leaves me embarrassed so that I alter what I do.</p>
Assessment with imaging techniques (scans)	<p>#MRI assessment of fistula volume</p> <p>Fistula response on endoanal ultrasound</p> <p>Abcess on MRI following treatment</p> <p>T1 enhancement on MRI</p> <p>Hyperintensity on T2-weighted MRI</p> <p>MRI assessment of rectum (proctitis)</p> <p>Fistula response on MRI imaging</p> <p>#An activity based MRI score, for example, Van Assche Score</p>	<p>Calculating the size of fistula on an MRI scan to generate a number, and then comparing the size/number over time.</p> <p>A rectal probe is inserted into the bottom to look for and assess the fistula using an ultrasound machine to see if the fistula is better/worse/the same.</p> <p>A collection of pus on MRI scan.</p> <p>A specific way to assess inflammation within a fistula on a MRI (it adds time to a normal MRI but allows doctors to better decide what is fistula and what is blood vessel).</p> <p>A specific way to assess inflammation within a fistula on an MRI—this is standard care.</p> <p>Looking for inflammation of the rectum (last part of the intestine/bowel) on MRI.</p> <p>The fistula looks 'better' or 'about the same' or 'worse' on MRI.</p> <p>A scoring system used by radiologists (MRI doctors) to assess whether a fistula is 'active', that is, acute inflammation or nearer to the other end of the scale of healing.</p>

Continued

Table 5 Continued

Themes	Outcome	Lay definitions
Fistula response to treatment (tests)	Time to loss of response to medical treatments Objective blood markers of inflammation	The length of time taken before you develop resistance to a medication (biologicals/anti-TNF). Blood tests looking for inflammation.
Safety implications related to treatment	C reactive protein Non-inflammatory blood markers (related biologicals) Instability of weight (assessed by body mass index (BMI)) Fever Nausea or vomiting Death Rash or other skin/hair problems Allergic reaction Cardiorespiratory complications Neurological complications Urinary complications Grading system for surgical complications, for example, Clavien-Dindo Safety (adverse events) and toxicity Surgical complications specific to the surgical procedure (eg, plug extrusion) #Medical complications specific to the immunosuppression (eg, opportunistic infections and cancers)	A specific blood test looking for inflammation. Blood tests looking for other things, such as anaemia, B12 levels and so on. Putting on weight or losing weight, assessed using BMI (a score based on weight and height). Feeling 'hot' and feverish/getting 'the chills' with a high temperature. Feeling sick or vomiting after treatment. Death as a result of a treatment. Changes in the skin (rash, dryness, acne and so on), hair thinning or hair loss. A reaction to a treatment (ranging from a rash to swelling of the throat). Complications of treatment related to cardiovascular system—heart attacks and abnormal heart rhythms. Complications of treatment related to nervous system—visual symptoms, headaches and nerve damage. Complications of treatment related to urinary system—waterworks infections, damage to the any of the anatomical structures during surgery. A generic validated grading system of all complications related to surgery (covers all systems—cardiovascular, neurological and so on). Measuring how safe and tolerable a given treatment is. Specific surgical complications, for example, plug extrusion (following anal plug insertion). Increased risk of cancer (eg, lymphoma) and an increased risk of any infection as a result of being on an immunosuppressive medication (anti-TNF/ biologicals/thiopurines).
Impact on the patient over time	Duration of healing/improvement Biological-free remission Cost-effectiveness Increasing analgesia* Antibiotic-free remission* Use antidiarrhoeal drugs Recovery time after intervention Financial implications*	How long the treatment helped you to feel better for. Period of time not needing to take biologicals/anti-TNFs (eg, infliximab/remicade, humira/adalimumab). A measure of how effective the treatment has been but also factoring in the cost of this treatment. Needing more painkillers to get through the day. Period of time not needing to take antibiotics. Taking medication to make the stool less runny (eg, loperamide). Length of time off work/study after treatment intervention. Financial hardship including loss of income, career stagnation, extra expenses, for example, buying pads, clean underwear and so on.
Origin	From SR (n=76) Added from patients (n=11)* #Added from SMG (n=5)	
Excluded by the SMG (n=14)	Faecal calprotectin Steroid-free remission Abdominal discomfort Dietary supplements as oral intake low A validated Crohn's disease activity score Remission of Crohn's disease Identification of endoscopic signs suggestive of failure of treatment (relating to systemic/overall Crohn's disease) MRI features (luminal) Abdominal mass Extraintestinal manifestations of Crohn's disease Comparison with other individuals (luminal) Haemorrhage Feasibility of technique Decrease in size of fistula	Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. This relates to luminal relapse, and we have included assessment of the rectal mucosa separately. Not specific to Crohn's disease and more to luminal disease. Not specific to Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Not specific to perianal Crohn's disease and more to luminal disease. Definition unclear and not defined within the study. Likely to have covered through other forms of clinical assessment (consensus to remove).

*Added from patients (n=11).
#Added from SMG (n=5).

SMR, study management group; SR, systematic review; TNF, tumour necrosis factor.

Table 6 Top 10 outcomes voted after phase 1

Item	Outcomes	Panel SuRa high	Panel SuRa low
30	Faecal diversion or proctectomy	97	0
75	Death	97	3
15	Development of a new fistula	89	0
20	Incontinence to solid stool	89	0
28	Perianal-related hospitalisation	89	0
29	Surgical reintervention	89	2
14	Recurrence of fistula	86	0
16	Perianal abscess on clinical assessment after intervention	86	2
56	Unable attend school/work	84	0
19	Incontinence to liquid stool	83	0
		Panel GaNu high	Panel GaNu low
75	Death	100	0
30	Faecal diversion or proctectomy	98	0
15	Development of a new fistula	97	0
84	Medical complications specific to the immunosuppression (eg, opportunistic infections and cancers)	97	0
14	Recurrence of fistula	94	0
20	Incontinence to solid stool	94	0
28	Perianal-related hospitalisation	94	0
19	Incontinence to liquid stool	92	0
56	Unable attend school/work	92	0
21	Pads for continence/leakage	91	0
		Panel Pa high	Panel Pa low
19	Incontinence to liquid stool	96	0
30	Faecal diversion or proctectomy	96	0
20	Incontinence to solid stool	93	1
16	Perianal abscess on clinical assessment after intervention	92	6
15	Development of a new fistula	92	0
28	Perianal-related hospitalisation	91	3
75	Death	91	5
17	Wound infection	90	0
39	Social interaction avoidance	89	6
29	Surgical reintervention	86	5

Panel GaNu, gastroenterologists and IBD specialist nurses; panel Pa, patients; panel SuRa, colorectal surgeons and radiologists.

individual outcome making up this overarching domain should be voted on and prioritised by patients alone.

DISCUSSION

This is the first study to standardise outcome reporting in fistulising pCD. An exhaustive list of candidate outcome measures was generated through a systematic review of contemporary outcomes, together with patient views. Using an online tool, a large number of stakeholders were able to participate in a pragmatic Delphi consensus process that ensured emphasis on patient perspective and clinical relevance. Consensus voting and discussion generated a COS that all stakeholders supported with applicability to all study designs. The aim is to improve research and to use this COS as an impetus to drive improvement in clinical management within the field. The COS allows measurement of outcomes for all cohorts of adult patients with pCD, regardless of disease state, the intervention under assessment or

the presence of luminal disease. In this study, we established an eight-domain COS for use in studies evaluating interventions in fistulising pCD. A two-domain radiological module is also strongly advocated for use wherever possible.

Fistulising pCD denotes a severe and disabling disease course characterised by the need for multiple hospitalisations and operations. It also has a high economic cost, particularly with the use of biological agents as the mainstay of treatment.^{23–26} The James Lind Alliance, a national Priority Setting Partnership group of patients and clinicians, identified pCD and specifically the individual factors that influence various treatment strategies and outcomes as one of the ‘Top 10 unanswered questions’ in the field of IBD.²⁷ However, the criteria by which success is measured in the management of Crohn’s perianal fistula have hitherto been a challenge to researchers.²⁸ Most studies have used a measure of the degree of clinical healing as their primary outcome; however, deep tissue healing has been shown to lag behind simple closure of the external openings²⁹ and, crucially, success measured this way has generally been disappointingly poor. Moreover, if control of symptoms is the primary objective of treatment, these measures are wholly inappropriate and will fail to demonstrate a benefit, even if patients perceive one. The multimodal treatment of perianal fistulas in Crohn’s disease: seton versus anti-TNF α versus advancement plasty (PISA) trial group have proposed a set of primary outcomes, which aim to address this deficit.³⁰ Of note, the primary outcome is pragmatic and clinically relevant, measuring reinterventions following treatment. The secondary endpoints include quality of life, disease activity and importantly use an MRI-based assessment to determine fistula closure as a long-term measure at 18 months. Recently, the first randomised controlled trial of stem cell therapy in fistulising pCD was published.³¹ The authors used a new composite primary endpoint, comprising clinical and radiological healing, further revealing the lack of agreement on which fistula outcomes to use and also recognising the inadequacy of a single outcome measure to define success.

The International Consortium for Health Outcome Measurement (ICHOM) has recently been published for IBC. It emphasises the importance of patient-reported outcome measures in IBD research but as it has been designed for IBD in general it has minimal information for patients with fistulas.³² This COS aims to address an unmet need in pCD where standardising outcome measurement is particularly difficult due to changes in the patient’s goals of treatment over time, the refractory nature of perianal disease compared with luminal disease and the specific symptoms associated with the condition.^{33 34}

A strength of this study is that every stage of the process, including amalgamation, addition and exclusion of outcomes, was performed by consensus and always included patient representation. Examples include the interventional complications and morbidity, which featured in the outcomes presented on the consensus day but were excluded from the final COS, as the participants felt these would be reported as a minimum in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses harms checklist.³⁵ A similar discussion excluded ‘death’ as an outcome. The initial design of this study followed the guide set by the OMERACT³⁶ group, but at the consensus meeting, it was felt that ‘death’ was less suitable for this COS and a more relevant hard endpoint would be ‘faecal diversion’. Another consensus decision was that of an optional imaging module, but because MRI is not universally accessible, it did not reach threshold for inclusion as a mandatory outcome measure. Another strength was the diversity in the study management group with stakeholder leads and methodologists from a number of different institutions and geographical locations, and the crucial stakeholders (patients) were always prioritised. For

Table 7 Outcomes to be included in the COS at the consensus meeting

Question	% In			Overall (%)	Patient vote alone (%)	Final consensus
	Panel SuRa (%)	Panel GaNu (%)	Panel Pa (%)			
1	Patient-reported reduction in fistula drainage	57.1	53.3	30.0	46.8	
2	Development of other perianal features	53.8	73.3	70.0	65.7	
3	Complete fistula healing assessed clinically	53.3	40.0	44.4	45.9	
4	Validated score to assess perianal disease activity	100.0	93.8	77.8	90.5	IN
5	Development of a new fistula	69.2	83.3	87.5	80.0	IN
6	Incontinence to solid stool	26.7	33.3	40.0	33.3	
7	Pads for continence/leakage	26.7	40.0	40.0	35.6	
8	Recurrence of fistula	85.7	68.8	80.0	78.2	
9	Perianal abscess on clinical assessment after intervention	86.7	100.0	90.0	92.2	IN
10	Incontinence to liquid stool	71.4	93.3	100.0	88.3	Combined†
11	Perianal-related hospitalisation	35.7	50.0	10.0	31.9	
12	Faecal diversion or proctectomy	100.0	100.0	100.0	100.0	IN
13	Wound infection	0.0	0.0	30.0	10.0	
14	Anal pain	66.7	87.5	90.0	81.4	
15	Discrimination between passing stool and gas	6.7	33.3	12.5	17.5	
16	Surgical reintervention	93.3	93.8	80.0	89.0	IN
17	Anal bleeding	0.0	14.3	60.0	24.8	
18	Reversal of defunctioning stoma	33.3	37.5	22.2	31.0	
19	A global assessment of incontinence that covers all aspects of leakage	92.9	100.0	100.0	97.6	IN
20	Fistula response on MRI	85.7	86.7	80.0	84.1	IN
21	Hyperintensity on T2-weighted MRI	46.7	38.5	62.5	49.2	
22	MRI assessment of fistula volume	35.7	53.8	55.6	48.4	
23	Fistula T1 enhancement on MRI	13.3	45.5	60.0	39.6	
24	Abscess on MRI following treatment	66.7	87.5	60.0	71.4	
25	An activity-based MRI score	86.7	93.3	88.9	89.6	IN
26	A global quality of life score	100.0	93.8	100.0	97.9	n/a IN
27	Physically restricted in caring for oneself	15.4	26.7	70.0	37.4	70.0
28	Change in lifestyle based on toileting needs	23.1	53.3	87.5	54.6	90.0 IN
29	Embarrassment and feeling bloated	25.0	42.9	60.0	42.6	60.0
30	Unable to attend school/work	36.4	86.7	100.0	74.3	100.0 IN
31	Restriction of sexual activity	58.3	80.0	90.0	76.1	100.0 IN
32	Lethargy and fatigue	0.0	20.0	66.7	28.9	60.0
33	Limitation to moderate activities	8.3	12.5	30.0	16.9	40.0
34	Change in general health	16.7	64.3	80.0	53.7	80.0
35	Avoidance of intimacy	36.4	60.0	88.9	61.8	88.9 Combined‡
36	Anxiety and worries	8.3	25.0	55.6	29.6	75.0
37	Change in physical ability to do things	0.0	12.5	77.8	30.1	80
38	Feeling depressed, down, hopeless, unable to cope	7.7	42.9	90.0	46.8	90 IN
39	Modifying how you sit, walk and stand because of your fistula	33.3	57.1	70.0	53.5	80
40	Lifestyle alterations (pain/restriction)	25.0	53.8	80.0	52.9	100 IN
41	Social interaction avoidance	50.0	46.2	70.0	55.4	80
42	Duration of improvement	53.8	80.0	88.9	74.2	
43	Death	46.2	42.9	55.6	48.2	
44	Allergic reaction	7.7	6.7	37.5	17.3	
45	Safety (adverse events) and toxicity	7.7	7.1	50.0	21.6	
46	Urinary complications	38.5	76.9	77.8	64.4	
47	Cardiorespiratory complications	7.7	0.0	44.4	17.4	
48	Neurological complications	0.0	8.3	60.0	22.8	
49	Medical complications specific to immunosuppression	0.0	15.4	44.4	19.9	

*'Patient Priorities' - consensus agreement by all to allow these items to be voted on by patient alone.

†Combined with 'A global assessment of incontinence that covers all aspects of leakage'.

‡Combined with 'Restriction of sexual activity'.

COS, core outcome set.

example, we found that patients tended to rank most outcomes highly, gastroenterologists slightly less so and surgeons least of all. This meant that the outcomes that fell below the inclusion bar tended to do so as a result of the views of the clinicians, rather than the patients, potentially deviating from the

aim of a patient-centred COS. There is currently no guidance on how to discuss outcomes with patients and carers in qualitative research,³⁷ but in efforts to ameliorate this effect, the study management group used separate thresholds for clinicians and patients to allow for prioritisation of outcomes scored

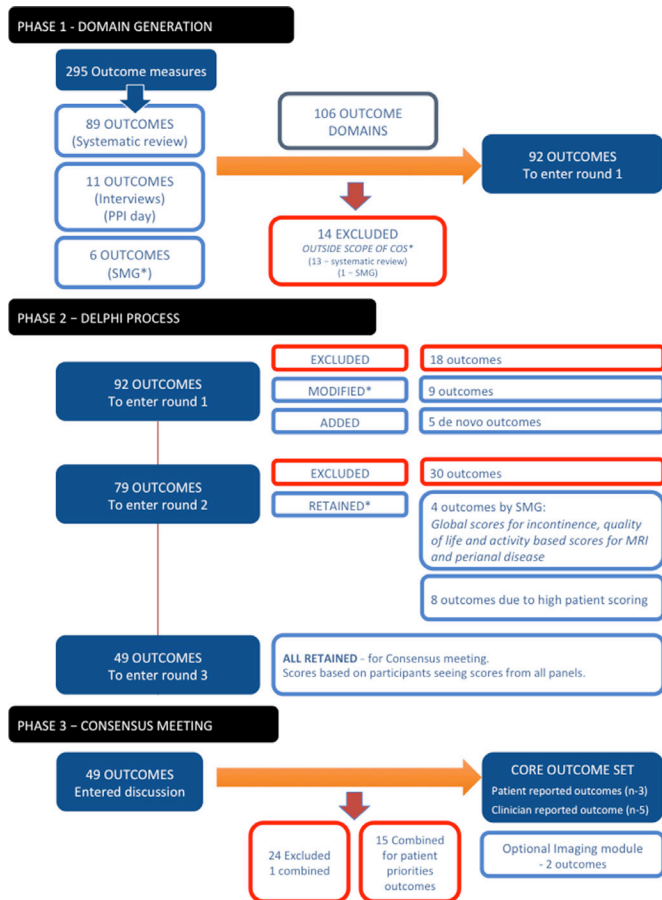


Figure 2 Outcome flow diagram. COS, core outcome set; PPI, patient and public involvement.

particularly highly by the patients. In addition, some outcomes seemed to score poorly despite very similar outcomes scoring highly. This was taken as evidence of poorly worded descriptions or concepts difficult to explain in pithy prose. For example,

Box 2 Core outcome set for fistulising perianal Crohn’s disease

Patient-reported outcomes

- ▶ Global assessment of quality of life.
- ▶ Combined score of patient priorities.
 - Lifestyle restriction (general)
 - Lifestyle restriction based on toileting needs
 - Depression
 - Inability to attend school/work
 - Restriction of sexual activity and avoidance of intimacy.
- ▶ Global assessment of incontinence.

Clinician-reported outcomes

- ▶ A validated score to assess perianal disease activity.
- ▶ Development of a perianal abscess.
- ▶ Development of a new/recurrent fistula.
- ▶ Unplanned surgical reintervention.
- ▶ Faecal diversion or proctectomy.

Imaging (optional module)

- ▶ Fistula response on MRI.
- ▶ An activity-based MRI score responsive to change.

the concept of a global assessment of quality of life reached the threshold for exclusion in the online Delphi but was discussed at the consensus meeting for the reasons above and was selected as part of the final COS once it was adequately explained to the patients by whom it was then championed.

A limitation of this study is that all the participants were based in the UK, which could potentially affect generalisability to other populations, especially in low-income countries. There was an active decision by the study management group to minimise attrition through the rounds and to achieve maximum recruitment. One missing stakeholder was industry; this was discussed and specifically excluded due to concern about potential bias. An online survey was chosen due to its ease of use, increasing the feasibility of national sampling, as well as removing interview bias.³⁸ To date, this study has one of the largest numbers of participants and one of the lowest attrition rates.

Given the poor rates of fistula closure experienced by most patients, the range of new medical and surgical treatments emerging and the high cost of many of them determining their relative efficacy and cost effectiveness is important. Comparison of different techniques from different studies mandates standardised outcome reporting, which this COS will provide. Outcomes specific to a given study as a result of the technique used or population studied, such as the rate of plug extrusion, or complications relating to immunosuppression, remain important to measure and are not excluded by a COS. Innovation, progress and pragmatism will require researchers to measure other outcomes, but in order to appraise interventions completely and ensure relevance to patients, a COS should also be used. Although MRI is crucial to determine deep tissue healing, its value in the assessment of symptom palliation is less clear, and it is not readily available to all studies or institutions, so it could not be considered a core outcome but is a strongly advocated addition where appropriate.

The Evaluating goal-directed management of fistulising perianal Crohn’s disease research group is building a portfolio of foundation research, of which this COS is a central part. This COS requires international validation if it is to be used outside the UK. It is also necessary to develop a core measurement set, a collection of measurement tools and standards by which these outcomes can be assessed in a given study. For example, there is no validated, disease-specific, patient-derived quality of life measurement tool for Crohn’s anal fistula. This is another ‘unmet need’ described by the European Crohn’s and Colitis Organisation’s consensus group.²⁰ Creation of such a measurement tool is underway, and development of a core measurement set to complement this COS is also underway.

CONCLUSION

Using rigorous methodology and representative stakeholder engagement, we have generated a COS for use in fistulising pCD studies. Groups assessing treatment in fistulising pCD should be strongly encouraged to adopt and use this COS to reduce the heterogeneity of outcome reporting and improve the quality and comparability of future research.

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REFERENCES

- Silverberg MS, Satsangi J, Ahmad T, *et al.* Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19 Suppl A:5A–36.
- Afşarlar CE, Karaman A, Tanir G, *et al.* Perianal abscess and fistula-in-ano in children: clinical characteristic, management and outcome. *Pediatr Surg Int* 2011;27:1063–8.
- Sahnan K, Adegbola SO, Tozer PJ, *et al.* Perianal abscess. *BMJ* 2017;356:j475.
- Tozer PJ, Burling D, Gupta A, *et al.* Review article: medical, surgical and radiological management of perianal Crohn's fistulas. *Aliment Pharmacol Ther* 2011;33:5–22.
- Panés J, García-Olmo D, Van Assche G, *et al.* Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *The Lancet* 2016;388:1281–90.
- Meinero P, Mori L. Video-assisted anal fistula treatment (VAAFT): a novel sphincter-saving procedure for treating complex anal fistulas. *Tech Coloproctol* 2011;15:417–22.
- Wilhelm A. A new technique for sphincter-preserving anal fistula repair using a novel radial emitting laser probe. *Tech Coloproctol* 2011;15:445–9.
- García-Olmo D, Herreros D, Pascual I, *et al.* Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. *Dis Colon Rectum* 2009;52:79–86.
- Ellis CN. Outcomes with the use of bioprosthetic grafts to reinforce the ligation of the intersphincteric fistula tract (BioLIFT procedure) for the management of complex anal fistulas. *Dis Colon Rectum* 2010;53:1361–4.
- Han JG, Wang ZJ, Zheng Y, *et al.* Ligation of intersphincteric fistula tract vs Ligation of the intersphincteric fistula tract plus a bioprosthetic anal fistula plug procedure in patients with transsphincteric anal fistula: early results of a multicenter prospective randomized trial. *Ann Surg* 2015.
- Allin B, Knight M, Allin B. Trials NETS1G study: development of a core outcome set for use in determining the overall success of gastrostomy treatment. 2015.
- Gargon E, Gurung B, Medley N, *et al.* Choosing important health outcomes for comparative effectiveness research: a systematic review. *PLoS One* 2014;9:e99111.
- Gargon E, Williamson PR, Altman DG, *et al.* The COMET Initiative database: progress and activities update (2015). *Trials* 2017;18:54.
- Klokner L, Tugwell P, Furst DE, *et al.* Developing an omeract core outcome set for assessing safety components in rheumatology trials: the OMERACT safety working group. *J Rheumatol* 2017;44.
- Allin B, Bradnock T, Kenny S, *et al.* NETS1HD: study protocol for development of a core outcome set for use in determining the overall success of Hirschsprung's disease treatment. *Trials* 2016;17:577.
- McNair AG, Whistance RN, Forsythe RO, *et al.* Core outcomes for colorectal cancer surgery: a consensus study. *PLoS Med* 2016;13:e1002071–14.
- Kirkham JJ, Clarke M, Williamson PR. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ* 2017;357:j262.
- Williamson PR, Altman DG, Blazeby JM, *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132.
- Kirkham JJ, Gorst S, Altman DG, *et al.* Core outcome set-standards for reporting: the COS-STAR statement. *PLoS Med* 2016;13:e1002148.
- Gece KB, Bemelman W, Kamm MA, *et al.* A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut* 2014;63:1381–92.
- Nuha A, Robin K, Ailsa L, *et al.* The anal fistula journal: effects on patients' life experiences. *In: Gastroenterology*. 2014;146:5:207–0.
- Harman NL, Bruce IA, Callery P, *et al.* MOMENT—Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials* 2013;14:70.
- Chaparro M, Zanotti C, Burgueño P, *et al.* Health care costs of complex perianal fistula in Crohn's disease. *Dig Dis Sci* 2013;58:3400–6.
- Juan J, Estiarte R, Colomé E, *et al.* Burden of illness of Crohn's disease in Spain. *Dig Liver Dis* 2003;35:853–61 <http://www.ncbi.nlm.nih.gov/pubmed/14703880>.
- Silverstein MD, Loftus EV, Sandborn WJ, *et al.* Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology* 1999;117:49–57 <http://www.ncbi.nlm.nih.gov/pubmed/10381909>.
- Bajji P, Gulácsi L, Brodsky V, *et al.* Cost-effectiveness of biological treatment sequences for fistulising Crohn's disease across Europe. *United Eur Gastroenterol J* 2017;1–12.
- James Lind Alliance. Inflammatory Bowel Disease Top 10. 2015 <http://www.jla.nihr.ac.uk/priority-setting-partnerships/inflammatory-bowel-disease/top-10-priorities/> (accessed 14 Jun 2017).
- Tiernan J, Cook A, Geh I, *et al.* Use of a modified Delphi approach to develop research priorities for the Association of Coloproctology of Great Britain and Ireland. *Colorectal Disease* 2014;16:965–70.
- Tozer P, Ng SC, Siddiqui MR, *et al.* Long-term MRI-guided combined anti-TNF- α and thiopurine therapy for Crohn's perianal fistulas. *Inflamm Bowel Dis* 2012;18:1825–34.
- de Groof EJ, Buskens CJ, Ponsioen CY, *et al.* Multimodal treatment of perianal fistulas in Crohn's disease: seton versus anti-TNF versus advancement plasty (PISA): study protocol for a randomized controlled trial. *Trials* 2015;16:366.
- Panés J, García-Olmo D, Van Assche G, *et al.* Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet* 2016;388:1281–90.
- Kim AH, Roberts C, Feagan BG, *et al.* Developing a standard set of patient-centred outcomes for inflammatory bowel disease - an International, cross-disciplinary consensus. *J Crohns Colitis* 2017.
- Tarrant KM, Barclay ML, Frampton CM, *et al.* Perianal disease predicts changes in Crohn's disease phenotype—results of a population-based study of inflammatory bowel disease phenotype. *Am J Gastroenterol* 2008;103:3082–93.
- Beaugerie L, Seksik P, Nion-Larmurier I, *et al.* Predictors of Crohn's disease. *Gastroenterology* 2006;130:650–6.
- Zorzela L, Loke YK, Ioannidis JP, *et al.* PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016;ii157.
- Boers M, Kirwan JR, Wells G, *et al.* Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745–53.
- Jones JE, Jones LL, Keeley TJ, *et al.* A review of patient and carer participation and the use of qualitative research in the development of core outcome sets. *PLoS One* 2017;12:e0172937.
- Van Selm M, Jankowski NW. Conducting online surveys. *Quality and Quantity* 2006;40:435–56.