An exploration of variation in the management of Crohn's anal fistula

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Plagiarism statement

I confirm that this thesis represents my own work and is not copied from other works (published or unpublished). Where work has been completed with the help of others, this has been signposted in the acknowledgements and explanation of my contribution is stated at the beginning of the relevant chapter.

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Abbreviation list

5-ASA	5-aminosalicylates
6-MP	6-mercaptopurine
ABX	Antibiotic
ACPGBI	Association of Coloproctology of Great Britain and Ireland
ADA	Adalimumab
AFP	Anal fistula plug
AGA	American gastroenterology association
ASC	Adipose derived stem cells
AZA	Azathioprine
BMedSci	Bachelor of Medical Science
BSG	British Society for Gastroenterology
CD	Crohn's disease
CDAI	Crohn's disease activity index
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CO2	Carbon dioxide
COREQ	Consolidated criteria for reporting qualitative research
CPS	Control preferences scale
CS	Corticosteroid
CZP	Certolizumab Pegol
DRS	Decision regret scale
ECCO	European Crohn's and Colitis Organisation
ENiGMA	Evaluating Goal-Directed Management of Fistulising Perianal Crohn's Disease
EMBASE	Excerpta Medica dataBASE
EQ5D	European Quality of Life 5 dimension tool
EUA	Examination under anaesthetic
FiLAC	Fistula laser assisted closure
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HBI	Harvey-Bradshaw Index
HLA	Human leucocyte antigen

IAR	Intersphincteric anal resection
IBD	Inflammatory bowel disease
ICC	Intra-class correlation
IDEAL	Idea, development, evaluation, assessment, long-term follow-up
IFX	Infliximab
IL	Interleukin
IM	Immunosuppressives
IPDAS	International Patient Decision Aid Society
LIFT	Ligation of fistula track
MAF	Mucosal advancement flap
MDT	Multi-disciplinary team
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical subject headings
MHC	Major Histocompatability Complex
MMP	Matrix metalloproteinase
MSC	Mesenchymal stem cells
MST1	Macrophage Stimulating 1 gene
NHS	National Health Service
NICE	National Institute for Health Care Excellence
NOD2	Nucleotide-binding oligomerization domain-containing-2
NWRC	North-West Research Collaborative
NS	Not stated
OR	Odds ratio
OTSC	Over the scope clip
pCD	Perianal Crohn's disease
PCDAI	Perianal Crohn's Disease Activity Index
PhD	Doctor of Philosphy
PICO	Population, intervention, comparator, outcome
PRISMA	Preferred reporting items in systematic review and meta-analysis
RCT	Randomised controlled trial
REC	Research ethics committee
REDCap	Research Electronic Data Capture

ROBINS	Risk of bias in non-randomised studies
RR	Risk ratio
SD	Standard deviation
SE	Standard error
S-IBDQ	Short-Inflammatory Bowel Disease Questionnaire
SYSuRG	South Yorkshire Surgical Research Group
TGF	Tissue growth factor
TNF	Tumour necrosis factor
TSE	Total Study Error
UK	United Kingdom
UREC	University research ethics committee
US(A)	United States (of America)
UST	Ustekinemab
VAAFT	Video Assisted Anal Fistula Treatment
VDZ	Vedolizumab
WGO	World Gastroenterology Organisation
WPAI:CD	Work Productivity Assessment Index for Crohn's disease

1 Abstract

Crohn's disease has a prevalence of 1 in 650 people in the UK. Of these, 30% will develop an anal fistula. This debilitating condition requires multiple medical and surgical interventions. Treatment goals may be preference sensitive for patients. This thesis assesses the evidence base for treatment of Crohn's anal fistula, explores clinician preferences, and patient informational needs. Systematic literature review identified 27 trials of pharmacological therapies. Anti-tumour necrosis factors (TNF) drugs were associated with induction (RR, 2.01; 95% CI, 1.36-2.97) and maintenance of response (RR 1.94 CI 1.25-3.02). Review of the surgical literature identified 63 studies, of which three were randomised-controlled trials. Interpretation of the literature was impeded by poor outcome reporting and methodological issues of included studies. A survey of gastroenterologists showed thiopurines and anti-TNF were first-line agents. Variation was noted in time to reassessment following treatment, and selection of subsequent interventions. A survey of colorectal surgeons showed consistency in the treatment in the acute setting, but a wide range in the definitive surgical procedures offered. Clinicians offered consistent indications for faecal diversion. Assessment of treatment pathways across three tertiary centres found the median time to receive anti-TNF agents was 204 days. The study suggested challenges in cross-specialty working. A consensus exercise conducted with colorectal surgeons and agreed a framework for surgical treatment. Semi-structured interviews with 17 patients found that participants wanted to participate in decision-making and suggested information needed to inform decisions. This informed the a survey conducted across 10 centres. Principal component analysis identified three items to inform decisions; immediate aftercare, effect on perianal region, severity of operation. This thesis shows variation in clinical practice. Patients wish to participate in decision-making about their treatment. The items identified may form the basis of a preparedness for decision-making tool. This thesis may form the basis for a patient decision aid.

1.1 Hypothesis

Clinicians and patients lack evidence-based information and guidelines for the management of Crohn's anal fistula, leading to variation in practice. Informational needs of patients when decision making may differ from that which is currently provided.

1.2 Aims

The aim of this thesis is to define current practice and evidence for the management of Crohn's anal fistula, and to explore patient preferences and informational needs around the surgical management of this condition.

1.3 Objectives

1. To undertake a systematic review of the literature to assess the evidence for surgical treatments of Crohn's anal fistula
2. To undertake a systematic review of the literature to assess the evidence for medical treatments of Crohn's anal fistula
3. To undertake a survey of Consultant Colorectal Surgeons to describe current surgical management of Crohn's anal fistula
4. To undertake a survey of Consultant Gastroenterologists to describe current medical management of Crohn's anal fistula
5. To establish consensus in the surgical management of Crohn's anal fistula
6. To describe current patient pathways from presentation to treatment of Crohn's anal fistula
7. To describe patient experiences and preferences related to surgical treatment of Crohn's anal fistula through semi-structured interviews
8. To explore patient decision making preferences and key informational items through a questionnaire

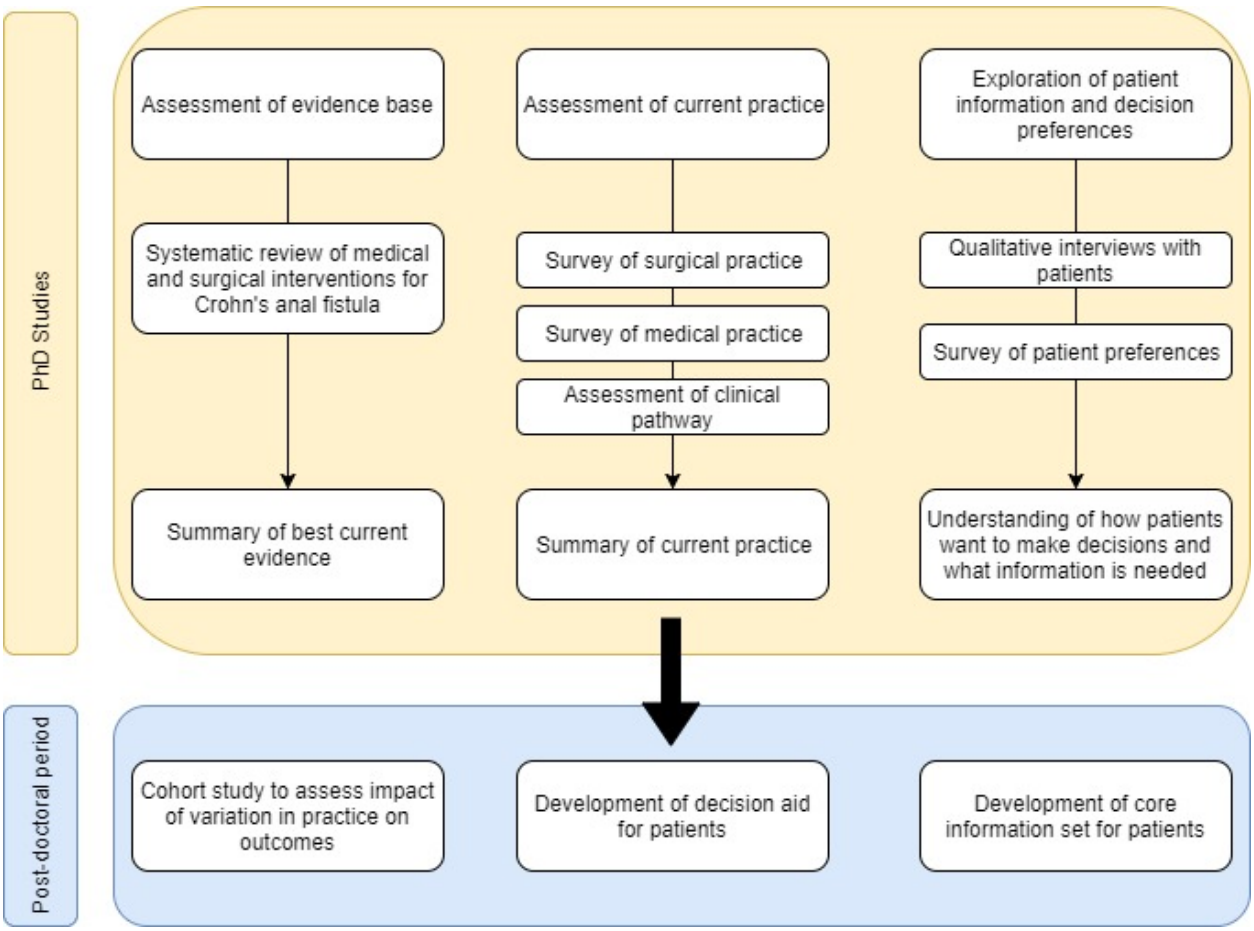

Figure 1: Summary of PhD work and planned future work

2. Introduction

2.1 Crohn's disease

2.1.1 Overview and incidence

Crohn's disease may affect any part of the gastrointestinal tract[1 2]. It has an incidence and prevalence in the United Kingdom of up to 11.4 per 100,000 and 262 per 100,000 respectively[3]. It can affect any age group, although 90% of patients are diagnosed between 10-40 years of age. There is a slight female preponderance. The highest incidence is in Northern Europe[2]. Disease onset at a younger age tends to predict a more severe course.

2.1.2 Pathology appearance

Crohn's disease is a granulomatous inflammation of the full thickness of the bowel wall[2]. Whilst it may affect any part of the gastrointestinal tract, it commonly affects the ileocolic region (approximately 42.5% cases), the colon only (30.8%) or ileum only (26.4%)[4] . Macroscopically, it is characterised by skip lesions, a cobblestone appearance of bowel mucosa, and mucosal oedema. There is typically rectal sparing. The affected bowel wall may be thickened, or fibrosed. There is typically encroachment of mesenteric fat onto the bowel wall, and a proliferation of mesenteric lymph nodes. Microscopic inspection shows transmural inflammation, intra-mural lymphoid aggregates, submucosal oedema, mucosal ulceration, and non-caseating granuloma in the bowel wall or lymph nodes[2]. There is also often evidence of peri-neural inflammation and angiogenesis within the mesentery[5].

2.1.3 Disease behaviour

Crohn's disease tends to follow distinct phenotypical behaviours in terms of distribution and behaviour of disease. These can be classified using the Montreal classification system[1]. This system uses three components: age at onset of disease, distribution of disease, and whether the disease causes

inflammation only, structuring, or penetrating behaviour. This classification is summarised in Table 1 below.

	1	2	3	4
Age at diagnosis (A)	<16 years old	17-40 years old	>40 years old	-
Location (L)	Terminal Ileum	Colon	Ileocolonic	Isolated upper GI
Behaviour (B)	Non-stricturing, non-penetrating	Stricturing	Penetrating	-

Table 1 Summary of components of Crohn's disease phenotypes.

If perianal disease is present, a modified of 'p' is added.

The clinical presentation of Crohn's disease varies according to underlying disease behaviour. Clinical presentations include abdominal pain, diarrhoea, mouth ulcers, weight loss, anaemia, intestinal obstruction or intestinal perforation. It often follows a relapsing-remitting course with periods of increased or decreased disease activity[6]. Onset of symptoms before the age of 40, and perianal disease are markers of an aggressive disease phenotype[7].

2.1 Aetiology

Crohn's disease is thought to have a complex, multifactorial aetiology. It is most likely related to an aberrant immune process with a genetic basis, which is modified by other lifestyle and environmental factors.

2.1.1 Genetic evidence

The role of genetic susceptibility has long been recognised due to familial segregation of the disease in related individuals[6]. Cohort studies have demonstrated that relatives of Crohn's patients tend to follow the same disease phenotype. Advances in technology such as gene sequencing, gene arrays and the creation of huge genetic population consortia have facilitated recent advances in our understanding of the genetic underpinnings of the disease. A genome-wide association study, which included more than 16,000 patients with Crohn's disease, demonstrated strong associations between three genetic loci and disease phenotype. These loci were 3p21, 6p21, and 16q12, which code for Macrophage Stimulating 1 Gene, class 2 and 3 Major Histocompatability Complex genes, and Nucleotide-binding Oligomerization Domain-containing-2 respectively[8].

Macrophage Stimulating 1 gene (MST1): This gene has a role in the innate immune system, as it codes for Macrophage Stimulating Protein (MSP). In the presence of inflammation, MSP is activated, and attracts macrophages through chemotaxis. It has a role in suppressing the production of inflammatory mediators and cytokines by macrophages. Missense mutations of MST1 have been detected in association with Crohn's disease [8]. These mutations are associated with loss of function of the gene. This is supported by the presence of downstream inflammatory markers which should otherwise be suppressed, in the intestinal mucosa of patients with IBD[9 10].

Major Histocompatability Complex (MHC): This refers to a region of genetic coding material on the short arm of chromosome 6, also known as the Human Leucocyte Antigen region. Variation at this locus is associated with a number of autoimmune diseases[11]. This region codes for molecules which present antigens to the host immune system. There are three main classes of MHC molecules. Class I MHC present peptide fragments from 'normal' cells to CD8+ T cells – those presenting recognised fragments are tolerated by the immune system. Class II MHC are typically found on B-cells, macrophages, dendritic and other antigen presenting cells. These present peptide fragments from abnormal cells as antigens to stimulate the activity of CD4+ cells, stimulating an immune response[12]. Whilst there are associations between MHC variants and both forms of IBD, variants affecting class II MHC alleles have shown a strong association with the development of Crohn's diseases i.e. HLA-DRB1*07, HLA-DRB1*0103, HLA-DRB1*04, and HLA-DRB3*0301[11 13]. Class III MHC genes are related to immune function, and lie between the Class I & II coding regions[14]. These genes are also implicated in the development of Crohn's disease, and polymorphisms can lead to up-regulation of Tumour Necrosis Factor, a pro-inflammatory cytokine[8 13].

Nucleotide-binding oligomerization domain-containing-2 (NOD2): This gene codes for a NOD-like receptor, which has a role in sensing and triggering a response to bacterial wall peptides. Polymorphisms in this gene causes loss of immune function and reduce rates of bacterial clearance, leading to changes in the intestinal microbiome[15].

2.1.2 Evidence for the role the microbiome in Crohn's disease

The role of bacteria in the aetiopathogenesis of Crohn's disease is not yet clear. Patients with Crohn's disease have changes in their intestinal microbiome when compared to healthy individuals, but it is not

clear whether this is cause or effect [16] [17] [18]. It is well established that the microbiome shifts towards one with less diversity, and with the presence of more invasive species of bacteria in Crohn's disease[16] [19]. Faecal microbiota transplanted from healthy individuals into those with Crohn's disease have been shown to restore biodiversity and leads to a clinical response or remission in small studies[20] [21]. Laboratory studies have also demonstrated the role of bacterial antigens in stimulation of run-away inflammatory processes which are commonly seen in Crohn's disease[22].

2.1.3 Environment and lifestyle factors

Lifestyle and environmental factors have a role in the development of Crohn's disease. This is partly supported by the increased rate of illness seen in migrants moving from low prevalence areas to high prevalence areas [23]. Smoking is one of the most widely investigated factors and shows a strong positive association with the development of Crohn's disease, as well as subsequent complciations [24]. Smoking triggers the inflammatory process through activation of CD4+ T cells[25]. Aside from the direct effects of inflammation, smoking may also increase intestinal permeability. *Escherichia coli* species have been found in the intestinal wall of smokers, which may lead to a sustained inflammatory stimulus[26]. Smoking is associated with a significant reduction of bacterial species with anti-inflammatory properties in the Crohn's population[27].

Being breastfed as a child is protective. Breast milk may modify the intestinal microbiome and provide additional benefits to the immune system. It is interesting to note that the protective effect is greater in Asian populations than Caucasian populations[28]. Other factors implicated in the development of Crohn's disease include use of antibiotics before age of 15 years, high intake of fast food, and childhood BCG vaccination[29] [30]. Having a pet dog may also confer protection, although evidence for this is weak[29].

More detailed description of the aetiopathogenesis of Crohn's is outwith the scope of this thesis.

2.2 Crohn's Anal Fistula

2.2.1 Definition of a fistula

A fistula is an abnormal connection between two epithelial surfaces. In the context of a perianal fistula, this is an abnormal connection between the anorectum and perianal/perineal skin or pelvic organs such as the vagina or bladder[31]. When this occurs in the presence of Crohn's disease, it is referred to as Crohn's anal fistula. This is a sub-phenotype of penetrating Crohn's disease in the Montreal classification . In around 15% of cases, anal fistula is the first presentation of Crohn's disease[32]. It can occur at any point during the disease, and therefore can affect patients of any age.

2.2.2 Clinical presentation of a fistula

Crohn's anal fistula can present to clinicians in a number of different ways. Patients may complain of anal pain, or bleeding. If the fistula has completed the connection between anus and surrounding skin, the patient may complain of foul smelling discharge or incontinence-like symptoms. If the tract has not completed the connection between the two surfaces, this means it is blind ending. This allows a space for discharge to stagnate, becoming infected and eventually forming an abscess.

2.2.2 Aetiopathology of fistula in Crohn's

The classic theory of fistula formation was described by Parks' in his cryptoglandular hypothesis [33]. This postulates that the anal glands become blocked, leading to accumulation of mucus which is normally used for lubrication in the anal canal. The resulting accumulation of mucus discharges through the path of least resistance, which is typically through the skin. In some cases, the path remains open, leading to the formation of a fistula.

The aetiology of perianal fistula in Crohn's disease differs from the cryptoglandular theory, in part due to the underlying disease process, and in part due to the different behaviour of the fistula. The two key

mechanisms involved in the formation and persistence of Crohn's anal fistula are epithelial-mesenchymal transition and matrix-metalloproteinase activity, both described in detail below. This mechanism is summarised in Figure 2.

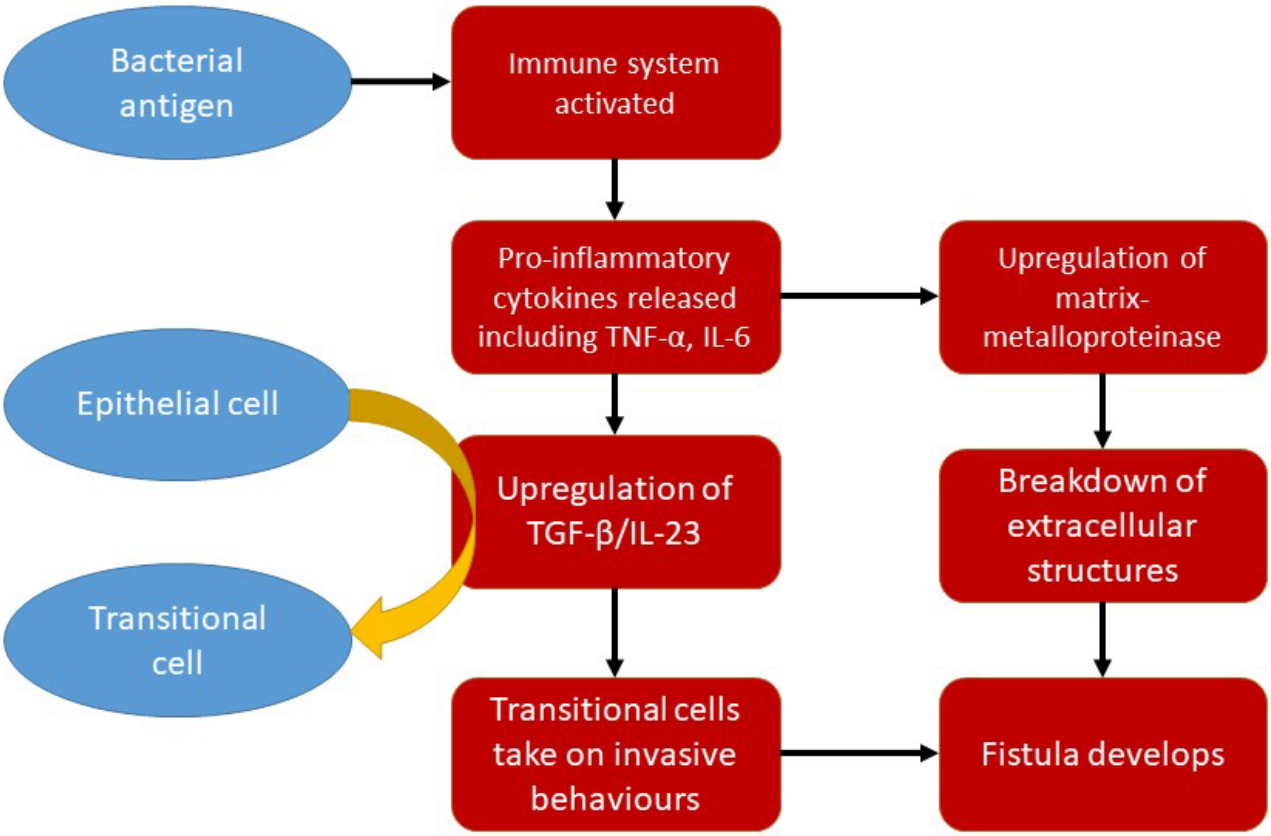

Figure 2 Summary of proposed mechanisms underlying anal fistula formation in Crohn's disease.

2.2.2.1 Epithelial-Mesenchymal Transition

The cells present on the gastrointestinal surface are of epithelial type. These cells can transition to become mesenchymal type (i.e. transitional cells), gaining the ability to penetrate surrounding tissues – a behaviour also seen in primary and metastatic cancers[34]. Support for this theory comes from the identification of transitional cells with epithelial origins within fistula tracts[22 35]. Mechanistic evidence has shown that this epithelial-mesenchymal transition can be induced by high levels of pro-inflammatory

cytokines including Tumour Necrosis Factor (TNF)-α[22]. This leads to upregulation of Transforming Growth Factor (TGF)-β, which in turn upregulates expression of interleukin (IL)-13 in intestinal epithelial cells, promoting invasive behaviour of cells[36]. High levels of these cytokines are present in the anorectal mucosa of patients with Crohn's disease[37]. This may be in response to bacterial antigens[22].

2.2.2.2 Matrix MetalloProteinases

Matrix metalloproteinases (MMP), are enzymes with a role in the remodelling of the extracellular matrix. They may have a role in micro- and macroscopic remodelling of the gastrointestinal tract, leading to fistula formation. MMPs have been implicated in the pathogenesis of Crohn's disease, as deletion or silencing of relevant MMP regulatory genes confers protection in murine models of colitis, wheareas over expression of these genes worsens disease phenotype[38]. In humans, increased MMP activity is seen in inflammatory bowel disease, although activity seems to be higher in Crohn's disease versus Ulcerative colitis[39]. Differing activity of MMP subtypes has been noted in Crohn's disease – raised MMP-1 activity is seen in active luminal disease, whereas MMP-9 activity may be downregulated in perianal disease[40]. This may partly explain the differing behaviour seen in different disease phenotypes. Examination of resected fistula specimens has shown increased presence and activity MMP-3 & MMP-9, particularly in relation to mononuclear cells and fibroblasts within the associated inflammatory infiltrate[41]. These data are drawn from a mix of cohort studies and smaller case series, although is consistent across all studies.

2.2.3 Clinical impact of Crohn's anal fistula

Crohn's anal fistula has been identified as a priority condition in two research prioritisation exercises in the last five years[42 43]. It is recognised that rates of healing are low; around 20% of patients in trial placebo groups achieve fistula closure[44], and as few as 30% of actively treated patients achieve long term healing in observational studies[45].

The poor rates of healing and response have a direct impact on the health and well-being of patients[46 47]. Trials in Crohn's anal fistula using patient reported outcomes have measured the effect of treatments on quality of life using a range of tools. The generic tools used include the Short form survey (SF)-36, or the European Quality of Life 5 dimensions tool (EQ5D). These address factors related to quality of life in general, and do not address items or factors specific to inflammatory bowel disease or Crohn's disease. The Short-Inflammatory Bowel Disease Questionnaire (S-IBDQ), is a validated and disease-specific four domain tool addressing bowel symptoms, systemic symptoms, emotional impact of disease and social impact. The Work Productivity Assessment Index for Crohn's disease (WPAI:CD) has been shown to correlate with quality of life and assess the impact of disease behaviour on absenteeism, presenteeism (attending work when unfit or unwell), and the proportion of this attributable to inflammatory bowel disease. Other less frequently used tools include assessments of disability due to IBD using the IBD Disability Index, fatigue using generic fatigue measures, and anxiety and depression, again using generic measures[46]. When these tools are used to compare patients with fistula to the healthy population, or to compare poorly controlled Crohn's disease to controlled Crohn's disease, they demonstrate a significant negative impact on quality of life.

A survey of 130 patients treated for Crohn's anal fistula identified anal pain, anal discharge, physical activity restriction, sleep interference and perceived cleanliness as highly important to patients[48]. A

criticism of this study was that it is not clear how the list of quality of life items was generated. This means that the patient voice may not be present in this list, and therefore the report is incomplete. A separate report of the same study assessed self-reported depressive symptoms. This found that patients with a stoma were more likely to feel that life is not worth living (OR 8.67 (95% C.I. 2.7-27.4)). This is likely to be the effect of severe perianal disease along with stoma, rather than the effect of a stoma alone. A history of anal stricture or anal stenosis was associated with suicidal feelings (OR 11.2 (95% C.I. 2.1-5.9). The study notes that there was an association between longer duration of disease and both of these measures[49]. This may however be confounded as these complications are more likely to develop over a longer disease course. The finding that a stoma is associated with a poorer quality of life is interesting. A study comparing quality of life in patients with perianal disease between those with and without stoma, found no difference in global quality of life measures. It did find a small difference in the gastrointestinal symptoms domain of the gastrointestinal quality of life index[50].

The literature suggests that people with Crohn's disease have impaired sexual function compared to the healthy population, with greater impact in women[51]. One study reports quality of life following surgery on a retrospective cohort of patients who had undergone surgery for Crohn's anal fistula, and compared their sexual function to healthy controls using the Female Sexual Function Index for women, and the International Index of Erectile Function for men. There was a trend towards lower scores in the operated female group, but this was not apparent in the male group[52]. This study excluded patients with a stoma, and lost a significant number of responses as a result. This, in combination with the separate analyses of male and female patients means that the study was likely to be underpowered.

2.2.4 Classification of fistulae

A number of systems can be used to describe Crohn's anal fistula. These varyingly describe anatomy and disease behaviour. There is no common consensus on a tool for common use; each of the systems described below fulfils a specific role, to describe anatomy, disease activity, or associated manifestations of Crohn's disease

2.2.4.1 Parks' Classification

Parks' classification was originally proposed for fistulae of cryptoglandular origin[53]. This describes the anatomical location of a fistula in relation to the anal sphincters, and whether it lies close to the anal verge (low), or away from it (high). This classification system is widely used as it clearly communicates the anatomy of the fistula. It does not provide prognostic data, nor provide a treatment framework based upon anatomic classification.

2.2.4.2 Cardiff-Hughes

The Cardiff-Hughes system is a classification system designed for perianal Crohn's disease. It recognises the presence of ulceration, fistula or stricture, and allocates up to two points for severe presentations of these disease manifestations. These numbers are added together to give an overall score; the higher the score, the worse the perianal disease is[54]. The major criticism of this score is that it is not specific to fistula, and does not allow meaningful description or classification of a fistula to guide clinical treatment.

2.2.4.3 Van Assche MRI Score

The Van-Assche score is based upon magnetic resonance imaging of the pelvis to describe fistula activity and number. It records data on whether fistulae are single or multiple, branched or unbranched, the location of the tract in relation to the sphincters and levators, hyper intensity on T2 imaging; the presence of collections and evidence of rectal wall involvement[55]. Intra-rater reporting of this measure is only moderate, and inter-rater reliability is poor[56].

2.2.4.4 American Gastroenterology Association

The American Gastroenterology Association (AGA) dichotomises Crohn's anal fistula into 'simple' or 'complex'. It defines a 'simple' fistula as a low sub-sphinteric fistula without proctitis. Mid or high transphincteric or intra-sphincteric fistulae, or those associated with proctitis or recto-vaginal involvement are considered complex. As with Park's classification, this provides broad groups of fistula types, but does not provide definitive guidance on fistula treatment.

3. Assessment and treatment of a patient with Crohn's anal fistula

3.1 Assessment of patients with suspected Crohn's anal fistula

A number of investigations are available to assess the patient with suspected Crohn's anal fistula. These can be broken down into endoluminal assessment, measures of disease activity, and radiological assessment. A potential minimum investigation set is presented in Table 2.

3.1.1 Endoluminal assessment

Endoluminal assessment refers to a range of investigations that allow visual inspection of the intestinal and colonic mucosa. These are categorised according to mechanism of visualisation, and anatomic region assessed. Current endoluminal investigations are capsule endoscopy and fibreoptic endoscopy of colon.

2.3.2 Capsule endoscopy

In capsule endoscopy, a small capsule containing a camera, light source and transmitter is swallowed by the patient. This takes photographs at frequent intervals and transmits them to a receiver worn by the patient. Capsule endoscopy is typically used for the detection of small bowel Crohn's when other investigations are inconclusive. It has high sensitivity for detection of Crohn's (100%) but moderate specificity (69.2%)[57].

Data required	Potential Investigation Tool/Modality	Justification
Fistula anatomy including number, location and presence of abscess	MRI Pelvis Endoanal Ultrasound	To plan surgical strategy for drainage +/- overall multidisciplinary strategy
Anatomical assessment of intestinal disease	Colonoscopy	Assessment for large bowel disease – a prognostic factor for failure of healing+
	CT Abdomen or MRI small bowel	To assess for complications of Crohn's disease (e.g. fistula or abscess) affecting small bowel or colon
Assessment of disease activity	Harvey Bradshaw Index Crohn's Disease Activity Index Faecal calprotectin Perianal Disease Activity Index	Assessment of disease activity in general Assessment of perianal disease activity
Safety screening	Thiopurine-S-Methyl Transferase assay Chest Radiograph Interferon gamma	Safety screening prior to use of immunosuppression with thiopurines or anti TNF agents

Table 2 Investigations potentially required to 'stage' & plan treatment in Crohn's anal fistula

2.3.3 Fibreoptic endoscopy

This investigation uses a flexible endoscope to visualise the colonic mucosa from rectum to the ileo-caecal valve, allowing inspection of the terminal ileum (colonoscopy). Biopsies may also be taken. The procedure is aided by insufflation of the colon with air or carbon dioxide gas – this distends the lumen and allows passage of the endoscope[58]. This procedure is not without risk. Some patients are not able to tolerate flexible endoscopy, despite adequate use of analgesia. The procedure is technically difficult in some patients, especially where there has been previous pelvic surgery. There is also the risk of bleeding from a biopsy site, and the risk of colonic perforation. This risk is higher in colonoscopy than sigmoidoscopy, with rates as high as 5% vs 0.08% respectively[59].

2.3.4 Assessment of disease activity

Disease activity can be assessed in a number of ways. These include faecal calprotectin, composite measures of global disease activity, and composite measures of perianal activity.

2.3.4.1 Faecal Calprotectin

Faecal calprotectin is a 35kDa protein which binds calcium and zinc. Levels of this are typically raised in the presence of increased neutrophil activity[60]. The diagnostic performance of faecal calprotectin in the diagnosis of IBD has a sensitivity of 93% and a specificity of 96%[61]. It is reproducible and a non-invasive test and may therefore be of value in the diagnosis and monitoring of inflammatory bowel disease, particularly in primary care[61 62].

2.3.4.2 Crohn's Disease Activity Index

The Crohn's disease activity index (CDAI) is a clinical assessment of disease activity which has previously been widely reported in clinical trials in Crohn's disease. It is not widely used in clinical practice. However it correlates poorly with direct assessments of mucosal inflammation[63]. The index includes deviation from ideal body weight, frequency of liquid or soft stools, abdominal pain, abdominal mass, general wellbeing, anti-diarrhoeal drug use, haematocrit and the presence of extra-intestinal manifestations to assess activity. Wellbeing, pain and abdominal mass are rated on an ordinal scale from 0-3, and other categories rated 1 if present, 0 if absent. Multipliers are applied to each response, and a total composite score is reached. A CDAI <150 indicates remission of disease, a CDAI >450 indicates severe disease[64].

2.3.4.3 Harvey Bradshaw Index

Harvey-Bradshaw Index (HBI) was proposed in 1980 as a refinement of the CDAI and remains in use. This composite measure addresses five domains: general wellbeing, abdominal pain, number of liquid stools per day, abdominal mass, complications of disease. Wellbeing, pain, and abdominal mass are scored 0-3 on an ordinal scale. Similarly to CDAI, it shows limited correlation with mucosal inflammation[65].

2.3.4.4 Perianal Disease Activity Index

Both the CDAI and HBI focus on global disease activity and do not assess perianal disease specifically. The Perianal Disease Activity Index (PDAI) was first described in 1995. It includes five domains rated 0-4. The domains are discharge, pain/restriction of activities, restriction of sexual activity, type of perianal disease and degree of induration. Three domains are rated by patients and two by clinicians[66]. Despite the relative subjective nature of this index, it performs well when compared to other measures of activity, with a score >4 indicating active disease[67].

2.3.5 Radiological assessment

A number of radiological tools are available for the assessment of the extent and complications of Crohn's disease. These include cross-sectional imaging with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). Endoanal Ultrasound has also been described in the assessment of perianal disease.

2.3.5.1 Computed Tomography Imaging

CT scanning provides three dimensional images of the structures being assessed, using X-ray technology. It is accepted as an appropriate modality in Crohn's disease[68]. Whilst it can demonstrate inflammation of a viscus, it is typically more helpful in the assessment of complications of disease such as fistula or abscess. It performs poorly in assessment of the perianal region[69].

2.3.5.2 Magnetic Resonance Imaging

MRI scanning relies on the use of powerful magnets to affect the spin of protons in the tissue undergoing assessment. The resulting images can be viewed as 'T1', where tissues containing water are dark, or 'T2', where tissues containing water are bright. Tissues which are bright on T2 imaging are typically inflamed. MRI assessment of the small bowel can provide evidence of inflammation and stricturing and provide more accurate data on the location of the pathology than is possible with CT scanning. Given the nature of T1 and T2 sequences, it is also possible to tell whether strictures in small intestine are active (high signal on T2) or inactive (low signal on T2). This suggests whether disease may be amenable to a trial of medical therapy, or, if it is burned out disease, it is likely to require surgical intervention. Small bowel MRI has sensitivity and specificity of 97% and 96% respectively[70]. MRI assessment of the pelvis is well established in the context of perianal fistula. If can be used to describe the relationship of a fistula track to the sphincter muscles and surrounding structures, identify abscesses deep within the pelvis or ischiorectal

fossa, and identify secondary tracks[68]. Sensitivity and specificity for detection of fistula using MRI is 87% and 69% respectively[71]. There has been recent exploration of 3-dimensional rendering of MRI pelvis images, although these are still in an exploratory phase[72]. Whilst activity and inflammation may be assessed in MRI of the abdomen, equivalent tools to assess for inflammation in the pelvis have yet to be developed.

2.3.5.3 Endoanal Ultrasound

Endoanal ultrasound is performed by insertion of an ultrasound probe into the anal canal. This allows 360 degree assessment of the sphincter complex, and for any surrounding sepsis. Sensitivity and specificity for this modality are 0.87 and 0.43 respectively[71]. This investigation is performed by limited numbers of physicians as it is operator dependent, and not as widely available as other imaging modalities.

3.2 Current management

Current treatment options for Crohn's fistula involve multidisciplinary management, and are typically shared between gastroenterologists and colorectal surgeons[73]. The interventions offered can be split into medical and surgical therapies. Whilst considered separately here, they are typically offered as a package of treatments.

3.3 Medical Treatments

Drugs used in the treatment of Crohn's anal fistula include biologic agents, immunosuppressants, and antibiotics. These can be used alone (monotherapy) or in combination.

3.3.1 Systemic Monotherapy

The currently favoured systemic medical therapy is one of the class of drugs which impedes anti-TNF-α signalling and so reduces the inflammatory process. Infliximab is a chimeric anti-TNF-α monoclonal antibody. Present and colleagues undertook a three-armed randomised controlled trial of Infliximab in 94 patients with fistulating Crohn's, of whom 90 had perianal disease. The primary endpoint (a 50% reduction in the number of fistulae), was reached by 8/31 (25.8%) patients in the placebo group and 39/63 (61.9%) patients in the treatment arms [74]. In the randomised 'A Crohn's Disease Clinical Trial evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn's Disease' (ACCENT II), patients were allocated to a 5mg/kg dose of Infliximab or placebo [75]. This included patients with fistulating Crohn's disease, 90% of whom had perianal fistula. The primary outcome was defined as a reduction in the number of draining fistulae of 50% or more across two visits four or more weeks apart. When assessed at week 54 of the study, complete fistula resolution was seen in 36% of treated patients vs 19% in the placebo group (p=0.009). A post-hoc subgroup analysis from this trial found that in treated patients, 64% had closure of their recto-vaginal fistula. This subgroup represents just 25 patients, of whom only 14 were included in the treatment arm, so caution should be exercised in interpreting these results [76].

Adalimumab is a humanised recombinant monoclonal antibody to TNF-α. The Crohn's Trial of the Fully Humanized Antibody Adalimumab for Remission Maintenance (CHARM) trial was designed to assess Adalimumab in the induction and maintenance of remission of Crohn's disease [77]. This study assessed the outcomes of enterocutaneous and perianal fistulae as one entity, and demonstrated fistula closure rates of 30% vs 13% in the treated and placebo groups respectively (p=0.04). Patients with fistula response were entered into a two-year open label trial where adalimumab was administered on a weekly or alternate week dosing regime vs placebo for two years. At the end of this study, patients on placebo had a mean of 1.88 draining fistulae vs 0.88 in the treatment groups (p=0.002). A four-year open label extension of this trial found that fistulae remained closed in 25% of patients who entered the study with a draining fistula[78].

The effect of adalimumab as a 'rescue' therapy for fistulating disease has been assessed in the Crohn's Disease WHO Failed Prior Infliximab to Collect Safety Data and Efficacy via Patient-Reported Outcome Measures (CHOICE) trial [79]. This trial took patients who had never responded to Infliximab (PNR), or had initial response, which was lost (PI). Follow-up data were available at 4-36 weeks for the 88 patients with fistulae, 34 of whom demonstrated clinical remission.

Certolizumab, a pegylated Fab fragment, did not show any difference in fistula closure rates between placebo and treatment groups in the Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy 1 (PRECISE 1) trial (31% vs 30% at 34 weeks) [80] In the subsequent Pegylated Antibody Fragment Evaluation in Crohn's Disease Safety and Efficacy 2 (PRECISE 2) trial, 54% of patients treated with certolizumab had fistula closure, vs 43% of the placebo group (p=0.064) at 26 weeks [81]. Post-hoc analysis of the 58 patients with fistulating disease found a 100% fistula closure rate at 26 weeks in 4/30 placebo treated patients and 10/28 treatment arm patients (p=0.038). The number of patients with 50% closure of fistulae was 7/30 and 11/28 respectively (p=0.125) [82].

These studies suggest significant benefit from these drugs alone. On review of the baseline characteristics of participants there is evidence of combination of therapies including aminosalicylates, steroids and thiopurines. A summary of additional therapeutic agents received in monoclonal antibody trials is presented in table 3.

Study	ACCENT II	CHARM	CHOICE	PRECISE I	PRECISE II
Monoclonal Antibody	Infliximab	Adalimumab	Adalimumab	Certolizumab	Certolizumab
Total N	282	854	673	659	425
Additional therapies:					
5-aminosalicylates	132	334	239	-	-
Thiopurines	92	356	-	-	-
Methotrextate	5	90	-	-	-
Steroids	81	376	285	256	153
Antibiotics	83	-	-	-	-
'Immuno-suppressants'	-	-	277	247	173

Table 3 Summary of additional medical therapies in anti-TNF-α trials reporting fistula outcomes.

Demonstrates polytherapy in up to 50% of patients. The CHOICE, PRECISE I & II trials did not report on specific immunosuppressants used.

3.3.2 Local monoclonal antibody

Infliximab has also had open-label trials assessing local injection of the drug into the fistulating area rather than traditional systemic administration. Allesandroni and colleagues [83] assessed the efficacy of local Adalimumab in a case series of twelve patients. Four were withdrawn from the trial due to the need for systemic therapy. Seven of the eight patients treated had fistula closure at twelve months [83]. This assessed the outcome of 20mg local injections of infliximab into the fistulae of eleven patients. After a mean of 10.5 months, 6 patients had complete response and four had remission of symptoms [84]. Tonelli assessed

local injection of adalimumab into the fistula of twelve patients and demonstrated complete response in nine patients, with symptomatic response in the remaining three [85]. These are small trials with only one-year follow-up. This approach or other combined modalities such as anti-TNF impregnated collagen paste would be interesting ways to develop this. These studies did not assess local absorption or tissue concentrations. To understand mechanisms and dosing of therapy, this pharmacodynamic and pharmacokinetic data are required.

3.3.3 Combination Therapy

The monoclonal antibody class of drugs have been the focus of most clinical trials reporting fistulating Crohn's disease in the last decade, although fistulating perianal disease was assessed as post-hoc subgroup analyses rather than as a primary focus of the study. As these have not achieved total resolution of fistulating Crohn's, therapeutic studies have addressed 'augmented' therapy. Recent studies have assessed combinations of anti-TNF therapy with other classes of drug. Thiopurines (Azathioprine, 6-Mercaptopurine) have been evaluated in a prospective cohort study. This non-randomised investigation followed a protocolised management plan, with changes in treatment where clinical remission was not achieved. In this study, thiopurines were combined with Infliximab (n=32) or Adalimumab (n=9) in the case of Infliximab non-response. This study reported a clinical response in 40% of patients for the first 18 months of therapy, falling to 37% at 36 months [86]. This study reported that at 36-months of follow-up, infliximab induced clinical remission and response rates of 33% and 33% respectively. The Adalimumab group had remission and response rates of 0% and 43% respectively. Whilst this study commenced with 43 patients, only 12 of the infliximab group and 7 of the Adalimumab group completed the 36-month follow-up.

Further studies have compared the effect of combining multiple medical therapies. Dewint and colleagues[87] undertook an RCT comparing adalimumab (anti-TNF-α) monotherapy vs adalimumab combined with ciprofloxacin (quinolone antibiotic) – (the adalimumab combined with ciprofloxacin was superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease (ADAFI) trial). The arm combining adalimumab and antibiotic therapy showed a trend towards increased rates of fistula closure after 12 weeks of therapy (65% vs 33%, p=0.09). The power calculation was based upon an open label study of 36 patients and the effect size estimate was optimistic at 20% absolute increase in patients reaching the primary outcome (closure of at least 50% of fistula). As well as being unable to detect the true effect size, it is likely that the study did not adjust for other variables associated with disease in the randomisation process such as fistula duration or anatomic complexity. West and colleagues undertook randomised placebo controlled trial of Infliximab with ciprofloxacin vs infliximab with placebo. This included a total of 24 patients with 12 allocated to each arm. This found no statistically significant difference in rates of clinical response at week 18; 8 (73%) responded in the intervention group vs 5 (39%) in the control group, although numbers were small [88]. The authors did not perform a power calculation or sample size estimate, and the study seems to have been conducted with convenience determining the sample size.

Author & Year	Design	Anti-TNF agent	Additional agent	Number of patients in study	Anti-TNF only success	Combined agent success
Dewint 2014	RCT	Adalimumab	Ciprofloxacin	76	33%	65%*
Tozer 2012	Prospective observational	Infliximab or Adalimumab	Thiopurine	41	-	42%**
West 2004	RCT	Infliximab	Ciprofloxacin	24	62%	91%*

Table 4 Studies assessing impact of augmented anti-TNF.

**outcome at week 12. **outcome at 12 months.*

3.3.4 Stem cell therapy

Stem cells have been used in trials of healing chronic wounds during recent years[89]. This has been extended to assessment of efficacy in Crohn's anal fistula[90], but the exact mechanism of healing in a fistula is not clear. Studies in analogous conditions such as chronic wounds suggest that stem cells in such an environment release signalling molecules including micro-RNA's to promote fibroblast development and angiogenesis[91]. Adipose derived, autologous mesenchymal Stem cells are administered directly into the fistula during a surgical procedure, however they are considered here as a medical therapy due to their mechanism of action. One randomised trial has been completed in which 50% of patients receiving stem cells into their fistula achieved remission at 24 weeks vs 34% in the control arm (p=0.024)[92]. This response rate is notable as it is double that typically seen in placebo arms of trials in this condition[44]. The control arm included extensive fistula track preparation and closure of the internal fistula opening, suggesting that the stem cells were not the only aspect of the intervention which supported healing.

3.4 Surgical management

Whilst there are trials reporting the outcomes of medical therapy for this condition, albeit post-hoc analysis of subgroups, there have been no large randomised controlled trials of surgical therapies. This may be due to the high degree of heterogeneity inherent in the disease. This includes factors relating to disease course (phenotype of Crohn's disease, mild or fulminant disease, duration of disease), prior treatment (anti-TNF antibodies, loss of response to treatment), and fistula anatomy (simple vs complex, number of fistula tracks, primary and secondary track behaviour). As all these factors could impact on clinical decision making and therefore a well-designed surgical trial would either need to stratify recruitment for these variables or limit recruitment to very specific characteristics which would make recruitment of adequate numbers challenging. Senejoux and colleagues recruited a small number of patients with tightly controlled characteristics to a trial evaluating a fistula plug and obtained a negative result[93]. This study is discussed below. There is currently a trial running with very rigorous entry criteria which may limit its' ability to recruit to time and target[94].

Several small studies have assessed results from a range of surgical therapies including;

I. Seton drainage alone
II. Fistula plug
III. Mucosal advancement flap
IV. Intersphincteric ligation of fistula tract (LIFT) procedure
V. Over the scope clip (OTSC).
VI. Fibrin glue
VII. Faecal diversion procedures

These are summarised in table 5 and discussed in more detail below.

3.4.1 Seton drainage

A seton is a length of thread or a rubber sling which is inserted into the fistula track and secured to itself, allowing continued drainage. Where the surgical procedure is seton drainage alone, it is usually combined with adjunctive medical therapy. Two recent observational studies have assessed seton drainage combined with anti-TNF therapy, followed by removal of the seton. These reported fistula closure rates of 50-75%, with low levels of long-term recurrence, offering improvement above anti-TNF therapy alone [95 96]. A similar study in adolescents showed response to treatment (partial or complete remission) in 85% of patients [97]. This result is particularly impressive given that it was limited to patients with complex perianal fistulae.

3.4.2 Fistula plug

A fistula plug is an option for closure of the track. This is typically a cone of collagen that is inserted into the fistula from inside the anal canal, effectively blocking it. Where this is done, a flap of mucosa may be advanced to cover the plug, sealing off the track. A systematic review of use of a plug for anal fistula included 42 Crohn's patients. Use of this treatment lead to closure of the tract in 55% [98]. A subsequent trial randomised 106 patients with Crohn's fistulae to sepsis drainage followed by fistula plug alone vs sepsis drainage with seton alone. This demonstrated no significant benefit from the use of an anal fistula plug. Remission rate at 12 weeks was 34% (95% CI 19.5%-45.5%) vs 23.1% (95% CI: 12.5–36.8%) in the control arm[93]. This study required patients to be receiving a stable dose of medication for the previous 3 months and did not mandate the use of biologic-class agents. There was no difference in remission, response, disease specific quality of life, disease activity or MRI scores at 12 weeks or 12 months. The analysis of this study is compromised as 12 patients (22.2%) in the intervention arm were lost to follow-up before week 12, compared to 1 in the control arm. As a result, the study does not meet the minimum of 52 patients in each arm to detect a 30% difference. Subsequently, these results do not compare favourably with seton drainage and/or anti-TNF therapies, although no direct comparison has been made.

This comparison is further complicated as there is no consensus or standardisation on the timing of seton removal.

3.4.3 Advancement flap

An advancement flap is a sphincter-sparing approach for a transphincteric fistula. In this treatment, a full or partial thickness 'U' shaped flap of rectum is raised adjacent to the internal defect, and advanced to cover the defect. A review by Soltani and Kaiser found 35 studies reporting outcomes following advancement flaps; these were predominantly retrospective cohorts. Of these, six reported the outcomes for patients with Crohn's fistula, and estimated a success rate of 64% in Crohn's disease, and an associated incontinence rate of 9.4%[99]. Concomitant medical therapy and disease activity were not reported.

3.4.4 Ligation of intersphincteric fistula tract (LIFT)

The LIFT procedure was first described in 2007 then modified in 2009 [100 101]. This technique preserves the anal sphincters by approaching the fistula track through the intersphincteric plane and ligating it, then closing the internal portion and excising the external portion of the fistula. There is little data specifically on use of LIFT in Crohn's disease. A prospective study published in 2014 reported outcomes of fifteen LIFT procedures for Crohn's fistulae [102]. The procedure was successful in nine cases at two-month follow-up. At twelve-month follow-up, one repair had failed and three patients had developed a new fistula. In clinical practice, a definitive procedure such as LIFT would often be preceded by placement of a drainage seton. A subgroup meta-analysis of 228 patients compared the effect of pre-operative seton placement or no seton in patients undergoing LIFT and showed no difference in success rates [103]. Reporting of Crohn's disease in the included studies was incomplete so this may not be generalisable to the Crohn's population.

3.4.5 Over the scope clip (OTSC)

Over the scope clip (OTSC) is a relatively novel technique. The external portion of the track is cored out. The internal opening of the fistula is identified, and the fistula track cleared of debris using a narrow brush. A small circle of mucosa 8-10mm in diameter is excised around the internal opening to expose the

underlying muscle. Interrupted sutures are placed to close the defect in the muscle. The suture ends are left long and passed through the clip applicator. After 2-3 sutures have been placed, the clip applicator is guided down the suture to the site for clip application. The applicator deploys an oval 'bear claw' metal clip. The grips on the edge of the clip hold the muscle edges together, facilitating fistula healing. This has been used successfully in upper gastrointestinal fistulae. There is a single paper reporting on the use of this technique in ten anal fistula patients, of whom six had Crohn's disease. Treatment was successful in five of these patients with a follow-up period ranging from 157 to 523 days [104].

3.4.6 Fibrin glue

Fibrin glue is applied into the fistula tract as a paste and activates the thrombin system, causing mechanical obstruction of the fistula tract. Grimaud and colleagues undertook a trial with patients randomised to fibrin glue or observation. At eight weeks, the primary end-point of fistula closure was seen in 38% of the fibrin group compared to 16% of the observation group (OR 3.2 (95% C.I. 1.1-98) p=0.04) [105]. The same group reported that 14 patients with refractory fistulating Crohn's disease underwent fibrin glue treatment. This study found clinical improvement in 75% of patients at three months follow-up and complete healing at two-years in 57% of patients [106]. Despite this, fibrin glue has fallen out of favour with clinicians in both Crohn's and cryptoglandular fistulae due to poor perception of efficacy.

Surgical technique	Author & Year	Design of reporting study	Number of Crohn's patients treated	Success rate in Crohn's patients
Seton only	Haennig 2014	Retrospective Observational	81	75%
	Hukkinen 2014	Retrospective Observational	13	77%
	Kotze 2015	Retrospective Observational	78	52%
	Senejoux 2015	Randomised Controlled Trial	52	23%*
Fistula plug	O'Riordan 2012	Systematic Review	42	55%
	Senejoux 2015	Randomised Controlled Trial	54	31%
LIFT	Gingold 2014	Case series	15	60%
Fibrin Glue	Vitton 2005	Case series	14	57%
	Grimaud 2010	Randomised Controlled Trial	34	38%
OTSC	Menningen 2015	Case series	6	83%

Table 5 Surgical procedures for Crohn's disease and their outcomes.

Observational studies of seton-only with anti-TNF therapy show excellent results, but when compared with the control arm of a randomised controlled trial, there is a much lower success rate.

3.4.7 Faecal diversion procedures

This group of procedures includes two main interventions; stoma formation and proctectomy. In current practice, these are typically reserved for recurrent complex perianal sepsis, or patients with poor continence and anorectal/pelvic muscle function.

Stoma

A stoma is described based upon the part of the intestine from which it is formed i.e. if it is formed from the ileum, it is an ileostomy, from the colon, a colostomy. In a patient with extensive colonic disease, it may be preferable to form a proximal stoma using the ileum. This diverts faeces from the perineum and tends to improve colonic disease. In the presence of extensive small bowel disease, but no colonic disease, it may be preferable to form a colostomy. In many cases, these will be loop stomas. This allows easier reversal in the future, although in reality as few as 22% patients have their stoma reversed[107]. A definitive end stoma will be formed where there is a clear intention to excise the distal diseased segment.

The procedure to form a stoma is relatively simple, and can be achieved using conventional open surgery, or using a laparoscopic approach. Using either approach, an appropriate segment of bowel is identified. This is mobilised and brought to the abdominal wall in a tension free manner. Parastomal hernia is a relatively common long-term complication, occurring in 30-50% of patients[108]. Other complications include stenosis and retraction of a stoma. In Crohn's disease, there is also the risk of fistulation from the stoma to the surrounding skin. Stoma is one of the few surgical interventions where a clear benefit in quality of life has been demonstrated[50].

Proctectomy and end colostomy

Proctectomy is typically performed after stoma formation to improve the surgical field and allow the clearance of residual sepsis, although there is still a risk of pelvic abscess formation[109]. The employment

of strategies to reduce perineal dead space and control sepsis pre-operatively may reduce the risk of perineal wound complications[110].

3.4.7 Selection of surgical procedure

Considerations around disease behaviour, fistula anatomy, and treatment goals all factor into the selection of a procedure. Procedures may also be placed into three main groups according to treatment aim: 'drainage', 'fistula closure', and 'faecal diversion'. Procedures and indications in this framework are presented in Figure 3.

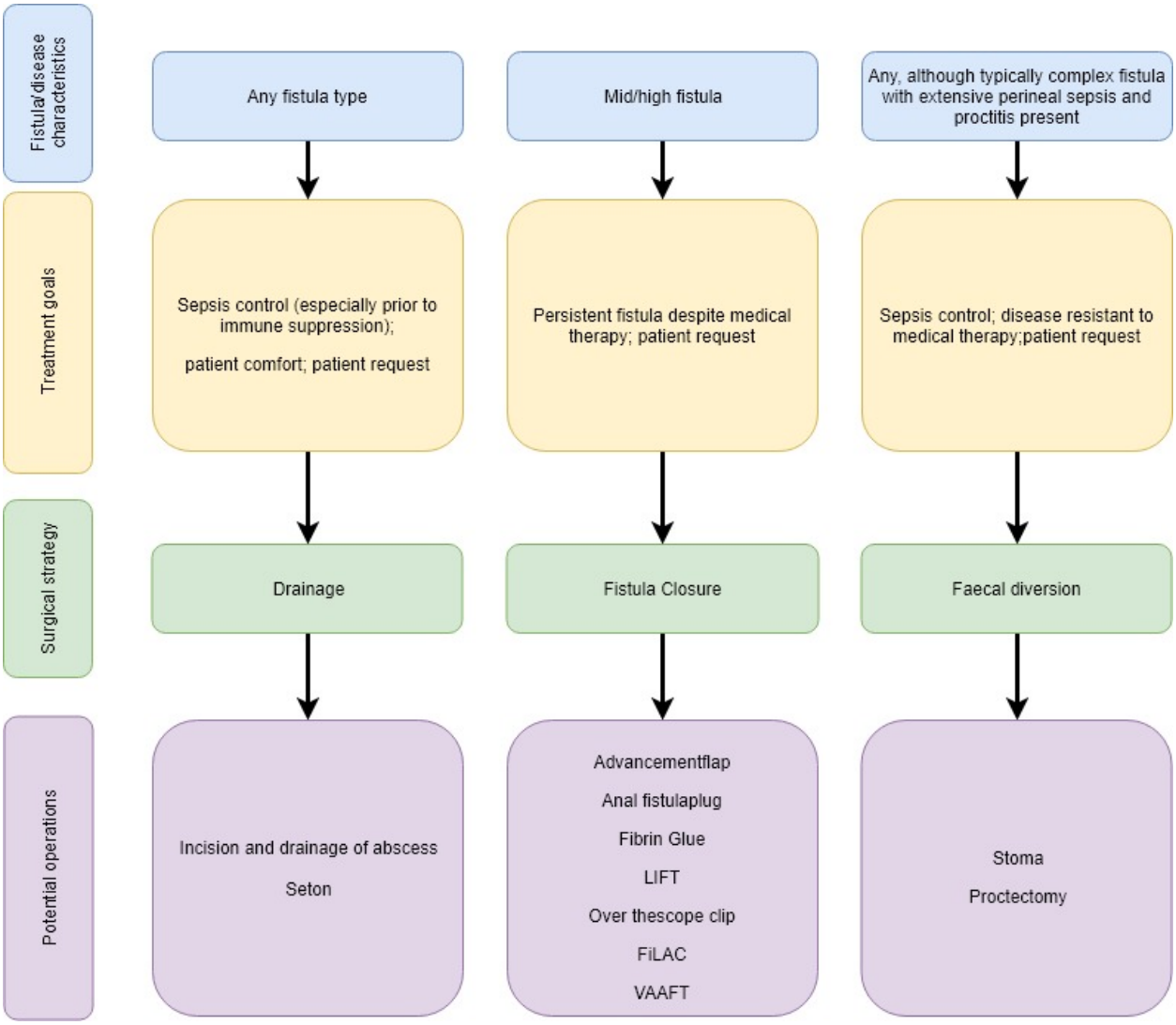

Figure 3 Surgical procedures for Crohn's anal fistula and their indications

As can be seen from the overview above, treatment strategies are highly variable and only some of the treatments have been evaluated with comparative randomized trials, some of which have been flawed or underpowered, and many of the local therapies only evaluated with case series at the present time. A further significant hindrance to establishing an optimized treatment pathway is the lack of standardisation of reported outcomes and the co reporting of Crohn's and non-Crohn's fistulae in aggregate.

3.5 Current guidance

The European Crohn's and Colitis Organisation (ECCO) offers the following advice on surgical management in their 2016 guidelines[111]:

- Sepsis control with a draining seton is the first step in management. This should be supported with anti-TNF-α therapy.
- A 'low' fistula might be considered for fistulotomy.
- Fistula plug and advancement flap might be considered as reparative procedures that can aid healing.
- Faecal diversion or proctectomy may be required in patients who do not respond to medical therapy.

There is no clear guidance on the subsequent management, including escalation and de-escalation of medical therapy.

3.6 Summary

The above studies describe the value of combining medical therapy with surgical therapy to obtain the optimal outcome, whether it is minimalist surgery such as a seton, or other procedures such as a fistula plug. A recent systematic review assessed outcomes of studies comparing surgical monotherapy vs

combined surgical and medical therapy. This descriptive analysis found that healing rates were approximately double in the multimodal group (55% vs 25%) [112]. The authors noted that heterogeneity of data and variable outcome measures precluded meta-analysis[112].

The literature shows consensus on early sepsis control, with abscess drainage and seton placement. The optimum choice and combination of subsequent therapies is not clear. Because of challenges in controlling factors related to disease severity and additional medications, it may not be feasible to undertake a high quality randomised trial to answer questions around optimum drug combination and timing whist controlling for these other variables. Given the incidence of Crohn's anal fistula, such a trial would take a long time to complete. If this is the case, careful consideration should be given to how decisions are made about treatment of this condition.

4 Making decisions about treatment

Where there is no clear answer on which treatment offers the most likelihood of a cure, then the factors informing the decision may change. The treatment selected may be offered as one likely to reach a patient's treatment goals e.g. reduce drainage from a fistula, or as one to minimise harm e.g. prevent future abscess formation. The priority and values attached to these goals may vary, depending upon who is making the decision, making this a 'preference sensitive' decision.

Decision making in medicine can be broadly divided into three categories: paternalistic, consumer-driven, and shared. The paternalistic approach was historically prevalent[113]. In this model, the physician shares only the information needed to obtain consent and makes all decisions themselves. This places the locus of control firmly with the clinician. In the consumerist approach, all information necessary to decision making is given to the patient by the physician, and all decisions are made by the patient, placing the locus of control with the patient. Shared decision making is a model with two way communication between the patient and physician, and both parties contribute to treatment decisions, sharing the locus of control between the two parties[114]. The above descriptors cover three common models of decision making, although it is also important to consider aspects of agency in decision making. Agency refers to the state where the patient has delegated to the physician some, or all, of their authority to make decisions. For the clinician to make the 'best' decision for the patient, one which takes into account their preferences and perceived utility of outcomes, they must be a 'perfect' agent. This implies extensive knowledge of treatments, and a holistic understanding of the patient to make a decision that is concordant with the preferences and needs of the patient[115]. The concept of perfect agency appears favourable, although in real-life it is likely to be challenging and time consuming. Given this, two-way communication and elicitation of preferences is required – this leads us towards shared decision-making.

The concept of shared decision has been supported by the National Institute for Health Care Excellence (NICE) since at least 2012[116]. This model has been brought into the spotlight by the recent *Montgomery vs Lanarkshire Health* ruling[117], and subsequent guidance from the Royal College of Surgeons of England[118].

4.1 Benefits of shared decision making

The perceived benefit of a shared decision making approach is that engagement of both parties in the decision making, allows the 'best' decision to be made, supports patient autonomy, and improves patient satisfaction with decisions[119]. The use of a decision aid as part of shared decision making has been shown to reduce the rate of additional investigations, or select less invasive diagnostic tests[120].

The nomenclature used in these schema focuses on decision making, and specifically, where the locus of control lies. This may be misleading to an extent. Qualitative work exploring shared decision making across a range of conditions in general practice found that patients who experienced a high degree of information sharing reported a high level of satisfaction, regardless of where they felt the locus of control was, and who made the decision about treatment[121].

4.2 Shared decision making in inflammatory bowel disease

Given the chronic nature of inflammatory bowel disease, and the nature of decisions made, it is a condition where shared decision-making might be of use. Surveys of US gastroenterologists suggest that they are willing to employ this model of decision making, and many already incorporate elements of it in their practice[122]. The same study identified a number of barriers to this, including the time required, the need for supporting materials, and appropriate reimbursement. Similar survey work has demonstrated

that patients drawn from the general IBD population would also like to participate in shared decision making about their care[123].

4.3 The process of shared decision making

The process for conducting a consultation using a shared decision making approach has been described by Elwyn in the 'three talk' model[124] (Figure 4). It is conceivable that this process could be completed in one single clinic visit, however it is likely to require two or more visits. The first talk highlights that a decision must be made, and typically assesses whether the patient wishes to participate in that decision. The second talk involves the presentation of options including the trade off between risk and benefits, exploration of patient preferences, sharing of physician ideas and supported deliberation, which may use a decision aid. In the third talk, the decision for treatment and the underlying reasons are confirmed.

The literature has identified a number of barriers to the embedding of shared decision making in clinical practice. The most common barrier relates to the extra time required to do this well. The Shared Decision Model is typically supported by a well-designed decision aid specific to the condition. There is no such decision aid for Crohn's anal fistula[125].

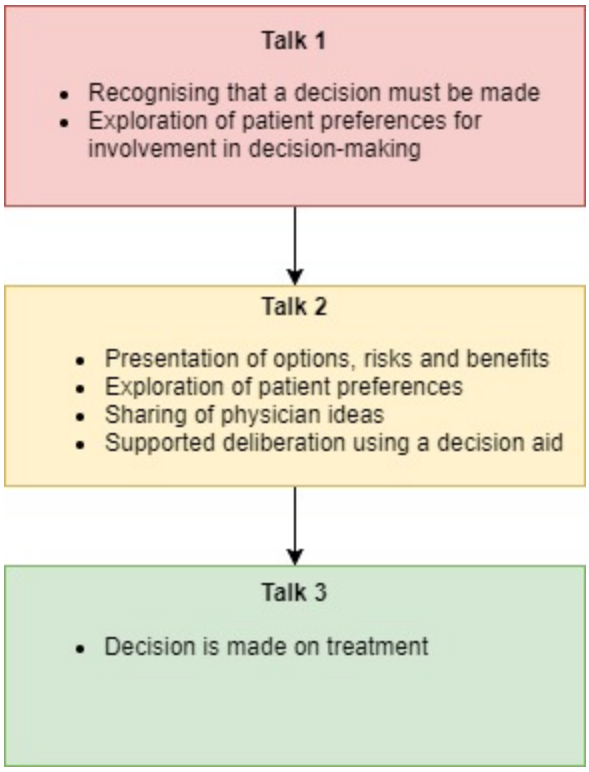

Figure 4 The three talk model for shared decision making

4.4 What makes a decision aid?

A decision aid is used to support deliberation of treatment options by providing patients with information in an accessible manner. The key components of a decision aid have been defined by the Cochrane Collaboration[120] and are summarised in Table 6. It is important to recognise that a decision aid is designed to support shared decision making[126]. Use of a decision aid in lieu of supported deliberation does not constitute shared decision making.

Component	Explanation
Information tailored to patient's health status	Information should be related to the disease which has triggered the decision. It should list potential treatment options, and the risks and benefits of each of these.
Values Clarification	This involves the exploration of risks and benefits of choosing each treatment option, and the value placed upon each of these by patients.
Examples of other patients	The risks and benefits of each treatment can be illustrated with examples of what other patients chose and why.
Guidance in shared decision making	Decision aids support patients with the identification of their values in treatment, and the discussion of how this affects their treatment choice. This facilitates shared decision making.
Delivery format	Decision aids can be delivered in a number of ways. These can include decision boards, option grids, interactive webpages, and leaflets.

Table 6 Components of a decision aid

4.4.1 When is it appropriate to use a decision aid?

Four scenarios have been proposed where a decision aid, and by extension shared decision making principles, may be of benefit[127]. These are:

- When the potential treatment options have major differences in outcomes or potential complications;
- Decisions where a trade-off must be made between short term and long term outcomes;
- One or more treatment options carry a small chance of a serious complication;
- Where there are marginal differences in outcomes between options.
- Where there is no single best option but a range of options that may provide similar outcomes, (or a lack of evidence proving superiority of any option) as is the case in Crohn's

These are quite broad terms of reference, and may be interpreted to encompass all of medicine. The exclusion is most likely in acute settings where time constraints prevents full exploration of treatment options, or where there is one proven treatment e.g. antibiotics in meningitis.

4.5 Developing a decision aid

Development of a decision aid is more complex than simply writing a leaflet. The International Patient Decision Aid Society (IPDAS) have provided a frame work to ensure that newly developed aids meet specific standards in development of the aid[128]. This includes:

- Systematic review, appraisal and synthesis of the evidence base. This can include highlighting the lack of evidence as communication of uncertainty is important.
- Establishing what treatment options are available

- Establishing what potential users of the tool want to know. This can be achieved using a range of research methodologies, including interviews, focus groups, and surveys.

The work described in this thesis addresses these components as outlined in figure 5.

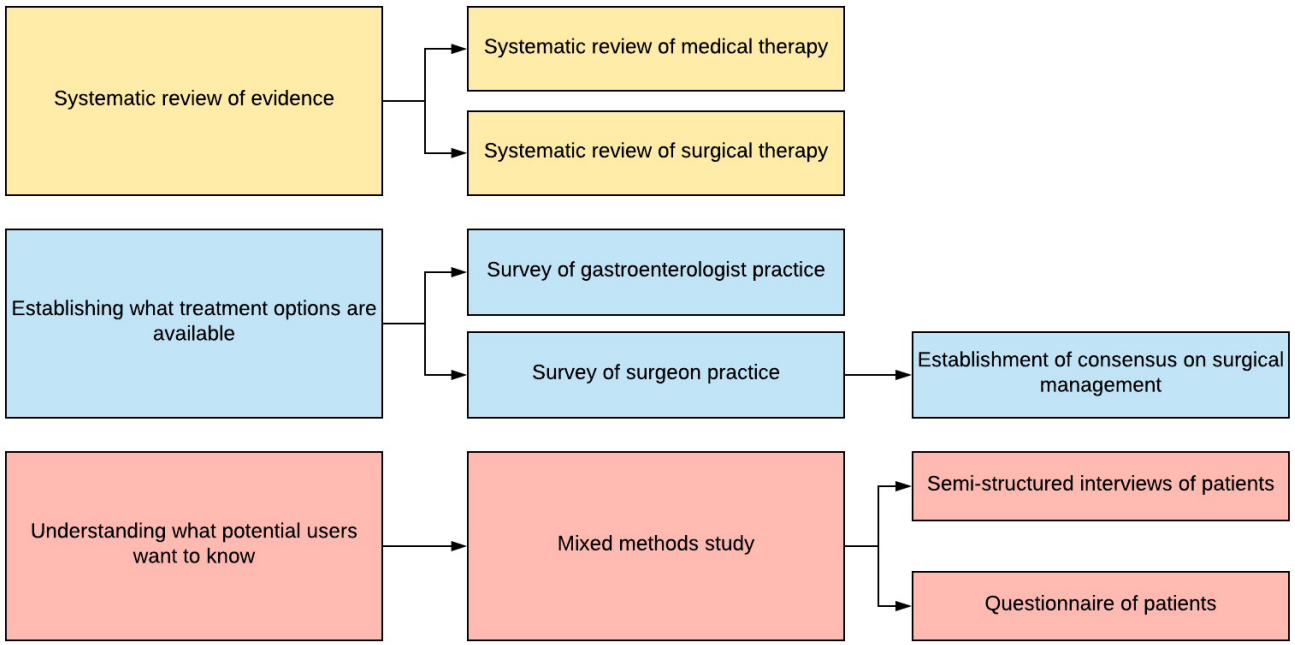

Figure 5 How this thesis maps to the IPDAS checklist for development of a decision aid.

5 Aims and significance

5.1 Aim

The aim of this thesis is to define current practice and evidence for the management of Crohn's anal fistula, and to explore patient preferences and informational needs around the surgical management of this condition. This will provide the basis for development of a future decision aid.

5.2 Significance

Anal fistula affects a significant proportion of patients with Crohn's disease. This is a condition which typically requires multiple treatments and has a significant negative impact on the lives of those affected. This work provides a reflection of current practice, a synthesis of current best evidence, and an exploration of patient informational needs and preferences when considering surgery. This provides the basis to support decision making in the future care of this patient group.

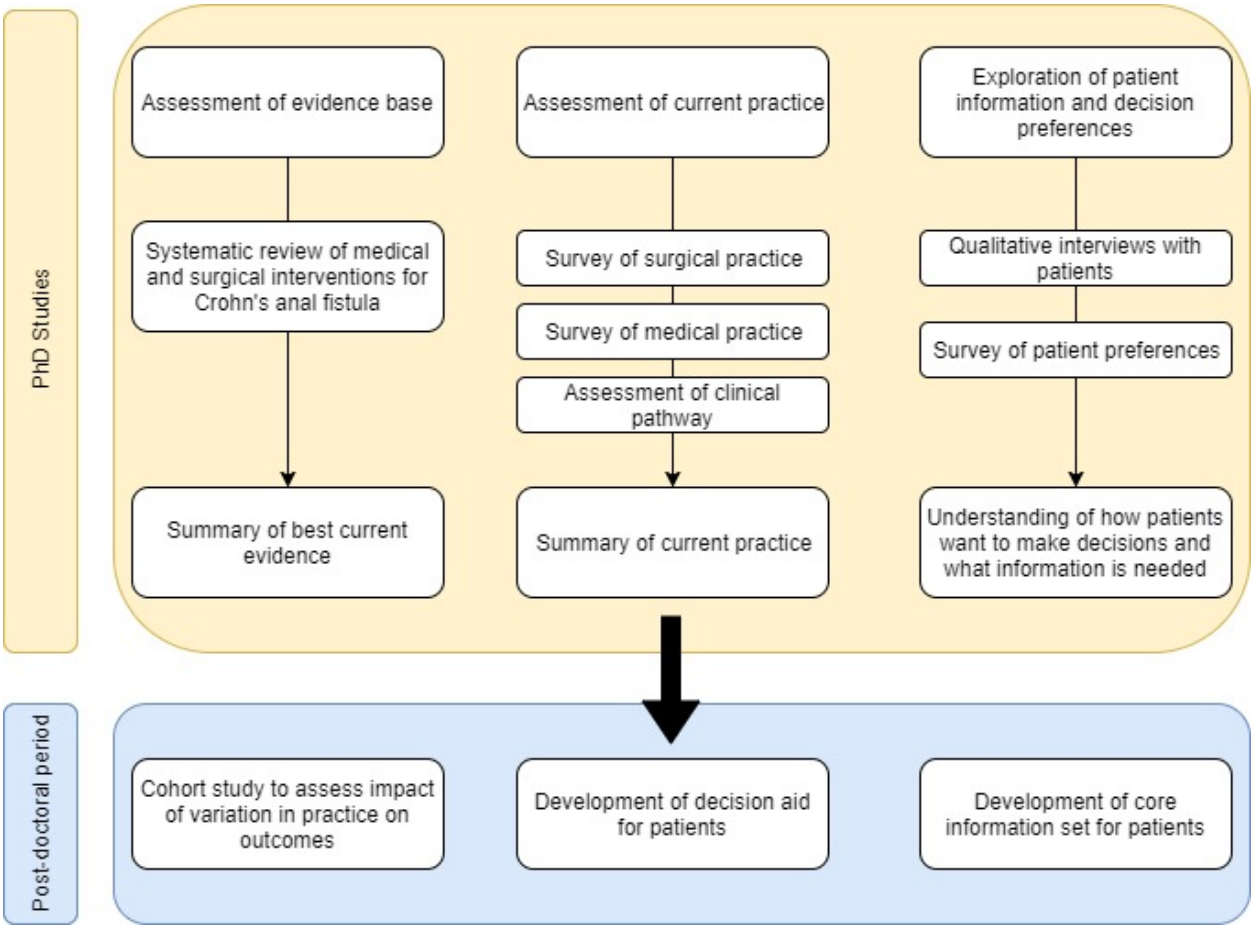

Figure 6 Summary of PhD work and planned future work

6 Overview of Systematic review & meta-analysis methodology

Systematic review is a widely practiced method of secondary research. This allows collation of findings of prior studies to identify where there is certainty, or to identify gaps in the literature.

6.1 Methodology of systematic review

Systematic reviews follow a common methodology, the practice of which is largely guided by the Cochrane collaboration, who have developed a methodological handbook to guide the conduct of systematic reviews[129]

6.1.1 Formulation of research question

Formation of an appropriate question within the PICO framework (population, intervention, comparator and outcome). This can be adapted depending on the nature of systematic review being undertaken e.g. intervention can be substituted for performance of a diagnostic test.

6.1.2 Defining inclusion criteria

Selection of inclusion and exclusion criteria. With the question set, inclusion and exclusion criteria must be set. The team conducting the systematic review need to carefully consider the studies of interest. They may wish to restrict by study design (e.g. randomised trial, cohort study), they may wish to limit by date of publication, by disease state or by language of publication. Each of these factors may introduce their own elements of bias, so should be considered carefully with the authors able to provide justification for each of these.

6.1.3 Development of search strategy

Development of search strategy. There are a number of electronic databases through which articles can be identified i.e. PUBMed, EMBASE, CINAHL, Cochrane Central. Each of these has different search engines and search terms. The correct Medical Subject Heading (MeSH) terms and operators must be used. The appropriate combination can be developed through identification of manuscripts of interest and 'mining'

the MeSH terms and combinations that have been applied to them. This allows the development of a comprehensive list of terms, allowing searches to encompass all potential candidate papers.

6.1.4 Registration of protocol

Registration of a protocol is not a strict requirement for publication. Development and registration of a protocol for the conduct of a systematic review may encourage the researcher to consider aspects of the planned research which require clarity, and to define meta-analyses in advance. Evidence suggests that registration is associated with better reporting of domains identified in reporting guidelines, indirectly improving reporting of such studies[130].

6.1.5 Study selection

In this phase, a minimum of two reviewers independently screen abstracts against the review eligibility criteria. Results are cross checked and conflicts resolved by a third reviewer. This exercise is then repeated with the full texts of manuscripts. If the study is excluded at this stage, the reason for exclusion is recorded. Results are again cross checked and conflict resolved by a third reviewer[129].

6.1.6 Data extraction

Key information on study reference, design, participants, interventions and other factors of interest are recorded into a pre-designed study proforma by two independent reviewers. Results are cross checked and conflicts resolved by a third reviewer[129].

6.1.7 Bias and quality assessment

As well as extraction of data, the reviewers assess the paper for bias. This is done systematically using a

recognised tool such as the Cochrane risk of bias tool[131], the risk of bias in non-randomised studies tool (ROBINS-2)[132], or other tools relevant to the review question.

6.1.8 Qualitative synthesis of data

In this stage, data is presented with outcomes or study types grouped. For example reporting the benefits of treatment in studies in one section, and reported harms or complications from treatment in another. This is purely narrative and does not include narrative synthesis.

6.2 Meta-analysis

Meta-analysis allows the combination of data across studies to estimate event rates, with adjustment for the contribution of each dataset based upon sample size. Pooling of data improves the precision and accuracy of estimates of effect sizes, and allows generalisation to the wider population.

The pooled data may be presented in a number of ways, including odds ratio or relative risk, along with a 95% confidence interval for the effect. These can be presented graphically as Forrest plots, with a summary estimate accounting for effect and study size. Pooling of data is typically undertaken using one of two analysis models; fixed effects or random effects.

A fixed effects model assumes that the effect size of an intervention is the same in all populations, and independent of the study size. This leads to the assumption that any variation in effect size comes from errors in the measurement of effect within the study. A random effects model assumes there to be a distribution of effect sizes across studies, and attempts to estimate the general trend of the effect. This assumes that there are different effects in different populations and allows for variation within the characteristics of the intervention and the population[133].

Meta-analysis is not always possible due to a small number of studies, or limitations in reporting e.g. inconsistent use of outcomes. Even where meta-analysis is possible, the quality or reliability of findings are only as good as the studies upon which they are based[134].

In addition to pooled effect sizes, it is possible to assess for heterogeneity within the reported effects – i.e. do all studies point the effect in the same direction and have overlapping effect sizes. This heterogeneity is reported using the I^2 statistic, where 0% suggests no heterogeneity and 100% suggests a high degree of heterogeneity of results[129].

6.3 Publication bias

Where five or more studies report the same outcome, it is possible to assess for publication bias through the use of a funnel plot. This assesses the effect size and sample size against the pooled effect and its confidence interval. If a study falls outside this window, it is possible that it is subject to publication bias[129].

6.4 Clarity of reporting

In order to ensure that a study has been conducted in a methodologically robust manner, it should be reported according to accepted standards. For systematic review and meta-analysis, the above points are addressed in preferred reporting items in systematic review and meta-analysis (PRISMA) guidelines[135].

6.5 Selection of methodology

As outlined in Chapter 3, it is important to collate data from the literature in order to describe the outcomes from treatment. It also allows us to judge the quality of the literature, and understand potential confounders when designing future studies.

7 Systematic Review of Medical Therapies for Crohn's Anal Fistula

Data from this chapter has been published following peer review:

Lee MJ, Parker C, Taylor SR, Guizzetti L, Feagan BG, Lobo AJ, Jairath V. A systematic review and meta-analysis of medical therapies for fistulising Crohn's disease. *Clinical Gastroenterology and Hepatology* 2018 Jan 31. pii: S1542-3565(18)30098-3. doi: 10.1016/j.cgh.2018.01.030. [Epub ahead of print]

My role in study was drafting of protocol, screening of papers and extraction and analysis of data, preparation of manuscript.

Claire Parker provided support on study design, undertook searches and checked conflicts, as well as preparation of manuscript.

Sarah Taylor supported screening of studies and critically reviewed the final manuscript.

Leonard Guizzetti is a statistician and undertook analyses of extracted data.

Brian Feagan, Alan Lobo and Vipul Jairath are senior gastroenterologists and provided oversight and were involved in drafting the manuscript.

Permission to reproduce from co authors and the publisher have been obtained.

7.1 Background

As described in chapter 2, Crohn's disease can be associated with a penetrating phenotype, i.e. one associated with fistula formation. Classification of fistula is based upon location and connection to contiguous organs or anatomic structures. External fistula, including perianal and abdominal forms, are most common, respectively representing 55% and 6% of all cases.[136] Approximately one-third of fistula are internal, including enteroenteric, enterovesical, enterouterine or enterovaginal types. There is likely a common pathological pathway underlying fistulation regardless of origin, so it is reasonable to consider the medical management as one process regardless of location.

As outlined in chapter 2, current evidence supports the role of uncontrolled inflammatory response in the propagation of fistulating disease, including TNF-α and downstream cytokines. The role of anti-TNF-α antagonists in the treatment of fistulating CD was established almost 15 years ago[137]. More recently, novel therapies and biologics with alternative mechanisms of action such as anti-integrins and inhibitors of the interleukin (IL) 12/23 pathway have emerged, although their efficacy in the management of fistulating disease is uncertain. In the treatment of inflammatory bowel disease, the use of drugs falls into two broad categories: induction and maintenance. The use of a drug as an induction agent means that it is used to change the disease state from active to controlled, responding, or in remission, depending on the study design and terminology. This may be measured based upon anatomical manifestations of disease (fistula) or upon disease activity. Maintenance refers to the use of a drug in a patient where disease is controlled, and the ability of the drug to keep the patient in that state. It is important to understand the role of medical therapies in this condition, as they are the main drivers of cost[138].

7.2 Aim

The aim of this study was to perform a systematic review and meta-analysis of all published randomized controlled trials (RCTs) evaluating the efficacy of medical therapy for the management of fistulating CD.

7.3 Method

7.3.1 Protocol and registration

This systematic review and meta-analysis was conducted using the methods described in the Cochrane Handbook of Systematic Reviews[129], and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[139]

7.3.2 Eligibility criteria

Eligible studies were randomized, placebo- or active comparator-controlled trials that enrolled adult CD patients (16 years or older) with any form of fistulating disease (i.e. perianal, enterocutaneous, enteroenteric, enterovesical, enterovaginal or enterouterine fistula). The decision to include all forms of fistula was made for two reasons. As outlined in the earlier chapter

Interventions of interest included any pharmacological treatment administered alone or in combination. In the case of crossover trials, only first-stage data were collected. Evaluation of surgical therapies, or their combination with medical therapies, were not evaluated as they have been previously described[112 140]. Surgical conditioning of tracks with seton or other treatments was permitted.

7.3.3 Outcomes

The primary outcome was the proportion of patients with fistula response (closure of >50% external openings and absence of discharge on compression[74]). Secondary outcomes included the proportion of patients who achieved fistula remission; fistula resolution by diagnostic imaging (i.e. magnetic resonance

imaging or computed tomography); and maintenance of fistula closure. Data on health-related quality of life, incontinence or similar functional outcomes were also extracted when available.

7.3.4 Search strategy

The MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from inception to December 13, 2016 using pre-defined strategies (Appendix A). Language and date restrictions were not applied. The bibliographies of relevant articles retrieved from the electronic databases and conference proceedings from Digestive Disease Week and United European Gastroenterology Week (2012 to 2016) were hand searched to ensure that all eligible studies were identified. Fully published papers as well as abstracts and conference proceedings were included.

7.3.5 Screening and data extraction

Two authors (MJL and ST) screened the search results in parallel using the Covidence web tool.[141] The same two authors independently extracted information on the design, intervention, comparison, baseline characteristics, outcomes and risk of bias of the included studies using a standardized spreadsheet (Excel, Microsoft Corp., Redmond, WA, USA). Discrepancies encountered during screening or data extraction were resolved by discussion or recourse to a third author (CEP). In the case of unclear or missing data, attempts were made to contact the original study authors for clarification.

7.3.6 Risk of bias assessment

The Cochrane risk of bias tool was used to assess the methodological quality of the included studies.[142] Seven domains (i.e. random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias) were classified as being of unclear, low or high risk of bias.

7.3.7 Data synthesis and analysis

In studies with multiple dose arms, outcome data from the intervention groups were combined. If outcome data were reported at multiple timepoints, the pre-defined primary timepoint was used. Response and remission data were respectively combined regardless of whether the outcome definitions varied. All outcomes of interest were expressed dichotomously, with intervention effects reported as pooled risk ratios (RRs) and corresponding 95% confidence intervals (CIs). A fixed-effect model was used to pool data, however, we planned to use a random-effects model in the case of significant, unexplained heterogeneity. Data were analysed according to the intention-to-treat principle, and statistical analyses were performed using RevMan 5.3 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark).

A sensitivity analysis was conducted to determine whether excluding studies evaluating fistula disease activity as a secondary endpoint impacted on the strength of the results. Subgroup analysis according to fistula type (i.e. perianal versus other) was not pre-specified, since we anticipated that most studies would focus on perianal fistulating disease and the mode of action should be similar regardless of source or fistula origin.

7.3.8 Heterogeneity

The relative amount of observed heterogeneity was quantified using the I^2 statistic, which ranges from 0%-100%.[143] A value of 0% indicates no observed heterogeneity, and substantial heterogeneity was defined as an $I^2 > 50\%$.[143]

7.3.9 Quality of the evidence

The GRADE approach was used to assess the quality of evidence for the primary and secondary outcomes. Results from RCTs were initially considered high-quality, but potentially downgraded due to risk of bias; indirectness of evidence; unexplained heterogeneity; publication bias or sparse data.[144] Outcomes with less than 35 events were reduced by two GRADE levels; outcomes with less than 300 events were reduced by one GRADE level.

7.4 Results

7.4.1 Search results

Electronic database and hand searching identified a total of 802 records, from which 164 duplicates were removed. Of the remaining 638 records, 604 were deemed ineligible based on the information provided in the title and abstract. Full-text review was required for 34 records. Seven of the 34 records were excluded:2 had no control or comparator arm, 2 had a mixed patient population, one was not available in English, and one was a post-hoc analysis of trial data. This left 27 studies enrolling a total of 2106 fistula patients met the eligibility criteria. The flowchart for studies through the review is shown in figure 7.

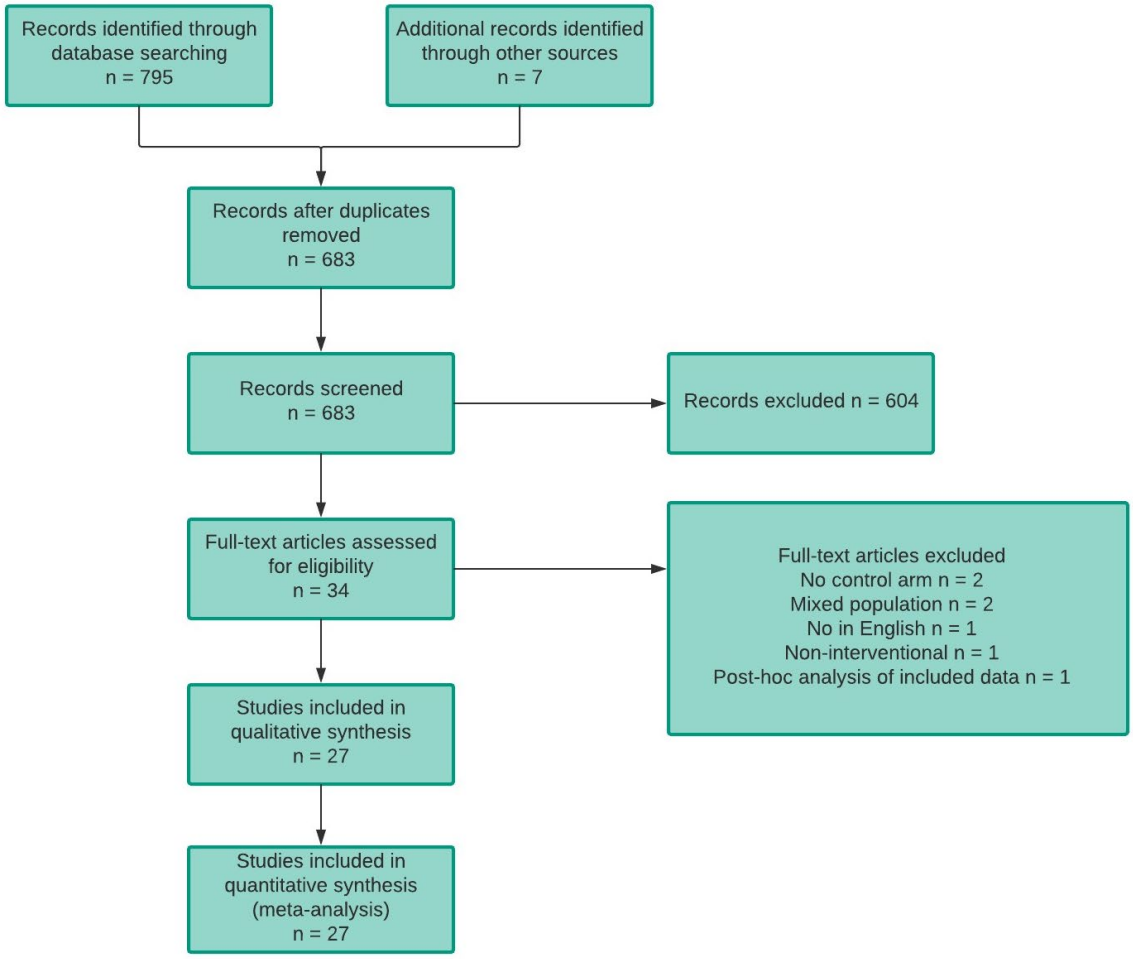

Figure 7 PRISMA flow chart

7.4.2 Description of included studies

A description of the included studies and definitions are provided in Table 7. Twenty-four RCTs compared a drug intervention to placebo.[92 137 145-164] Two antibiotics (ciprofloxacin and metronidazole) were evaluated in one study (n = 25).[163] Thiopurines, including azathioprine and 6-mercaptopurine (6-MP), were studied in five RCTs enrolling a total of 69 patients.[150 152 154 155 164] Tacrolimus was evaluated in one primary study of CD fistula, and one subgroup analysis (n = 58).[149 158] Four TNF-α antagonists (adalimumab, CDP571, certolizumab pegol and infliximab) were evaluated in eight RCTs (n = 821).[137 145 148 156 157 159 160 162] One post-hoc analysis of the GEMINI 2 RCT reported on the anti-alpha4beta7 (α4β7) antibody vedolizumab (n = 165).[146] Fistula results from five trials of ustekinumab, an anti-IL-12/23 antibody, were presented in one conference report (n = 318)[161] Two RCTs assigned patients to mesenchymal stem cell therapy (n = 233).[92 151] AST-120, an oral intestinal spherical carbon adsorbent, was evaluated in two studies enrolling a total of 311 patients.[147 153] Combination therapy with a TNF-α antagonist and an antibiotic versus treatment with a TNF-α antagonist and placebo was studied in two RCTs (n = 96).[87 165] Data from a single study comparing azathioprine to methotrexate (n = 10)[166] could not be meta-analysed.

The vast majority of included studies focused on patients with perianal fistulating disease. Eleven RCTs solely enrolled patients with perianal fistula,[87 92 147 149 151 153 161 163 165] eight trials included patients with both perianal and abdominal fistula,[137 145 148 155 158-160 166] and in three studies including various fistula types, the majority of patients were indicated to have perianal fistula.[150 152 162] Four additional studies included various fistula types, but did not specify whether the majority were perianal fistula,[146 156 157 164] and in one study most patients had abdominal fistula (see table 7).[154]

7.4.3 Risk of bias assessment

The results of the risk of bias assessment are presented in Appendix B. All included studies received low or unclear risk of bias appraisals except for Ardizzone 2003, an investigator-blind trial that was rated as high risk of bias for blinding of participants and selective reporting.[166]

Study	Trial design	Baseline status	Analysis type	Fistula Type (%)	Total N in study	Concomitant Therapy (%)	Intervention (n with fistula)	Comparator (n with fistula)	Definition of response (timepoint)[1]	Definition of remission (timepoint)[1]
Rhodes 1971[154]	Induction	Active fistula	Subgroup	Perianal (17) Abdominal (67) Vesicocolic (17)	26	5-ASA (23) CS (23)[2]	AZA (5)	Placebo (5)	Physician assessed (8)	NS
Willoughby 1971[164]	Induction	Active fistula	Subgroup	NS	6	CS (100)[2]	AZA (2)	Placebo (1)	Healing[3] (24)	NS
Klein 1974[150]	Induction	Active fistula	Subgroup	Perianal (80) Enterocutaneous (10) Enterovesicular (10)	20	5-ASA (NS) CS (NS)[2]	AZA (5)	Placebo (5)	Improved[3] (16)	Healed[3] (16)
Rosenberg 1975[155]	Maintenance	Clinical remission with active fistula	Subgroup	Perianal (50) Enteric (50)	20	CS (100)[2]	AZA (3)	Placebo (1)	NS (26)	Healing[3] (26)
Present 1980[152]	Induction	Active fistula	Subgroup	Mostly Perianal[4]	72	5-ASA (52) ABX (NS) CS (72)[2]	6-MP (29)	Placebo (17)	Partial healing[3] (52)	Complete healing[3] (52)
Present 1999[137] *ACCENT-2*	Induction	Active fistula	Primary	Perianal (90) Abdominal (10)	94	5-ASA (55) ABX (30) CS (34) IM (40) TNF exposure (0)	IFX (56)	Placebo (29)	≥50% closure (18)[5]	100% Closure (18)[5]
Ardizzone 2003[166]	Induction	Active fistula	Subgroup	Perianal (100) Enterocutaneous	54	CS (100)	MTX (6)	AZA (4)	NS	Fistula closure[3]

				Enteroenteric Rectovaginal[6]						(24)
Sandborn 2003[158]	Induction	Active fistula	Primary	Perianal (93) Enterocutaneous (9)	46	5-ASA (41) ABX (70) CS (20) IM (59)	Tacrolimus (21)	Placebo (25)	≥50% closure (10)	100% Closure (10)
Sandborn 2004[156]	Induction	Active fistula	Subgroup	Perianal (NS) Abdominal (NS)	395	5-ASA (59) ABX (14) CS (41) IM (33) TNF exposed (23)[2]	CDP571 (60)	Placebo (26)	≥50% closure (28)	100% Closure (28)
Sands 2004[160]	Induction	Fistula non-response with induction IFX	Primary	Perianal (82) Abdominal (20) Rectovaginal (10)[7]	87	5-ASA (48) ABX (33) CS (30) IM (34) TNF exposed (0)	IFX (43)	Placebo (44)	≥50% closure (54)[8]	NS
	Maintenance	Fistula response with induction IFX	Primary	Perianal (90) Abdominal (11) Rectovaginal (8)[7]	195	5-ASA (46) ABX (28) CS (28) IM (34) TNF exposed (0)	IFX (96)	Placebo (99)	≥50% closure (54)	100% closure (54)
West 2004[165]	Induction	Active fistula	Primary	Perianal (100)	24	CS (17) Fistula surgery (13) IM (60) TNF exposed (8)	IFX + ABX[10] ciprofloxacin (11)	Placebo + IFX (13)	≥50% closure (18)	NS
Hanauer 2006[148] *CLASSIC-1*	Induction	Active fistula	Subgroup	Perianal (NS) Enterocutaneous (NS)	32	5-ASA (49) ABX (9) CS (33) IM (29)[2] TNF exposed (0)	ADA (26)	Placebo (6)	≥50% closure (4)	100% closure (4)

Hart 2007[149]	Induction	Active fistula	Subgroup	Perianal (100)	19	Fistula surgery (100) IM (58) TNF exposed (25)	Tacrolimus (6)	Placebo (6)	≥50% absence of drainage[3] (12)	100% absence of drainage[3] (12)
Sandborn 2007[157] *GAIN*	Induction	Active fistula	Subgroup	Perianal (NS) Abdominal (NS)	325	5-ASA (32) CS (39) IM (49) TNF exposed (100)[2]	ADA (20)	Placebo (25)	≥50% closure (4)	100% closure (4)
Sandborn 2007[159] *PRECISE-1*	Induction	Active fistula	Subgroup	NS	660	CS (22) IM (20) TNF exposed (28)[2]	CZP (46)	Placebo (61)	≥50% closure (26)	NS
Fukuda 2008[147]	Induction	Active fistula	Primary	Perianal (100)	62	5-ASA (88) ABX (16) CS (19) Elemental diet (68) Fistula surgery (33)[9]	AST-120 (31)	Placebo (31)	≥50% closure (8)	100% closure (8)
Colombel 2009[145] *CHARM*	Induction	Clinical response to ADA induction with active fistula	Subgroup	Perianal (97) Abdominal (3)	117	5-ASA (32) CS (42) IM (49) TNF exposed (62)	ADA (70)	Placebo (47)	NS	100% closure (26)
Thia 2009[163]	Induction	Active fistula	Primary	Perianal (100)	25	5-ASA (48) IM (24) Fistula surgery (52)[9] TNF exposed (20)	ABX[11] (17)	Placebo (8)	≥50% closure (10)	100% closure (10)
Schreiber 2011[162] *PRECISE-2*	Induction Maintenance	Clinical response to CZP induction with active fistula	Subgroup	Perianal (95) NS (5)	58	CS (19) IM (52) TNF exposed (38)	CZP (28)	Placebo (30)	≥50% closure (26)	100% closure (26)

Sandborn 2012[161] *CERTIFI-M*	Maintenance	Clinical response or nonresponse with active fistula	Subgroup	Perianal (100)	54	5-ASA (17) IM (25) TNF exposed (100)[2]	UST (24)	Placebo (30)	≥50% closure (22)	100% Closure (22)
Dewint 2014[87] *ADAFI*	Induction	Active fistula	Primary	Perianal (100)	72	CS (6) IM (36) Fistula surgery (21)[9] TNF exposed (34)	ADA + ABX[11] (35)	ADA + placebo (37)	≥50% closure (12)	100% Closure (12)
Reinisch 2014[153] *FHAST-1*	Induction	Active fistula	Primary	Perianal (100)	249	CS (27) IM (52) Fistula surgery (77)[9] TNF exposed (37)	AST-120 (122)	Placebo (127)	Partial healing[3] (8)	Complete healing[3] (8)
Feagan 2015[146] *GEMINI-2*[7]	Induction	Clinical response to VDZ induction with active fistula	Subgroup	Perianal (74) NS (26)	1,115	Fistula surgery (39-54)[9] TNF exposed (44-49)	VDZ (142)	Placebo (23)	NS	Fistula closure[2] (14)
Molendijk 2015[151]	Induction	Active fistula	Primary	Perianal (100)	21	5-ASA (14) ADA (62) CS (5) IFX (29) IM (62) Fistula surgery (100)[9]	MSC (15)	Placebo (6)	≥50% absence of drainage[3]	100% absence of drainage[3]
Panes 2016[92]	Induction	Active fistula	Primary	Perianal (100)	212	ABX (47) CS (6) IM (46) Fistula surgery (100)[9] TNF exposed (61)	MSC (107)	Placebo (105)	≥50% absence of drainage[3]	100% absence of drainage[3]
Feagan 2016[161]	Maintenance	Clinical response to	Subgroup	Perianal (100)	26	5-ASA (36) CS (46)	UST (15)	Placebo (11)	≥50% closure	100% Closure

IM-UNITI		UST with active fistula				IM (36) TNF exposed (40)[2]			(44)	(44)
Sands 2017[161] *UNITI-1* *UNITI-2* *CERTIFI*	Induction	Active fistula	Subgroup	Perianal (100)	1894	5-ASA (17-43) CS (39-46) IM (21-35) TNF exposed (0-100)[2]	UST (161)	Placebo (77)	≥50% closure (8)	100% closure (8)
TOTAL					5,980		2,099			

Table 7 Characteristics of included studies

[1]Timepoint of outcome assessment in weeks
[2]Concomitant medications for entire study population (not the fistula subgroup)
[3]Interpreted as partial (≥50%) or complete (100%) closure
[4]The most common types in descending order were perianal, abdominal-wall, enteroenteric, rectovaginal, and vulva
[5]Response and remission criteria had to be met at ≥2 consecutive study visits
[6]Enterocentric and rectovaginal data not reported; enterocutaneous data not meta-analyzed since both patients received AZA
[7]Women with rectovaginal fistulae were included if ≥1 abdominal draining fistula was present
[8]Treat-right-through design; non-responders at week 14 randomized to IFX or placebo
[9]Includes seton placement, fistula incision or fistula drainage
[10]Ciprofloxacin
[11]Ciprofloxacin or metronidazole

Abbreviations:
5-ASA, 5-aminosalicylates; 6-MP, 6-mercaptopurine; ABX, Antibiotic; ADA, Adalimumab; AZA, Azathioprine; CS, Corticosteroid; CZP, Certolizumab Pegol; IFX, Infliximab; IM, Immunosuppressive; MSC, Mesenchymal stem cells MTX, Methotrexate; NS, Not stated; PCDAI, Perianal Crohn's Disease Activity Index; SD, Standard deviation; TNF, Tumor necrosis factor-alpha antagonist; UST, Ustekinumab; VDZ, Vedolizumab

7.4.4 Drug therapy versus placebo

Antibiotics. Thia and colleagues (2009) provided data on induction of fistula response and remission rates among patients assigned to ciprofloxacin, metronidazole or placebo.[163] A total of 29% (5/17) of patients receiving antibiotics achieved fistula response compared to 12.5% (1/8) of placebo patients. However this effect was not statistically significant (RR 1.68, 95% CI 0.34-8.22, p = 0.52; Figure 8, 1.1.1). There was no observed heterogeneity (I^2 = 0%) and the overall quality of evidence was considered low due to very sparse data (Appendix C).

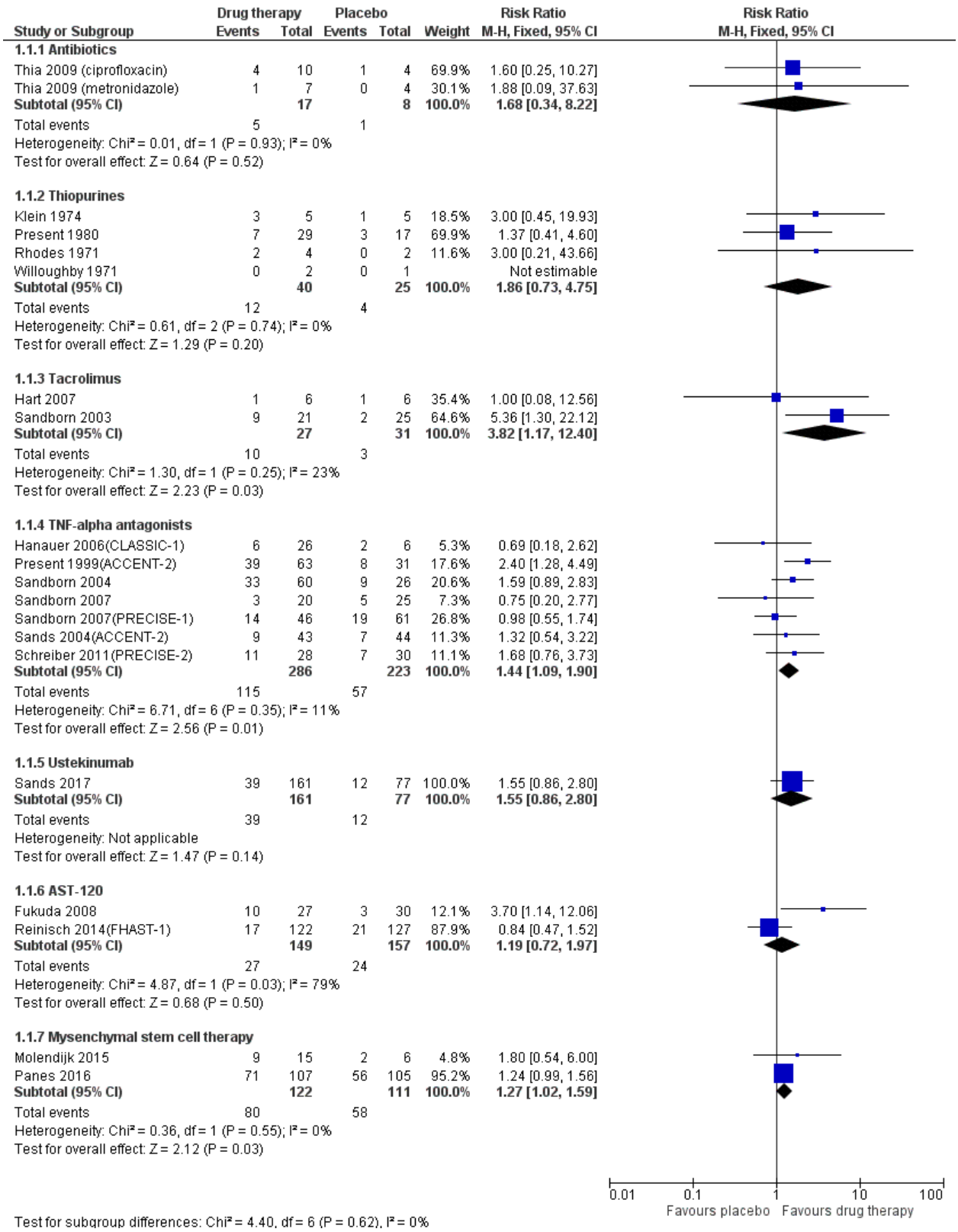

Figure 8 Forest plots of drug therapy versus placebo for induction of fistula response

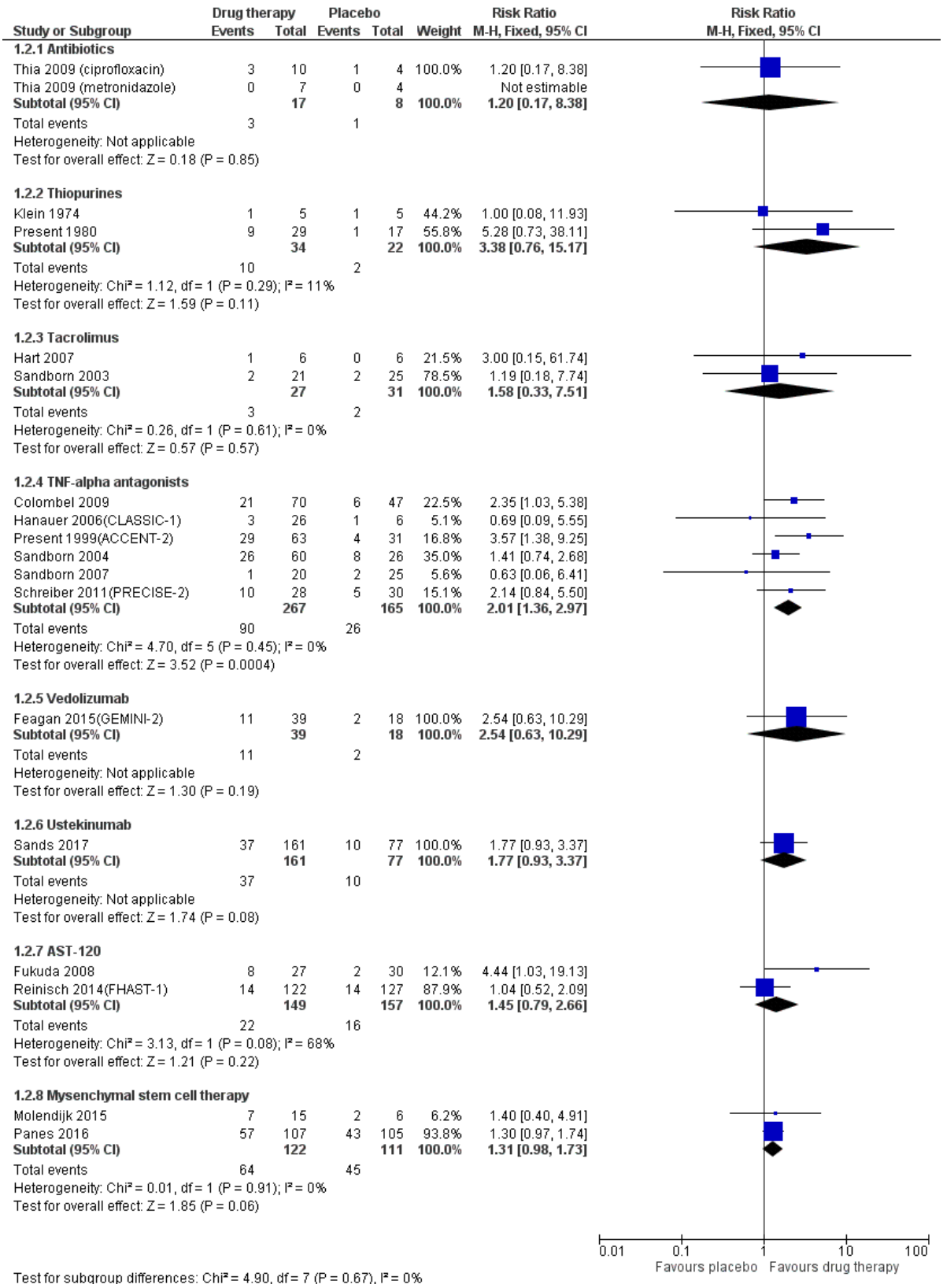

Figure 9 Forest plots of drug therapy versus placebo for induction of fistula remission

A total of 18% (3/17) of patients receiving antibiotics achieved fistula remission compared to 12.5% (1/8) of placebo patients. Again, the pooled RR indicated that this effect was not

statistically significant (RR 1.20, 95% CI 0.17-8.38, p = 0.85; figure 9). The overall quality of evidence for this outcome was considered low due to very sparse data (Appendix C).

Thiopurines. Four studies assessing azathioprine or 6-mercaptopurine versus placebo reported on induction of fistula response[150 152 154 164]. Thirty percent (12/40) of patients assigned to active treatment achieved fistula response compared to 16% (4/25) of placebo patients. The pooled RR failed to show a statistically significant effect between groups (RR 1.86, 95% CI 0.73-4.75, p = 0.20; Fig 8 1.1.3). There was no observed heterogeneity, and the quality of evidence was considered low due to very sparse data (Appendix C).

With respect to induction of fistula remission, 29% (10/34) of patients receiving a thiopurine achieved remission compared to 9% (2/22) of patients receiving placebo. The pooled RR was 3.38 (95% CI 0.76-15.71, p = 0.11; Figure 9 1.2.2), indicating no statistically significant difference in effect between treatment groups. The observed heterogeneity was not substantial, and the overall quality of evidence was considered low due to very sparse data (Appendix C).

Rosenberg 1975 was the only included study to report on maintenance of fistula response[155]. In this small study, the one fistula patient who responded to active therapy failed to maintain response, while the one fistula patient who responded to placebo successfully maintained response (Figure 10, 1.3.1). A reliable estimate of the RR for this study could not be estimated, and the quality of evidence was considered low due to very sparse data (Appendix C).

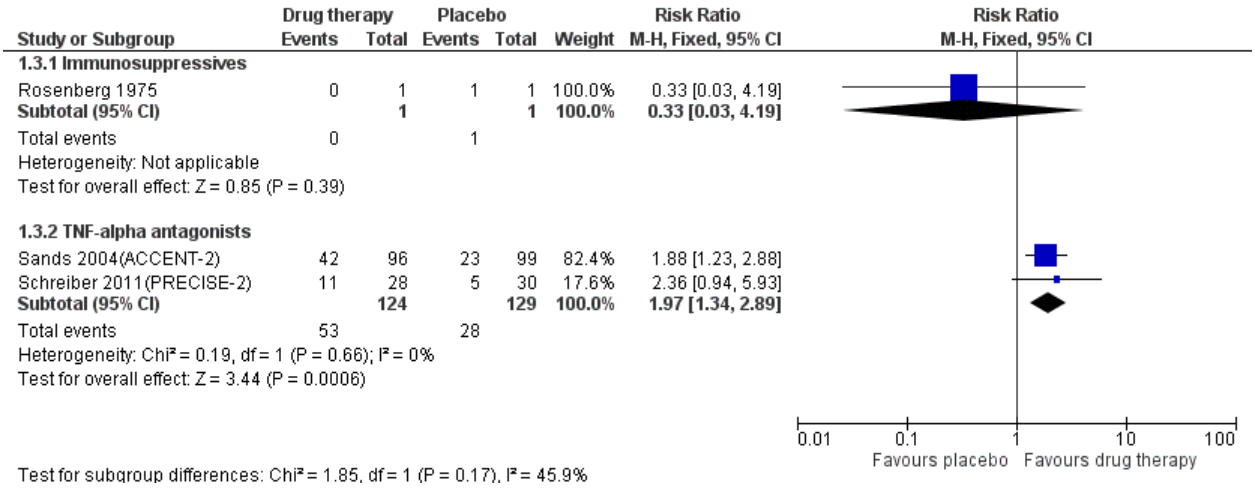

Figure 10 Drug therapy versus placebo for maintenance of fistula response

One head-to-head trial of immunosuppressives was identified.[166] In Ardizzone 2003, 67% (4/6) of patients receiving methotrexate achieved fistula remission compared to 30% (2/6) of patients receiving azathioprine (RR 2.0, 95% CI 0.56-7.09; p = 0.28; Figure 11). This effect was not statistically significant, and the quality of evidence was considered very low due to very sparse data and high risk of bias for blinding of participants and selective reporting (Appendix C).

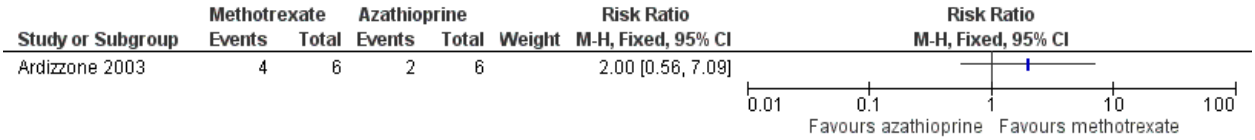

Figure 11 Methotrexate versus azathioprine for induction of remission

Tacrolimus. Two trials reported on induction of fistula response, and fistula remission.[149 158] Thirty-seven percent (10/27) and 10% (3/31) of tacrolimus and placebo patients achieved response, respectively (RR 3.82, 95% CI 1.17-12.40, p = 0.03). The between-group difference in effect was statistically significant. Heterogeneity was low (I^2 = 23%), and the quality of evidence was considered low due to very sparse data. With respect to fistula remission, 11% (3/27) of patients randomized to tacrolimus achieved remission compared to 6% (2/31) of

placebo patients. The pooled estimate failed to demonstrate a statistically significant between-group difference (RR 1.58, 95% CI 0.33-7.51, p = 0.57). No heterogeneity was observed, and the quality of evidence was considered low due to very sparse data.

TNF-α antagonists. Fistula response was reported in seven trials of TNF-α antagonists.[137 148 156 157 159 160 162] Forty percent (115/286) of patients receiving a TNF-α antagonist achieved fistula response compared to 26% (57/223) of placebo patients. The pooled RR was 1.44 (95% CI 1.09-1.90, p = 0.01), demonstrating a statistically significant effect in favour of TNF-α antagonist therapy. A low degree of heterogeneity was observed (I^2 = 11%), and the quality of evidence was considered moderate due to sparse data.

Six RCTs evaluating TNF-α antagonists reported on the proportion of patients who achieved fistula remission.[137 148 156 159 160 162] Thirty-four percent (90/267) of patients in the TNF-α antagonist therapy group achieved fistula remission compared to 16% (26/165) of patients in the placebo group. The pooled RR was 2.01 (95% CI 1.36-2.97, p < 0.001; Figure 9, 1.2.), demonstrating a statistically significant effect in favour of TNF-α antagonist therapy in comparison to placebo. There was no observed heterogeneity, and the quality of evidence was considered moderate due to sparse data (Appendix B).

Maintenance of fistula response was evaluated in two studies[160 162]. A total of 43% (53/124) of patients receiving a TNF-α antagonist maintained response compared to 22% (28/129) of placebo patients. The between-group difference in effect was statistically significant (RR 1.97, 95% CI 1.34-2.89, p < 0.001; Figure 14). No heterogeneity was observed, and the quality of evidence was rated as moderate due to sparse data (Appendix B). The same two studies reported on maintenance of fistula remission. Thirty-five percent (43/124) of patients treated with a TNF-α antagonist maintained remission compared to 18% (23/129) of patients receiving

placebo. The pooled RR was 1.94 (95% CI 1.25-3.02, p = 0.003; Figure 13), demonstrating a statistically significant effect in favour of TNF-α antagonist therapy. There was no observed heterogeneity, and the quality of evidence was considered moderate due to sparse data (Appendix B).

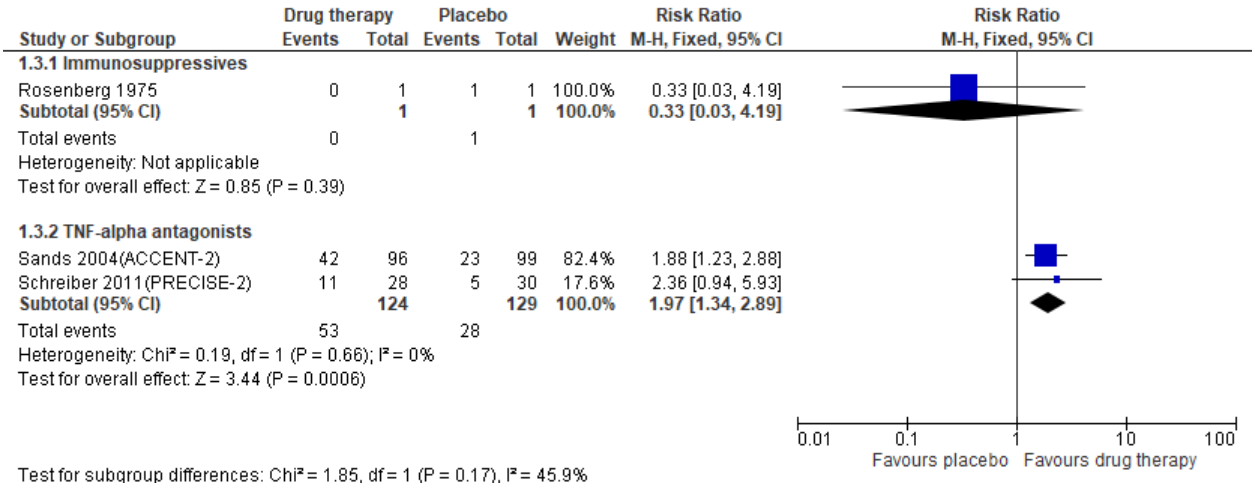

Figure 12 Drug therapy versus placebo for maintenance of fistula response

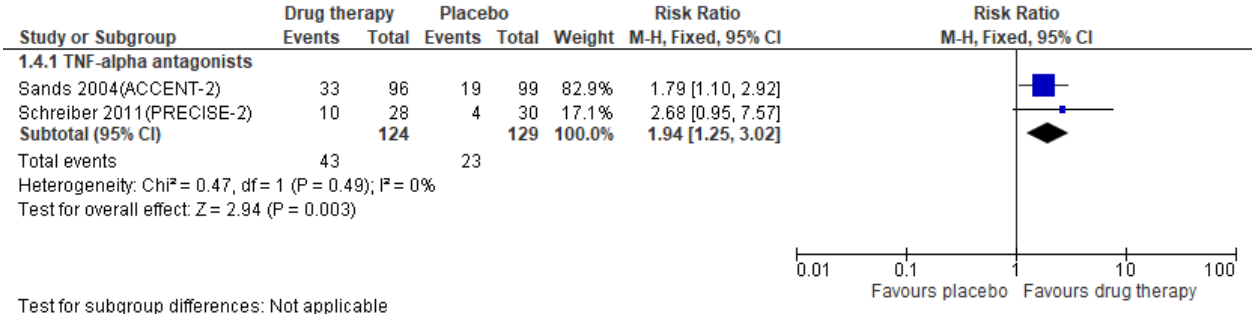

Figure 13 anti TNF-α for the maintenance of fistula remission

Vedolizumab. The GEMINI 2 trial was the only included study that assessed fistula healing among patients randomized to vedolizumab. In a post-hoc analysis of data from the GEMINI 2 trial reported in abstract form,[146] 28% (11/39) of patients in the vedolizumab group achieved fistula remission compared to 11% (2/18) of patients in the placebo group. However, the

relative improvement in fistula remission with vedolizumab was not statistically significant (RR 2.54, 95% CI 0.63-10.29, p = 0.19; Figure 9). The evidence supporting this outcome was considered low due to paucity of data (Appendix B).

Ustekinumab. A post-hoc pooled analysis of data from the CERTIFI, UNITI-1 and UNITI-2 trials (reported in abstract form) provided data on induction of fistula response and remission rates.[161] Twenty-four percent (39/161) of patients receiving ustekinumab responded to treatment versus 16% (12/77) of placebo patients. The pooled RR (1.55, 95% CI 0.86-2.80, Figure 8.) revealed a numerically, but not statistically, significant effect in favour of ustekinumab. The quality of evidence for this outcome was considered moderate due to sparse data (Supplementary Table 3).

For fistula remission, twenty-three percent (37/161) of patients assigned to ustekinumab achieved fistula remission compared to 13% (10/77) of placebo patients. The difference in effect between groups was not statistically significant (RR 1.77, 95% CI 0.93-3.37, p = 0.08), and the quality of evidence was considered moderate due to sparse data (Appendix B).

Two studies reported on maintenance of response. In the IM-UNITI and CERTIFI-M trials, 54% (21/39) of patients assigned to active therapy maintained response compared to 27% (11/41) of placebo patients (95% CI, 1.82 1.04-3.17, p = 0.04), suggesting a statistically significant difference in favour of ustekinumab. The quality of evidence was considered low due to very sparse data (Appendix B).

AST-120. Data from two trials of the oral spherical carbon adsorbent AST-120 were pooled for analysis.[147 153] Among patients assigned to AST-120, 18% (27/149) had a response compared to 15% (24/157) of placebo patients. The pooled RR indicated that there was no statistically

significant difference in effect between AST-120 and placebo (RR 1.19, 95% CI 0.72-1.97. p = 0.50; Figure 8), however, the observed heterogeneity was high (I^2 = 79%). Likewise, the pooled RR for induction of fistula remission failed to demonstrate a statistically significant between-group difference in effect (RR 1.45, 95% CI 0.79-2.66, p = 0.22), and observed heterogeneity was also substantial (I^2 = 66%) for this outcome. While Fukada 2008 reported a statistically significant treatment effect in favour of active treatment (RR 3.70, 95% CI 1.14-12.06), a large, multi-national, follow-up study by Reinisch et al. failed to confirm these findings (RR 0.84, 95% CI 0.47-1.52). Potential explanations for the discordant results include differences among the study populations with respect to nationality, genetics, diet, age, body mass index, prior TNF-α antagonist exposure and baseline disease activity[153].

Mesenchymal stem cell therapy. Two trials compared mesenchymal stem cell therapy to placebo for induction of fistula response.[92 151] Sixty-six percent (80/122) of patients receiving stem cell injections responded versus 52% (58/111) of placebo patients. The pooled RR was 1.27 (95% CI: 1.02-1.59, p = 0.03; figure 9), indicating that stem cell therapy was effective for inducing fistula response. There was no observed heterogeneity for this outcome (I^2 = 0%), and the overall quality of evidence was considered moderate due to sparse data.

Fifty-two percent (64/122) of patients in the stem cell therapy group achieved fistula remission versus 41% (45/111) of placebo patients. The pooled RR revealed that stem cell therapy was not more statistically effective than placebo for induction of fistula remission (RR 1.31, 95% CI 0.98-1.73, p = 0.06; Figure 1.2.). There was no observed heterogeneity (I^2 = 0%), and the overall quality of evidence was considered moderate due to sparse data.

7.4.5 Biologic combined with antibiotic versus biologic alone

Two trials compared combination therapy with a TNF-α antagonist and an antibiotic to TNF-α antagonist monotherapy.[87 165] Seventy percent (32/46) of patients in the combination therapy group had fistula response compared to 44% (22/50) of patients in the monotherapy group. The pooled RR demonstrated that a TNF-α antagonist coupled with an antibiotic was more effective than a TNF-α antagonist administered alone for induction of fistula response (RR 1.58, 95% CI 1.09-2.28; p = 0.01; Figure 14). No heterogeneity was observed (I^2 = 0%), and the overall quality of evidence was considered moderate due to sparse data.

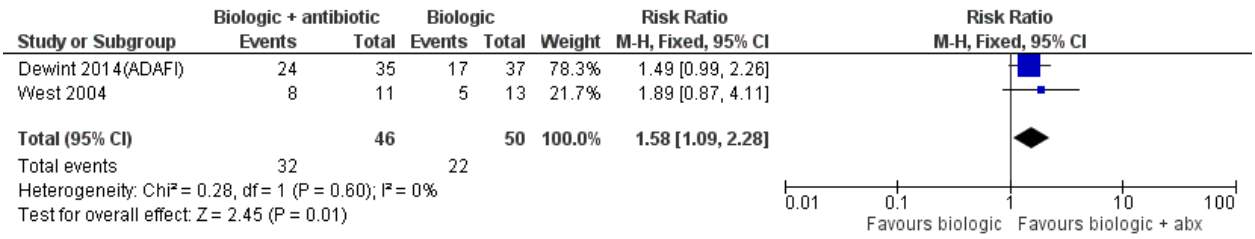

Figure 14 Biologic versus biologic combined with antibiotic for induction of response

One study reported on fistula remission rates. Sixty-one percent (22/36) of patients receiving combination therapy achieved remission versus 32% (12/37) of patients assigned to placebo. This difference in effect was statistically significant (RR 1.94, 95% CI 1.14-3.29, p = 0.01; Figure 15) and the overall quality of evidence was considered low due to very sparse data. None of the included studies in this review presented fistula-specific data on resolution by diagnostic imaging, health-related quality of life or functional outcomes.

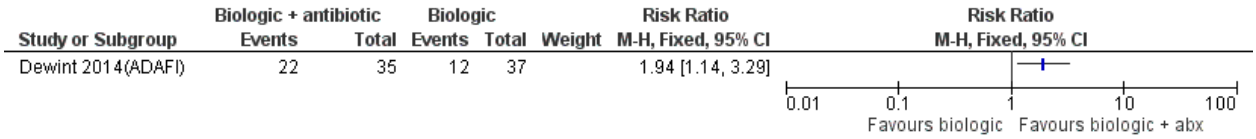

Figure 15 Biologic versus biologic combined with antibiotic for induction of remission

7.4.6 Sensitivity analysis

Ten of the 27 included studies evaluated fistula disease activity as the primary outcome and therefore exclusively enrolled patients with fistulating CD, whereas in 17 trials fistula disease activity was assessed as a secondary outcome. Sensitivity analyses showed that omitting the 17 RCTs that studied fistula disease activity as a secondary outcome did not change the overall results (Appendix C). Eleven of the 27 included studies solely included patients with perianal fistulae. Sensitivity analysis demonstrated that omitting the 16 RCTs with mixed fistula populations had a minimal impact on the overall results (Appendix D).

7.4.7 Assessment of bias between studies

Visual assessment of funnel plots was undertaken for induction of fistula response (figure 16), and induction of fistula remission (figure 17). These did not demonstrate any obvious outliers in reporting.

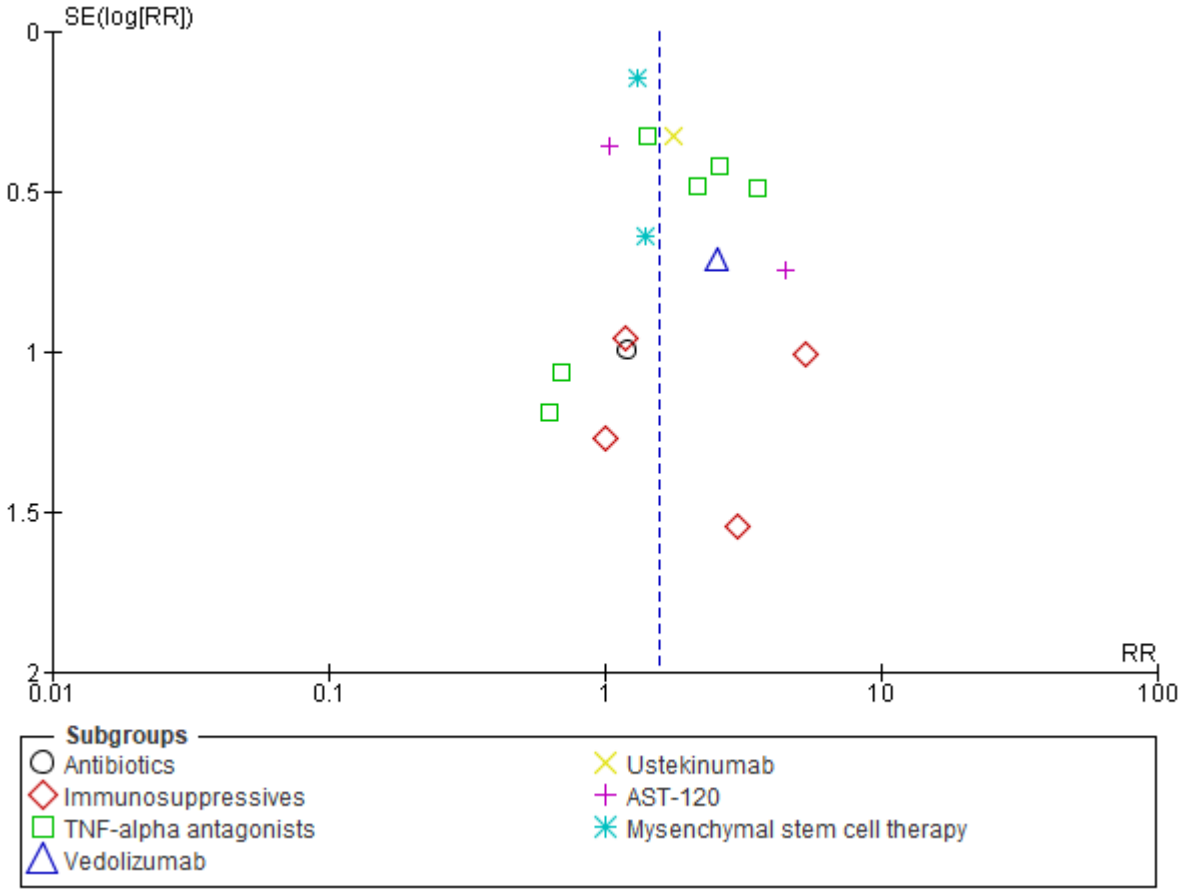

Figure 16 Funnel plot of drug therapy versus placebo: Induction of fistula response

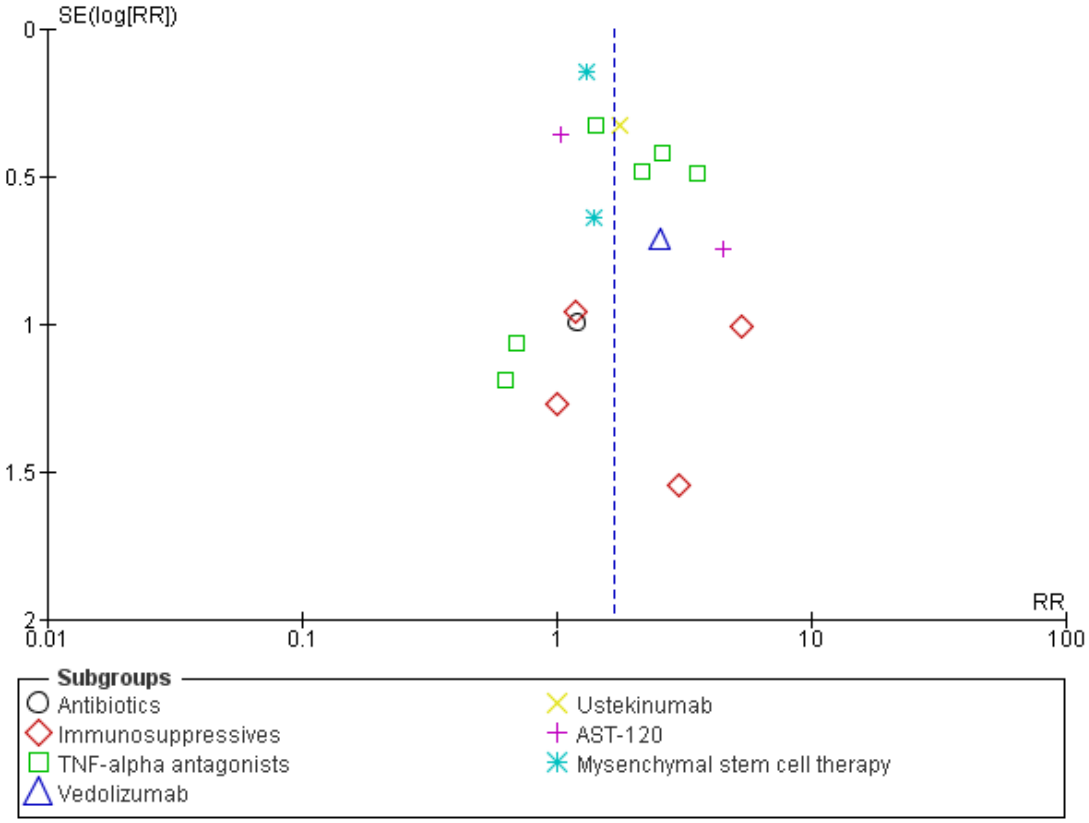

Figure 17 Funnel plot of drug therapy versus placebo: Maintenance of fistula remission

7.5 Discussion

This systematic review and meta-analysis has identified one class of drug (anti-TNF-α agents) with consistent evidence of benefit in fistulating Crohn's disease. Development of novel therapies for the treatment of fistulating disease is a large unmet need in the management of CD, and is recognised as a research priority[42 167].

7.5.1 Summary of evidence

In this meta-analysis, 27 RCTs evaluated 14 separate pharmacotherapies. Our key finding was that anti-TNF-α agents are the only drug class proven to both induce and maintain fistula response and remission. As a class, they were associated with an approximately 1.5-fold increase in likelihood of induction of fistula response, and a two-fold increase in likelihood of induction of fistula remission, maintenance of fistula response and maintenance of fistula remission. Furthermore, when combined with antibiotics, a statistically significant higher rate of induction of fistula response and remission was observed in comparison to a TNF-α antagonist administered alone. Future studies should focus on the efficacy of combination therapy with immunosuppressives and the relationship between anti-TNF-α trough levels and response status within the context of treatment optimization for fistulating CD.

While thiopurines were not found to be superior to placebo for induction of fistula response or remission, oral tacrolimus may be effective for induction of response. Unfortunately, the side effect profile associated with this agent has limited its use.

Recently, two additional biologic agents, ustekinumab (Stelara; Janssen Biotech, Horsham, PA)[168] and vedolizumab (Entyvio; Takeda, Deerfield, IL)[169], have become available in clinical practice for the management of moderate-severely active CD. Ustekinumab, a fully human IgG_K monoclonal antibody that blocks the common p40 subunit of IL-12 and IL-23, was

approved for the treatment of moderate-to-severely active CD on the basis of demonstrated efficacy for induction (UNITI-1 and UNITI-2) and maintenance (IM-UNITI) in both TNF-α antagonist naïve and failure patients.[168] To date, no phase 4 trial is underway to specifically investigate its effectiveness for the treatment of fistulating disease. In the absence such a study, a post-hoc analysis of patients in the pivotal trials provides some signal of treatment efficacy for patients with perianal fistulating CD. Pooled data from one phase 2 (CERTIFI) and two phase 3 induction trials (UNITI-1 and UNITI-2) of ustekinumab revealed a statistically significant 1.5-fold increase in the likelihood of inducing fistula response. These findings are not conclusive, but they should support future trials.

The α4β7 integrin antibody vedolizumab inhibits trafficking of subpopulations of T-cells to the gut mucosa. In the pivotal registration trial, at week 6, 14.5% (versus 6.8% in placebo, $p = 0.02$) and at week 52, 39.0% and 36.4% of patients who received vedolizumab every 8 and 4 weeks respectively were in clinical remission (versus 21.6% in the placebo group, $p < 0.001$ and $p = 0.004$ respectively). Post-hoc, exploratory analyses published in abstract form reporting on the efficacy of vedolizumab for induction of fistula remission (mixed fistula population) demonstrated a trend in favour of active treatment, although this was not statistically significant. The efficacy of vedolizumab for the induction and maintenance of perianal fistula response and remission is subject to a phase 4 clinical trial that is currently underway (NCT02630966).

Intra-lesional injection of stem cell therapy is a promising treatment for patients with refractory perianal fistulating disease. The pooled analysis of a small trial of bone marrow derived mesenchymal stromal cells and a larger phase 3 trial of adipose derived stem cells using an a combined clinical and imaging endpoint demonstrated a 30% increase in the likelihood of achieving fistula remission over placebo.[92 151] High rates of placebo remission

were observed in the trial of adipose derived stem cells through surgical curettage and injection of saline in fistula tracts, indicating the importance of good adjunctive surgical techniques in the management of perianal fistulating disease. A phase 3 trial is underway in North America (NCT03279081).

7.5.2 Limitations

There are several limitations to this review and meta-analysis. This review does not take surgical or combined medical-surgical treatments of fistulating CD into account, as a comprehensive review of this topic already exists[112]. Systematic reviews are only as good as the studies upon which they are based. As Crohn's anal fistula is a relatively rare condition, the included RCT's are limited both in number of studies and number of participants. Whilst the majority of patients in the eligible studies had perianal fistulating disease, some had other fistulating disease, therefore it is unclear whether our findings are generalisable to all fistula types. A post-hoc subgroup analysis of data from the ACCENT II study that assessed the efficacy and safety of infliximab for the treatment of rectovaginal fistula was the sole report identified that exclusively focused on a non-perianal fistula population.[170] Only results from the main ACCENT II study were pooled for meta-analysis in the current systematic review. A small number of trials contained pooled results of mixed fistula populations, although it is reasonable to hypothesize that biological treatment effects are similar regardless of fistula origin. Results arising from trials of the newer biologics, ustekinumab and vedolizumab, should be considered exploratory as they come from post-hoc analyses published in abstract from involving a small number of patients. Finally, there was some heterogeneity in endpoint definitions for fistula response and remission, although this is previously summarized in the field of IBD[171] and initiatives are underway to develop core outcome sets to standardise outcome measures for clinical trials.[172 173]

7.6 Conclusion

Within the current literature, anti-TNF-α agents are the only drug class to demonstrate efficacy for induction and maintenance of fistula response and fistula remission. Injection of stem cell therapy into fistula tracts offers a promising therapy for those with fistulae resistant to conventional pharmacological treatment, and may be an appropriate treatment for patients who do not respond to first line therapy. and more efficacy data are needed on the novel biologic agents ustekinumab and vedolizumab.

8 Systematic Review of Surgical Interventions for Crohn's Anal Fistula

Data from this chapter has been published following peer review:

Lee MJ, Heywood, N, Adegbola S, Tozer P, Sahnan, K, Fearnhead NS, Brown, SR (2017), Systematic review of surgical interventions for Crohn's anal fistula. BJS Open, 1: 55-66. doi:10.1002/bjs5.13

My role was the design and registration of study, conduct of searches, screening, extraction of data, bias assessment, analysis of findings and preparation of manuscript.

Nick Heywood supported study design, screening of data, bias assessment and preparation of manuscript.

Sam Adebola, Phil Tozer and Kapil Sahnan supported screening of studies and manuscript preparation.

Steven Brown and Nicola Fearnhead provided oversight of all stages of the study.

8.1 Introduction

Chapter 4 shows that drugs have a role in the treatment of Crohn's anal fistula. However, even in modern studies just one in three patients will achieve long term fistula healing[174]. This is a condition which should be managed in concert between a surgeon and physician[112]. Published guidelines advocate sepsis control and use of anti-TNF-α therapy[175 176]. Some patients will improve or heal with this treatment, although many will require further surgical intervention. The selected intervention may vary, dependent upon whether the treatment aim is cure, or symptomatic relief/palliation.

Previous work has shown that a range of surgical techniques are used[177]. These include the use of a draining seton alone, anal fistula plug, fistulotomy, stoma and proctectomy. Newer techniques such as video assisted anal fistula treatment (VAAFT) (Karl Storz GmbH (Tuttlingen, Germany)) and over the scope clip ©(OTSC) (Ovesco Endoscopy AG, Tübingen, Germany) have also been used by some. This variation in practice suggests that either a widely acceptable and reproducible procedure has not yet been identified, or that additional factors may influence choice. Given the range of procedures offered there is a need to collate available data on surgical outcomes for this condition.

8.1.1 The IDEAL Framework

It is well recognised that surgical research lags behind medical intervention[178]. In response to this, the IDEAL framework was devised as a tool to describe the developmental state of surgical innovation. This categorises interventions from the 'idea' demonstrated with case series (stage one), through development, evaluation (including safety), and assessment, onto long term follow-up[179]. This allows a better understanding of the state and applicability of interventions to the wider patient cohort.

There is no current systematic assessment of all potential surgical interventions for the treatment of perianal Crohn's fistula.

8.2 Aim

The aim of this chapter was to collate data on the outcomes, including complications, of surgical interventions for the treatment of fistulating perianal Crohn's disease.

8.3 Method

8.3.1 Protocol and registration

This systematic review was registered on the PROSPERO database (CRD42016050316) prior to commencement. It was conducted in line with PRISMA guidance.

8.3.2 Eligibility

Studies were selected for inclusion if they reported a Crohn's perianal fistula specific outcome (including as part of studies on all types of perianal fistula), or treatment outcomes of Crohn's perianal fistula, following a surgical procedure. Only primary studies and bibliographies from identified systematic reviews were considered. Conference proceedings were included if related full text could be identified. Ineligible manuscripts were those which reported outcomes of Crohn's perianal fistula as part of all fistula types, or those with fistula related to ileoanal pouch only. Studies reporting on outcomes of Crohn's rectovaginal fistula only were excluded – surgeons in the field approach rectovaginal fistula as a separate entity to perianal fistula, and offer a different range of surgical options[177]. Eligible papers were limited to those published in English and since 1995 since when supporting medical therapy has changed significantly [74].

8.3.3 Information sources

The following databases were searched: MEDLINE, EMBASE and Cochrane Library from 1995 to current dates.

8.3.4 Search strategy

Searches were performed in March 2016. We combined the terms 'Crohn Disease', 'Rectal fistula' or 'anal fistula', 'surgery', 'Ligation of inter-sphincteric fistula tract' (LIFT), 'seton', 'fistula plug', 'advancement flap', 'VAAFT', 'OTSC' 'stoma', and 'proctectomy' (Appendix E).

.3.5 Study selection

Abstracts were screened by two of six reviewers against eligibility criteria. To progress to the next stage, two reviewers had to agree on inclusion. Where there was disagreement, this was arbitrated by a third reviewer (SB). The same six reviewers assessed the full text of these studies against inclusion and exclusion criteria. To progress to the next stage, two reviewers had to agree on inclusion. Where there was disagreement, this was arbitrated by a third reviewer (SB). If a study was excluded at this stage, the reason for exclusion was recorded.

8.3.5 Data collection process

Data were extracted from studies eligible for inclusion after full text review. Two reviewers recorded extracted data independently into a pro-forma. These were compared and any variation was discussed with a third reviewer. Where data were missing or unclear, the corresponding author was contacted by email for clarification.

8.3.6 Data items

Data items collected included study descriptors, data on patient cohort, primary outcome used (including definition) and corresponding event rate. Study descriptors were year of publication, first author, study design, number of participants and number of participants with Crohn's disease, originating hospital and country of author. Patient descriptors included mean or median age of patient cohort, gender, duration of Crohn's disease, fistula anatomy (defined either using Parks' classification or the American Gastroenterology Association definition), and where available, coincident medical therapy. Intervention details captured focussed on the primary surgical intervention, e.g. seton placement, LIFT procedure, fibrin glue, etc. Primary outcome was taken as defined by each paper, as was the interval to assessment.

Additional outcomes including complications such as abscess and incontinence were recorded. Rates of long -term recurrence were recorded where available.

8.3.7 Risk of bias

Risk of bias was assessed using the ROBINS-I tool for non-randomised interventions[132], and the Cochrane tool for bias assessment in randomised trials[129]. Bias was independently assessed by two reviewers and then reconciled. Where there was disagreement between the two reviewers, a third reviewer acted as an arbiter.

8.3.8 Summary measures, synthesis of results and risk of bias across studies

During protocol design, we considered the landscape of the literature on perianal fistula in Crohn's disease. Given the perceived paucity of randomised controlled trials and prevalence of small case series, we intended to undertake qualitative synthesis only. No assessment of heterogeneity, publication bias, or any other statistical assessment was planned. Studies were categorised according to the IDEAL framework[179].

8.4 Results

8.4.1 Study Selection

Initial searches identified 1628 references, of which 791 were duplicates. These were removed and 837 studies were screened against the eligibility criteria, with 685 of these excluded. Full-texts were retrieved and assessed for 152 references, of which 89 were excluded, leaving 63 studies reporting outcomes of 1,584 patients for inclusion in the qualitative synthesis. This process and reasons for exclusion of studies are presented in the PRISMA flow chart (Figure 18).

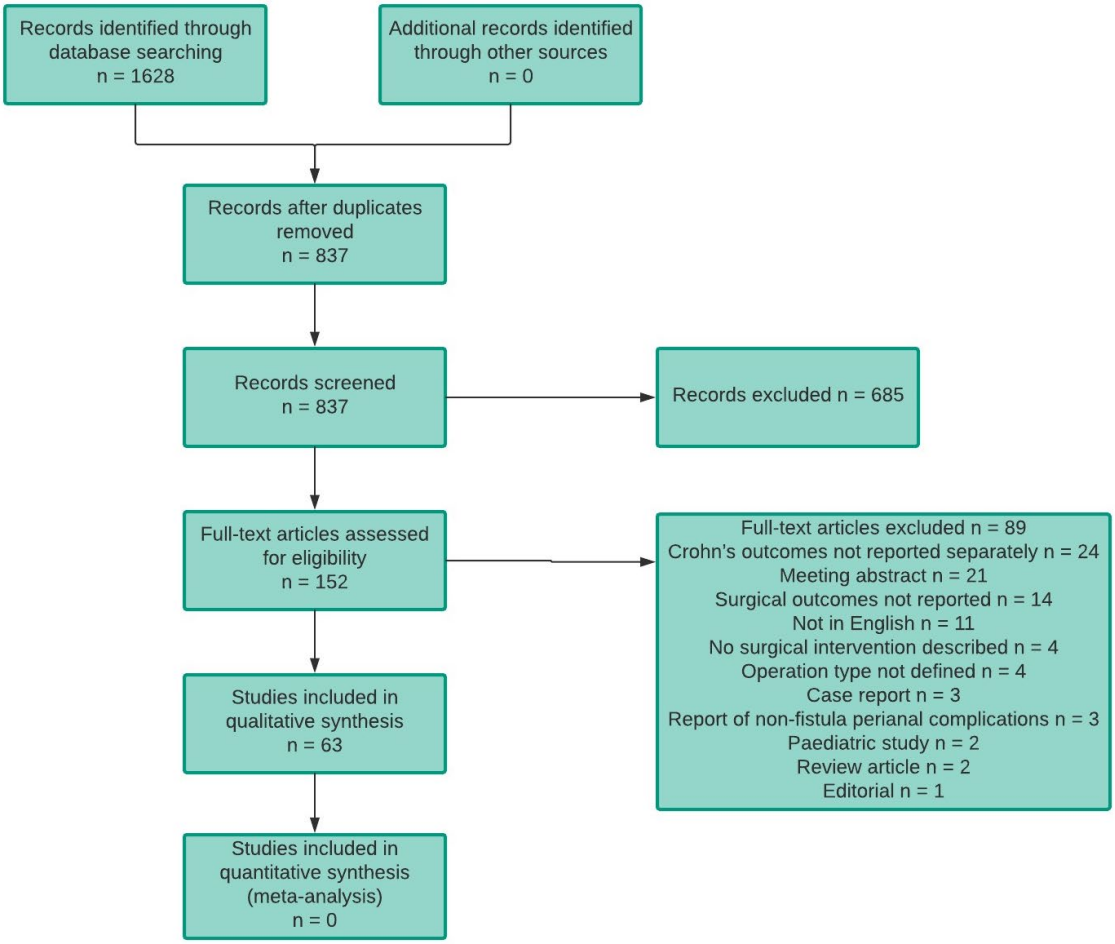

Figure 18 PRISMA flowchart for selection of studies of surgical interventions

8.4.2 Characteristics

Of the studies, 22 originated from the USA, 7 from Germany, 5 from Italy, 4 from the Netherlands, 3 from the UK, Australia, France, Spain and South Korea, 2 from Japan, Finland and Canada, and 1 each from Turkey, Sweden, Serbia, Saudi Arabia and Brazil. The studies were published between 1995 and 2016.

Study design was defined as retrospective cohort in 40 studies and prospective cohort in 15 studies. The design was open label or single arm trial in 5 studies, and there were three randomised controlled trials. The number of perianal Crohn's fistula patients ranged from 1-41 in prospective cohort studies, 1-119 in retrospective cohorts and 10-33 in open label/single arm trials. There were 106 patients in the RCTs.

The surgical interventions described were draining seton, examination under anaesthetic with local anti-TNF-α therapy, fistulotomy, fistulectomy, fistula plug, fibrin glue, advancement flap, LIFT procedure, VAAFT, OTSC©, Carbon Dioxide laser therapy, diverting stoma and proctectomy. A summary of study characteristics is shown in table 8.

Author & Year	Country of origin	Study design	Total number of patients	Number of pCD patients	Intervention(s)
Buchanan 2003	UK	Retrospective Cohort	24	6	Seton
Chung 2010	Canada	Retrospective Cohort	51	40	Seton, AFP
Gligorijevic 2010	Serbia	Prospective cohort	24	24	Seton
Gottgens 2015	Netherlands	Pilot trial	10	10	Seton
Hukkinen2014	Finland	Retrospective Cohort	13	13	Seton
Kotze 2014	Brazil	Retrospective cohort	78	78	Seton
Schiaduone 2010	Canada	Retrospective Cohort	35	35	Seton
Sugita 1995	Japan	Retrospective Cohort	67	67	Seton
Tanaka 2010	Japan	Retrospective cohort	14	14	Seton
Uchino 2011	Japan	Retrospective Cohort	62	62	Seton
Graf 2015	Sweden	Retrospective Cohort	119	119	Seton, Fistulotomy
Thornton 2005	Australia	Retrospective Cohort	28	28	Seton
Dursun 2014	USA	Retrospective Cohort	81	81	Seton, Fistulotomy
Alessandroni 2011	Italy	Prospective cohort	12	12	Local TNF
Asteria 2006	Italy	Prospective cohort	11	11	Local TNF
Faucheron 1996	France	Retrospective Cohort	41	41	Fistulotomy, Seton
Halme 1995	Finland	Retrospective Cohort	35	35	Fistulotomy
Scott 1996	UK	Retrospective Cohort	59	59	Fistulotomy, Seton
van Koperen 2009	Netherlands	Retrospective Cohort	61	61	Fistulotomy, MAF
de Paredes 2010	France	Retrospective Cohort	30	11	Fibrin glue

Sentovich 2003	USA	Retrospective Cohort	48	6	Fibrin glue
Sentovich 2001	USA	Retrospective Cohort	40	4	Fibrin Glue
Park 2000	USA	Prospective cohort	25	2	Fibrin Glue
Loungranath 2004	US	Retrospective Cohort	39	13	Fibrin Glue
Zmora 2003	USA	Retrospective Cohort	37	7	Fibrin Glue, MAF
Mizrahi 2002	USA	Retrospective Cohort	106	28	MAF
Hyman 1999	USA	Prospective cohort	33	14	MAF
Jarrar 2011	USA	Retrospective Cohort	98	19	MAF
Joo 1998	USA	Retrospective Cohort	26	26	MAF
Makowiec 1995	Germany	Prospective cohort	32	32	MAF
Ozuner 1996	USA	Retrospective Cohort	101	47	MAF
Rieger 1999	Australia	Retrospective Cohort	35	6	MAF
Sonoda 2002	USA	Retrospective Cohort	99	44	MAF
Marchesa 1998	USA	Retrospective Cohort	13	13	MAF
Van der Hagen 2006	Netherlands	Retrospective Cohort	103	21	MAF, Fistulotomy
Nelson 2000	USA	Retrospective Cohort	65	17	Dermal Advancement
Cintron 2013	USA	Prospective cohort, multicentre	73	8	AFP
El-Gazzaz 2010	USA	Retrospective Cohort	33	13	AFP
Ky 2008	USA	Prospective cohort	45	14	AFP
O'Connor 2006	USA	Prospective cohort	20	20	AFP
Ommer 2012	Germany	Retrospective Cohort	40	4	AFP

Owen 2010	Australia	Retrospective Cohort	35	3	AFP
Schwander 2009	Germany	Prospective cohort	16	10	AFP
Schwander 2008	Germany	Prospective cohort	19	7	AFP
Senejoux 2015	France	RCT	106	106	AFP, Seton
Zubaidi 2009	Saudi Arabia	Prospective cohort	22	2	AFP
Gingold 2014	USA	Prospective cohort	15	15	LIFT
Molendijk 2015	Netherlands	Phase II trial	21	21	ASC
Cho 2013	Seoul	Phase I trial	10	10	ASC
Cho 2015	Seoul	Observational study	41	41	ASC
Ciccocioppo 2011	Italy	Phase I Trial	12	12	MSC
de la Portilla 2013	Spain	Open label trial	24	24	ASC
Garcia-Olmo 2015	Spain	Prospective cohort	10	3	ASC
Garcia-Olmo 2009	Spain	Open label	49	14	ASC, Fibrin Glue
Lee 2013	South Korea	Phase II	43	33	ASC
Schwander 2013	Germany	Prospective cohort	13	11	VAAFT
Pini Prato 2016	Italy	Prospective cohort	9	1	VAAFT
Menningen 2015	Germany	Retrospective Cohort	10	6	OTSC
Reguiero 2003	USA	Retrospective Cohort	32	32	EUA
Schlegel 2015	Germany	Retrospective Cohort	11	11	IAR
Yamamoto 2000	UK	Retrospective Cohort	31	31	Stoma
Schaden 2007	Austria	Retrospective Cohort	69	5	Myocutaneous flap
Mattioli 2015	Italy	Retrospective Cohort	11	11	Cone resection

Ozturk 2014	Turkey	Retrospective Cohort	10	1	Free Cartilage
Bodzin 1998	USA	Retrospective Cohort	7	7	CO2 Laser
Moy 2006	USA	Retrospective Cohort	27	27	CO2 Laser

Table 8 Summary of included studies.

RCT = Randomised controlled trial, MAF = Mucosal advancement flap, ASC = Adipose derived stem cells, MSC = Mesenchymal derived stem cells, AFP = Anal Fistula Plug, LIFT = Ligation of intersphincteric tract, VAAFT= Video Assisted Anal Fistula Treatment, OTSC = Over the Scope Clip, EUA = Examination under anaesthetic, IAR = Intersphincteric anal resection, CO2 = Carbon dioxide.

8.4.3 Risk of bias within studies

Bias assessment of the identified studies was performed using the ROBINS-2 and Cochrane Risk of Bias) tools for non-randomised and randomised studies respectively. Summary tables are presented in appendix F and G respectively. Overall, bias in non-randomised studies tended to decrease as publication dates approached the present.

Potential bias from confounders arose in studies with mixed populations (i.e. cryptoglandular and Crohn's fistula), with incomplete characterisation of the cohort. This bias was reduced in cohorts limited to Crohn's fistula, where patient and disease factors were usually (but not always) more clearly defined. Characterisation was still suboptimal with regards to classification of fistulas, use of medical therapies, distribution of disease, smoking status, and duration of perianal fistula.

Selection bias was an issue in retrospective studies reporting outcomes of interventions in a single centre over a number of years. The criteria for offering interventions to patients were not clear – several studies stated that patients offered a procedure 'typically' had certain characteristics. Studies from teaching hospitals reported outcomes of patients referred to their centre. This introduces selection bias as this subset of the population may have disease that is particularly challenging to manage, and skews outcomes.

Bias associated with the classification of intervention tended to be low in studies reporting outcomes from one specific procedure. This detailed the procedure and perioperative care clearly. In studies reporting the use of setons, some issues arose around the timing of removal, whether setons were removed or not, and the timing and nature of concurrent medical therapy[180 181].

Bias due to deviation from intervention was limited as these were typically retrospective studies with no pre-defined protocol. It was difficult to judge the impact of missing data as little information was given on this domain. Some studies reported use of patient surveys to capture missing clinical data, although this was uncommon.

Outcome measurement was an area of significant concern. Many studies reported healing, without clear definition, as their primary outcome. Other commonly reported measures included absence of drainage from a fistula when compressed with a finger[182], or closure of the external and internal opening of a fistula tract. This was performed at variable timepoints in clinic settings. Occasional use of MRI to confirm fistula fibrosis was reported[83]. One study reported a successful outcome as 'one the patient and surgeon are both satisfied with'[183].

Bias was introduced in the selection of outcome measures as those which are easy to measure (absence of drainage, closure of external opening of fistula) were used. Whilst used in trials, fistula drainage is a snapshot assessment of a dynamic state – a fistula may discharge collected fluid prior to a clinic assessment where it is found to be dry. The person measuring outcomes was also a potential source of bias. Some authors had financial interests in their procedure and this might lead to conflicts of interest in reporting. Only one study had blinded assessors – a panel of three surgeons who reviewed perineal photographs to confirm fistula closure[182].

In the randomised trials, the main concerns were around allocation concealment and blinding of participants. One stem cell study had patients allocated to receive liposuction to harvest cells only if they were undergoing the intervention arm. The trial of fistula plug vs seton removal will have had similar difficulties of patient blinding as the absence of a seton likely feels different to the insertion of a fistula plug.

8.4.4 Outcomes after seton insertion

Setons were used in a number of different ways. Use of a seton alone, with removal at various time-points, was reported in six retrospective fistula cohort studies, and included a total of 329 Crohn's fistulae[184-189]. In the four studies which looked at short term healing, success rates ranged from 13.5-80.9%[185-188]. One study looked at symptom improvement, defined as improvement by at least one point in all domains of the perianal disease activity index. This endpoint was achieved in 72.2% of patients[189]. Long term recurrence was reported in 42.8%[187] and 83.3%[184] of patients. Further drainage of abscess was required in 42.8% and in one study, two patients developed a cancer related to their fistula[189].

Long term seton was used for symptom control in one study of 28 patients, of whom 26 noted symptomatic improvement. The two patients without improvement went on to have proctectomy or defunctioning stoma[190].

Seton therapy combined with anti-TNF-α therapy was the focus of two retrospective cohort studies[180 191] and one prospective cohort study[181], accounting for a total population of 126 patients. There was incomplete characterisation of group demographics. The timing of anti-TNF-α therapy in relation to sepsis drainage or seton insertion was not clear in these studies. Short term success was defined as absence of drainage in two studies (although the time point for measurement was unclear)[180 181] and complete fistula healing in one[191]. These outcomes were achieved in 30-45.8%, 52.5%, and 78.5% of patients respectively. Recurrence rates (where reported) were between 9.0-27.7%[181 191]. Abscesses occurred in up to 8.3%[181]. One study reported no serious adverse effects related to systemic drug therapy[191]. Seton with anti-TNF-α therapy also formed the control arm of a randomised trial, and found short term healing in 30.7% of patients, with recurrent abscess rate of 7.7%[192].

8.4.5 EUA with local or systemic anti-TNF-α therapy

Two prospective studies assessed responses to examination under anaesthetic and local injection of anti-TNF-α drugs. In the first of these, patients received between 3 and 5 injections, and eight of eleven patients achieved remission (cessation of fistula drainage) at the end of the treatment course[193].

The second prospective observational study reported outcomes of twelve patients with perianal Crohn's fistula who underwent fistulectomy and local anti-TNF-α injection. Definition of healing was based on clinical and MRI appearances at 1 year. With four patients lost to follow-up, healing was achieved in 87.5% (47.4-99.6%). One patient developed a new perianal abscess and one patient developed pulmonary tuberculosis following treatment[194].

One retrospective study assessed the use of EUA as an adjunct to systemic anti-TNF-α therapy, and found no discharge from fistulas at three months, although subsequent recurrence occurred in 44%[195].

8.4.6 Fistulotomy

Seven studies reported on the outcomes of fistulotomy in 178 patients, all retrospective in nature[183 186 196-200]. Although baseline factors are poorly reported, these were typically for low fistulae, i.e. those involving a small part of sphincter where division would not alter function. Outcomes were defined as initial healing[186] or three month healing[196].

Short term healing was successful in 72.2%-100% of patients[186 196 197 199]. Longer term (i.e. 6 months or more after treatment) fistula recurrence occurred in 5/28 patients[200], and 3/9 patients at 12 months[198]. One study found that 22 of 27 patients had a 'satisfactory' outcome,

although the 5 unsuccessful cases developed significant incontinence[183]. Higher rates of continence disturbance were seen in other studies[200].

8.4.7 Fibrin glue

Six studies reported the use of fibrin glue for fistula. Five were retrospective[201-205], including one report of long-term follow-up in a cohort previously described[201]. The sixth study was a prospective cohort[206]. In one of the retrospective cohorts, two patients had fibrin glue inserted into their fistula track, with endoanal advancement flap to close the internal opening[203]. These six studies included 140 patient, but only 26 of these had Crohn's disease. The long-term follow-up cohort only captured 4 of the 6 Crohn's patients from the original study[201]. As a result, details of fistulae in the Crohn's subgroup were not available.

Short-term success rates for fibrin glue ranged from 40.0-66.6%[202-204 206]. In the study reporting long term follow-up, three of four patients remained healed[201]. One of the two patients treated with a combined procedure achieved short term healing.

8.4.8 Fistula Plug

Results of anal fistula plug were reported in 11 papers, and a total of 191 patients with perianal Crohn's fistula. Study design included one RCT[192], six prospective cohort studies [207-212], and four retrospective cohort studies[185 213-215]. In the cohort studies, follow-up ranged from 0.75-29 months post-procedure. Definition of baseline demographics was poor in these studies, and included 14 complex fistula patients in one study (including 4 rectovaginal fistula)[208], patients with a single transphincteric track and no proctitis in another[210]. In the RCT, the American Gastroenterology Association (AGA) classification[216] was used, and included 18 complex fistula patients and 78 with simple fistula. Male:Female ratios were 3:1 and 41:68

where reported, and age ranged from 26-43 years old. Disease duration prior to the RCT was 3-13 years. One study included the use of faecal diversion in addition to the anal fistula plug in some cases[209].

Success rates of fistula plug ranged from 15.4-85.7%. Where reported, postoperative abscess formation occurred in 3.7-53.8% of patients[192 208 213 214]. Additional complications included one wound dehiscence[214], five plug extrusions and two significant pain episodes[192].

8.4.9 Advancement flaps

Eight retrospective[185 198 217-222] and two prospective observational studies[223 224] reported the outcome of mucosal advancement flaps in both Crohn's and cryptoglandular perianal fistulous disease. Of the 624 reported procedures, 240 of these were performed for Crohn's fistula. Where reported, treated fistulae were predominantly transphincteric, although studies included some rectovaginal fistulae.

Success in short term healing was seen in 50.0%-85.0% of patients. Where reported, recurrence at >1 year was 30.0%-50.0%[198 223]. Complications were reported in only one study, with occurrence of haemorrhage and flap retraction occurring in 6.6%[218].

A retrospective study has reported on the use of a circumferential advancement flap for severe and multiple fistula tracks in 13 patients, combined with stoma formation in 8 of these[225]. This led to symptomatic improvement in 8 patients, although all patients also had a stoma either prior to, or as part of their procedure.

One retrospective study reported on the use of dermal flaps to close the fistula opening, with 15/17 patients achieving short term healing[226].

An augmented approach was used in a pilot trial. This involved placement of a seton, followed by local treatment with with platelet rich plasma (PRP) and mucosal advancement flap in 10 patients [227]. Participants also received multiple concomitant medical therapies. At one-year follow-up, 70% of participants had a dry fistula.

8.4.10 Outcomes of LIFT procedure

One study reported the outcomes of patients undergoing LIFT[228]. This was a retrospective study of 15 patients with transphincteric fistula, followed-up for one year. At two-month follow-up, 9 (60%) had healed. At one year, 8 of these remained healed. Complications such as abscess were reported for this study, however they were calculated as mean numbers for the cohort. The author was contacted, but data from this study was no longer available.

8.4.11 Outcomes of Stem Cell therapy

Six studies reported the outcome of stem cell therapy; five open label/phase I or II trials[229-233], with longer-term follow-up of the cohort initially reported by Cho in 2013[234] assessed adipose derived stem cells (ASC) in a total Crohn's disease cohort of 143 patients. One phase I trial reported outcomes of mesenchymal stem cell treatment in 12 patients[235]. Follow up in these studies ranged from 8 weeks to 24 months. Cohorts were predominantly male and young, with median age of 32 years in several studies. Duration of Crohn's disease was approximately 4.5 years where reported. The anatomy of treated fistulae was predominantly transphincteric.

Success rates for healing ranged from 29.2%-78.8%. Improvement in symptoms was noted in a large proportion of patients. This was assessed for at 8 weeks[231], defined as a variable time-point of 'no discharge for 6 weeks'[233], or at clinic appointments at 12 and 24 months[234]. These studies were all either clinical trials, or observational studies following patients after a trial.

As this treatment has been explored predominantly through clinical trials, reporting on complications has been thorough. Symptoms associated with disease flare such as abdominal pain and diarrhoea were reported in up to 60%[232] and 7%[234] respectively. Local complications included anal pain 19%[232], anal inflammation 7.3%[234], perianal swelling 28.5%[233], and perianal abscess in 16.6-19.0% of patients[232 233].

A single study of recurrent anal fistula with a subgroup of 3 Crohn's patients found that one patient healed and one improved when ASC were injected into the fistula and the internal opening closed.[236]

8.4.12 Outcomes of VAAFT©

This procedure involves insertion of a fistuloscope through the external opening of the track. Secondary tracks are then identified and electrocautery performed through the scope. The internal opening is identified and closed using a full-thickness advancement flap, with excision of the primary track where possible.

One prospective study reported outcomes of patients treated with Video Assisted Anal Fistula Treatment[237].

Thirteen patients were treated, of whom 11 had anal fistula related to Crohn's disease[237]. Four patients were male. Of these fistulae, 9 were transphincteric, 1 was suprasphincteric, and 1 was rectovaginal. The mean age was 34. This study combined VAAFT with a rectal advancement flap and faecal diversion. 'Short-term success' was achieved in 9 patients. There was no reporting of complications.

8.4.13 Outcomes of OTSC©

Over the scope clip © is performed in lithotomy position. The track is prepared using a fistula brush. Anal mucosa is excised circumferentially around the internal fistula opening. Sutures are placed into the internal anal sphincter around the internal fistula opening and loosely tied all together in a knot with a few centimetres of length. The knot is then pulled through a clip applicator that guides a circular Nitinol metal clip onto the internal fistula opening in order to close it.

A single case series reported on the use of over the scope clip© in anal fistula[238]. Of the 10 patients treated, 6 had fistula associated with Crohn's disease. Four of these were female, and all had transphincteric fistula. No information was available on mean duration of disease. Median follow-up was 230.5 days (156-523).

This study reported short term healing in five of the six patients treated. It was not possible to extract complications specific to those treated with Crohn's fistula from this study.

8.4.14 Proctectomy and faecal diversion

A retrospective study reported the use of intersphincteric anal resection (IAR) for fistulating and fibrosing perianal Crohn's disease. In this series, 12 patients underwent IAR and 5 achieved closure of their fistulae[239].

A second retrospective case series looked at outcomes of proctectomy with one-stage myocutaneous reconstruction (gracilis) in five patients. Perianal fistula healed in four cases, and only two patients were free from complications at the end of follow-up (median 19.6 months)[240].

Faecal diversion was reported as a sole intervention in a series of 31 patients. In this cohort, 25 patients achieved early remission, although this was sustained in only 8 patients (median 81 month follow-up). One patient died as a result of Fourniere's gangrene and five patients developed stoma complications, of whom two required operative revision. No patient developed malignancy in the defunctioned rectum[241].

8.4.15 Other therapies

One retrospective study reported outcomes of patients treated with CO_2 laser to the fistula track. This included 27 patients, with a mean duration of disease of 36 months. At one month follow up, four patients had ceased fistula drainage[242]. Another retrospective study found that laser treatment healed improved symptoms in 5/6 patients[243]. One other study assessed the use of free-cartilage as an interposition material in Crohn's fistula. This was unsuccessful[244].

8.4.16 Synthesis of results

No quantitative synthesis of results was performed.

8.4.17 Risk of bias across studies

Risk of bias across studies was not assessed.

8.4.18 Additional analyses

A summary of the interventions by success rates, complications and highest level of evidence is shown in table 9. Interventions were compared to the IDEAL framework to describe evolution of surgical interventions for perianal Crohn's fistula. Only seton, fistulotomy and faecal diversion/proctectomy are classified as IDEAL 4 interventions. The majority of interventions are classed as IDEAL 1-2b interventions. This is summarised in Table 10

Intervention	Highest level of evidence	Success rates	Complication/Harm rates
Seton	IIb	13.5-80.9%	Abscess 7.1-8.3%
Fistulotomy	IIIb	72.0-100.0%	NR
Fibrin Glue	IIIb	40.0-66.6%	NR
Anal Fistula Plug	IIb	15.4-85.7%	Abscess 3.7-53.8% Avulsion 10.4% Dehiscence 2.1%
Advancement flap	IIIc	50.0-85.0%	Haematoma 6.6% Flap retraction 6.6%
LIFT procedure	IV	60.0%	NR
Local stem cells	Ib	29.2-78.8%	Pain 19.0% Anal inflammation 7.3% Abscess 16.6-19.0%
VAAFT	IV	8.1%	NR
OTSC ©	IV	83.3%	NR
Stoma	IIc	80.6%	Death 5.2% Stoma complication 16.1%

Table 9 Summary of key outcomes by intervention.

This includes classification of level of evidence[245].N R = Not reported, used where no outcomes reported, or outcomes in Crohn's patients not clear. LIFT = Ligation of intersphincteric tract, VAAFT = video asisted anal fistula treatment, OTSC = over the scope clip.

IDEAL Stage	1 (Idea)	2a (Development)	2b (Exploration)	3 (Assessment)	4 (Long term study)
Intervention	Circumferential advancement flap	Local TNF injection	Local stem cell therapy	Anal Fistula Plug	Seton
		LIFT	Advancement flap		Fistulotomy
	VAAFT				
		CO_2 laser	Fibrin Glue		Stoma/Proctectomy
	OTSC				
	Free Cartilage implant				

Table 10 Summary of surgical interventions according to the IDEAL framework

VAAFT = Video Assisted Anal Fistula Treatment, OTSC = Over the Scope Clip, LIFT = Ligation of intersphincteric tract, CO2= Carbon dioxide.

8.5 Discussion

8.5.1 Summary of evidence

This systematic review is the first to collate the outcomes and complications of a range of surgical treatments used in the management of fistulating perianal Crohn's disease, and classify them using the IDEAL classification. Seton, advancement flap, anal fistula plug, and stem cells have been used in several studies, although success rates vary.

Advances in the medical therapy of fistulating perianal Crohn's disease have been made thanks to large randomised controlled trials[74 77 80]. The previously identified limitations in surgical research[178] have again been noted here; only three randomised controlled trials comparing therapies were found. It should be noted that a number of feasibility studies were performed, particularly in relation to local stem cell therapy. Since searches for this review were performed, a randomised trial of stem cells has been reported[246]. A randomised trial of advancement flap vs seton drainage in the context of protocolised medical therapy is also underway[94].

8.5.2 Limitations

Part of the categorisation used in the IDEAL framework is the number and type of patients, with 'indication' being an important discriminator[179]. Whilst draining setons, fistulotomy and faecal diversion seem to have broadly agreed indications with long term follow-up, this does not appear to be the case for other interventions. Classification of fistula anatomy varies between the Cardiff Hughes classification[54], Parks classification[53] and the American Gastroenterology Association definitions[247]. It is not always possible to consolidate these

classifications. Some studies also specified whether or not patients had proctitis[210] as this is thought to be relevant to prognosis[175 176].

Current thinking suggests optimum therapy involves a combined medical and surgical strategy. Smaller case series often described the current medical therapy of their patients, but larger (retrospective) studies typically failed to do this. It is also likely that medical treatment strategies will have varied significantly in one study that included patients treated surgically over a 20-year period[241]. A number of patients also underwent surgical treatment prior to the reported procedure – the prior use of setons and formal 'track preparation' is poorly reported across all studies.

It is impossible to make meaningful comparisons of success rates between interventions, as selected outcomes and timepoints are heterogenous. Pooled analysis is further hampered by the bias inherent in the preponderance of retrospective studies, and the limited size of their cohorts. It is also impossible to compare risk between the operative procedures as reporting of complications, with the exception of clinical trials, is very poor. Some studies also reported 'long term recurrence' at the end of their follow-up period. In some cases this was in the order of 6-8 years[200 241], and we should consider whether this represents recurrence due to the surgical procedure or due to the natural history of the disease.

8.5.3 Findings in context

The current literature is inadequate to advise with certainty or clarity. Nevertheless some broad conclusions can be made; setons provide palliation and can be used long term; advancement flap and stem cell therapy may emerge as effective therapies, but require well designed randomised trials. A number of other procedures including LIFT, VAAFT and OTSC© require further evaluation. Whilst the data on stem cells are promising, it is important to note that these patients also receive high-quality basic fistula care, including curettage and

drainage, and advancement flap or suture closure of internal openings. These measures may have benefits that have not been adequately assessed. The ADMIRE-CD trial, published after searches were performed for this review, is a case in point. In this study, both the control and intervention procedures included extensive fistula curettage, advancement flap to cover internal opening of fistula, and sealing of the external opening with glue. The intervention arm had stem cells injected and instilled into their track prior to closure, whereas the control group underwent injection of normal saline. Despite this, healing of anal fistula in the placebo arm approached 50% at 24 weeks (vs 63% in the intervention arm)[246]. This chapter includes all study designs reporting use of stem cells whereas the previous chapter reported randomised trials only.

Studies often capture specific subsets of patients, and selection bias in many of these studies means that reported results are not always matched by real-world experience. Additionally, the lack of a classification system with prognostic value means that a benefit produced in one (unknown and undefined) cohort may be masked by failure in another.

Many of the reported studies excluded patients with proctitis, a phenotype that is often seen, and is associated with high rates of proctectomy[248]. Baseline demographic factors including smoking status, disease behaviour and fistula duration are also poorly reported. This was seen frequently in mixed cohorts of cryptoglandular and Crohn's fistulae. On the assumption of differing aetiology, whether it is appropriate to mix these cohorts in a study is questionable.

Fibrin glue has largely fallen out of favour and fistula plugs are felt to have limitations, including failure and associated sepsis. Advancement flaps may not be technically possible with a 'woody' rectum, extensive fibrosis or active proctitis. The combination of recurrent Crohn's disease and loose stool means that any sphincter disruption or alteration in

anocutaneous sensation may have an exaggerated impact on continence. Given this, clinicians and patients may be understandably keen to avoid procedures that pose additional risk to the sphincter, including fistulotomy. Given these technical considerations, fistula anatomy and the risk of recurrent episodes of anal perianal sepsis including fistula in the long term, it is unsurprising that most clinicians favour conservative interventions such as seton placement[177].

When considering these studies together, especially over longer-term follow-up, it may be inferred that Crohn's anal fistula is at best palliated by surgical intervention. The majority of studies report success in terms of short-term healing, and do not address the management or prevention of long-term recurrence. Whilst the idea of healing anal fistula is aspirational, work is required to understand how we can best control symptoms and limit recurrence using current medical and surgical techniques. In this respect, patient centred outcomes such as data on quality of life, impact on personal & social interactions, or lost work-days might be more helpful in decision making. For example, faecal diversion has been shown to improve gastrointestinal specific domains of quality of life measures in this setting[50].

8.6 Conclusion

There is clearly work to be done to improve the quality of the literature - researchers and editorial boards should strive for transparent and thorough reporting on studies involving these patients. Development and adoption of a core outcome set including a validated, disease-specific quality of life score would help achieve this[249]. A classification system based on prognostic factors and improved therapeutic options based on an understanding of the current mechanisms of treatment failure are also crucial.

9 Surveys of Clinical Practice

9.1 What is a survey

A survey is '*a systematic method for gathering information from (a sample of) entities for the purpose of constructing quantitative descriptors of the attributes of the large population of which the entities are members'*[250]. Surveys allow the collection of data from a large number of respondents, focusing on quantity rather than depth of responses. They are commonly used by government bodies to report national data, such as a census or unemployment rates[250-252].

Surveys have been used extensively in healthcare settings and have collected data from both patients and clinicians[253-255]. Whilst a survey can refer to a cross-sectional study of many designs, it is frequently used as a short hand term for self-administered questionnaire studies.

9.2 Stages of survey design

Survey design begins with identification of study aims. Domains or topics for questions are selected. These can be identified through a number of different methods, including existing literature, the opinion of an expert group, or from prior qualitative work with patients or other stakeholders. When the topics for inclusion have been identified, they must be transformed into a question format i.e. they must be 'operationalised'[256]. This can be achieved using previously designed and validated questions. These are questions with well described properties related to reliability and validity. Where no validated questions exist, the researcher must develop their own questions[250 251]. The proposed instrument must then be assessed by the research team, experts in the field and participants to test validity. The proposed instrument may be modified following feedback. The survey then undergoes pilot testing with a small sample of the target population. This can be used to refine questions further, to test the reliability of instruments, and to assess the acceptability of the

questionnaire in terms of wording, design and length. The questionnaire may then undergo further refinement before being delivered to the intended sample population[250 257]. A summary of this process is shown in figure 19.

Figure 19 Process for development of a questionnaire.

9.3 Ensuring a valid and reliable questionnaire

A question which is 'good' is one which is both valid and reliable; these are key concepts in questionnaire research.

9.3.1 Validity

Validity refers to the extent to which an answer is a true measure of something, and whether it is measuring what the researcher expects it to. There are several different aspects of validity which are commonly assessed or reported within questionnaire research. These include:

- Face validity: This is the most simple form of validity. When assessed by stakeholders and potential respondents, does the question seem to ask what the researcher wants i.e. on the face of it, does it seem valid? This can be achieved through focus group or similar discussion[250 256].
- Content validity: This form of validity assesses items or domains within a measure for their relevance to the research question. It also allows identification of missing items. This form of validity can be achieved by asking experts to rate the importance of each question, with low scoring items potentially being removed from the instrument[250].

9.3.2 Reliability

Reliability refers to how 'dependable' a measure is. This means that when posed, the question will lead to a reliable set of results that can be reproduced across different samples of the population. There are several forms of reliability in use in questionnaire research. Some of the common examples are:

- Test-retest reliability: This requires administration of an instrument to the same person after a short interval. The degree to which the responses correlate across the two tests can be used to estimate reliability. This is best used when health or psychological states do not change significantly over a short period of time[250 256].
- Internal consistency: This is a form of reliability to assess agreement between two measures assessing the same factor, e.g. subscale measures in an anxiety questionnaire. If the scale shows internal reliability then it will show positive correlation between complimentary statements and negative correlation between opposing statements. This is often measured using Crohnbach's alpha[251].
- Equivalent form: This assessment requires the same constructs to be tested using different forms of words. The questionnaires are randomly divided so that each form

of the question is answered by half of all respondents. If there is a strong correlation between the two forms, it shows that the construct is reliable. This method can be limited by the need to generate multiple forms of questions in long questionnaires[256].

- Split-half reliability: This method involves randomly dividing all items that measure the same construct into two sets. Correlation between the two groups can then be assessed. If there is a high level of correlation, then the questionnaire can be considered reliable. This is only of use where the entire questionnaire assesses the same construct throughout[256].

9.3.3 Designing questions for quality

For a questionnaire to be 'good' in terms of the above criteria, the individual questions must be designed in an appropriate manner. There is extensive advice on the construction of a well written question. This advice focusses on clarity, specificity, and brevity of the question. Specific guidance includes[250 251]:

- Ensuring the researcher proposes a full question i.e. complete sentences
- Ensuring neutrality of questions i.e. avoidance of leading statements or prompts within the questions
- Ensuring consistency of meaning across questions i.e. definition of all terms using specific terminology, avoidance of terms that could have multiple meanings
- Ensuring brevity and clarity of the question i.e. avoiding asking multiple questions within one stem.

9.4 Limiting errors in surveys

The aim of a survey is to capture data which is useful, meaningful and relevant to the study question[250 251]. With pragmatism in mind, it is recognised that no study design is perfect, and

that trade-offs must be made to complete the project. These constraints can be widely defined, but may include cost, resource and time limitations. The study should therefore be designed to deliver the 'best' results within these limitations. Close attention to areas associated with error in design can mitigate these as far as possible within the study constraints. This fits within a paradigm described as 'total study error' (TSE)[250]. TSE refers to the accumulation of all errors that may arise in the design, collection, processing, and analysis of survey data

The concept of TSE has developed over the 20th Century, and began with the recognition of sampling errors[250]. Work undertaken by the US census bureau demonstrated that it was possible to obtain a more accurate estimate of a population response by using a smaller, randomly selected population than with a larger, non-selected population[258]. Around 10 years prior to this, statisticians had described techniques to estimate variance in a population based upon sample size[259]. The combination of these two pieces of information was used to address sampling error[250]. It is recognised that errors in survey-based research can also arise from 'non-sampling errors'. These include factors related to measurement items and their delivery, as well as factors related to the administration of the survey. These factors are summarised in figure 20.

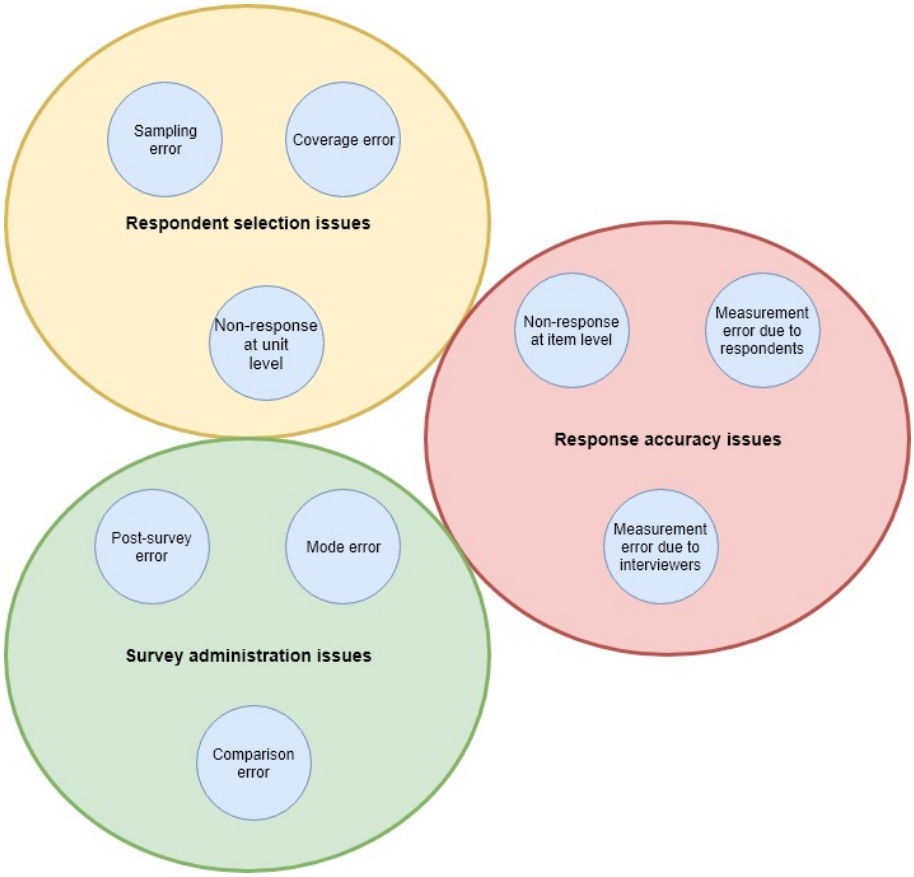

Figure 20 Factors associated with survey error.

9.5 Respondent selection

Errors related to respondent selection can arise in a number of ways. These can be addressed by ensuring adequate sample-size selection based upon the desired statistical power for the study[259]. Additional errors can arise when an inappropriate population is selected for sampling[258]. Responder bias; the phenomenon by which respondents select themselves to respond to surveys based upon good or bad experiences is well recognised, and this can contribute to non-response at the unit (person) level[250]. Strategies to optimise sample size and selection, and to improve recruitment rates should be considered during study development.

9.6 Response accuracy

Response accuracy can be affected by several factors. One of the most important of these is measurement error related to interviewer or survey tools. This typically relates to poor wording of questions (leading to impaired reliability)[256]. Non-response to items can limit interpretation of findings and may arise due to poor wording of questions or fatigue from overly long instruments[250]. Non-response may also arise when a respondent is uncomfortable disclosing potentially sensitive information with a human interviewer[250]. Measurement errors relating to the interviewer arise from incorrect capture or recording of data. These considerations are intimately related to the reliability of instruments and should be considered during the development and pilot phase to limit effect.

9.7 Survey administration

The management and analysis of data captured by survey is also subject to error. Post-survey error typically arises from issues related to data management, for example where a participant has not followed instructions and has provided too many or too few responses to an item. This can lead to the coder making subjective decisions about the final coding of a response[250]. The mode of response may also have a role, with differing effects of face to face survey compared to paper or online responses and those which are anonymous[260]. Comparison error refers to the inaccuracy of estimates of effect difference when comparing survey results across nations, cultures, or a significant period of time[250]. Consideration of these effects during protocol development can allow identification of strategies to reduce their effects.

9.8 Summary

This chapter has outlined the principles of survey design and considerations to reduce error in the conduct of survey-based research. This will be revisited in the subsequent chapters reporting questionnaire research of clinician and patient preferences in treatment of Crohn's anal fistula.

10 Survey of Gastroenterologists

This article has been accepted for publication in Lee MJ, Brown SR, Fearnhead NS, Hart A, Lobo AJ How are we managing fistulating perianal Crohn's disease? Results of a national survey of consultant gastroenterologists Frontline Gastroenterology Published Online First: 23 September 2017. doi: 10.1136/flgastro-2017-100866 following peer-review. The definitive copyedited, typeset version is available at https://fg.bmj.com/content/9/1/16

My role in this study included design of the questionnaire, piloting and initial analysis. Amendments to questionnaire, data-collection and analysis, preparation of manuscript.

All co-authors provided input on design, analysis and interpretation of data, and preparation of the manuscript. Ailsa Hart and Alan Lobo provided oversight of the study.

Permission to reproduce from co authors and the publisher have been obtained.

10.1 Background

10.1.1 Variation in medical practice

Variation in medical practice has been described across a number of specialties[261]. This relates to aspects of practice including diagnosis, initial treatment and modification of treatment strategies. Variation in care is associated with increased costs[262], and variation in outcomes, some of which will be undesirable[263 264]. As a complex condition, it is likely that there is variation in the management of Crohn's disease both in generalist practice[265], and specialist practice[266 267].

10.1.2 Current evidence and guidance

There are a number of guidelines for this condition from UK and international bodies[111 175 268]. In broad terms, these advocate treatment of sepsis by a colorectal surgeon, with or without an MRI scan to determine anatomy. This should be followed by medical therapy with biologic agents, with or without antibiotics or immunosuppression such as thiopurines. These guidelines lack explicit detail on the indications for duration of, and timing between, interventions. There is also little information on the management of refractory fistulae. Before developing clinical pathways and tools to improve the care of these patients, it is important to define variation in practice and areas of uncertainty. Chapter 7 provides the background evidence for the medical treatment of Crohn's anal fistula, but it is necessary to assess whether this evidence is reflected in real world practice.

10.2 Aim

The aim of this study was to explore variations in clinical practice of UK consultant gastroenterologists in the management of Crohn's anal fistula.

10.3 Method

10.3.1 Questionnaire design

10.3.1.1 Item generation

The aim of the item generation phase was to develop a list of areas where variation in practice might occur. The items were generated using three sources: 1) systematic review, 2) panel of clinicians, 3) expert patient input. A summary of included domains is presented in table 11.

10.3.1.2 Systematic review

The systematic review of medical therapies (chapter 7) identifies candidate agents for first line and maintenance therapy of Crohn's anal fistula. This supports the inclusion of first and second line therapies as a theme. The systematic review of surgical interventions (chapter 8) identifies a wide range of techniques. As stoma and proctectomy are considered late stage treatments, the theme 'consideration of stoma' was added.

The assessment of the clinical pathways presented in chapter 11 supports the inclusion of diagnostic tools and selection of first line medical therapy as areas for exploration. Indication for referral to a surgeon was also considered a relevant theme.

10.3.1.3 Clinician panel

An expert clinician panel, including two gastroenterologists and two colorectal surgeons, all with IBD focused practice, reviewed the themes identified from the systematic review. The

panel added time to reassessment of therapy and choice of agents in further treatment as themes.

10.3.1.4 Expert patient input

Patient input on the questionnaire design was solicited from members of the standing 'patient engagement' panel for the ENiGMA collaboration. This is panel involves patients who have been treated for Crohn's anal fistula. A representative from this group was asked to provide an opinion on areas where variation was suspected from the patient perspective.

Domain	Theme	Source
Acute management	Use of antibiotics	Systematic review
Planned assessment of patient with fistula	Use of diagnostic tools	Pathway assessment,
Management after sepsis clearance	Use of further investigations Role of MRI	Pathway assessment, systematic review
Medical therapy	Time to reassessment, choice of subsequent medical agent, choice of agent(s)	Systematic review, expert panel, pathway assessment,
Involvement of surgeons	When surgical opinion is sought	Expert panel, systematic review

Table 11 Domains and themes identified for inclusion in the questionnaire.

The expert clinical panel collated these themes and proposed a set of fields to include in the study:

Initial management and assessment

- Use of antibiotics

Management after sepsis clearance

- Route of access to treatment
- Initial assessment options
- Preferred imaging modality
- Minimum investigations required for patient with known Crohn's disease
- Minimum investigations required for patient with suspected Crohn's disease

First line medical therapy

- Access to IBD MDT
- Use of medical therapy for treatment of Crohn's anal fistula
- Preferred first line therapy medical therapy
- Timing of reassessment
- Second line therapy
- Dose optimisation strategies
- Indications for referral to surgeons

Definitive therapy

- Second and third line medical therapies
- Reasons for seeking a stoma
- Reasons for seeking proctectomy

It is recommended that questionnaires begin their design with questions that neither address sensitive areas nor challenge the respondent [256]. Given this, each section began with questions that were felt likely to fall into common or uncontroversial areas of practice (e.g. use of antibiotics in acute perianal sepsis). The section then moved into more in depth questions on specific aspects of management.

There were no validated questionnaires available to assess the topics of interest. The questionnaire was therefore developed using bespoke items, with validity of questions assessed during the pilot phase. The items generated included closed questions with binary answers or selections from lists, Likert scales, and free-text boxes.

Closed questions were used where a binary answer (yes/no) was appropriate. These were used to establish fact (e.g. whether the respondent had access to an IBD MDT). It was anticipated that respondents might have varying opinions or practice. Where this was the case, a list of potential responses was offered (e.g. choice of first line drug), with an 'other' option available. The list of options was generated based upon the literature reviews, pathway assessment and the clinical expert panel input. Some questions asked for clinicians to indicate the relative frequency of an event in an ordinal manner. A Likert scale was used to capture this data. A Likert scale typically offers an odd number of items, allowing respondents to select a non-committal response (a central tendency), meaning they appear to conform with the population in areas of potential controversy. As this study was designed to identify variation, it was decided to remove the middle option in order to force respondents to commit to an answer in either direction; a 'forced' Likert[269]. The minimum number of items required for a valid Likert scale is four[270].

The questionnaire was intended for paper completion and electronic return by local collaborators. The cover of the questionnaire included the title, an explanation of the aims of the questionnaire, a statement that responses were anonymous and contact details of the research team in case of query.

10.3.1.5 Questionnaire pre-pilot

The questionnaire was subjected to iterative review by the expert clinical group. The group ensured revision of questions to be neutral in form, and that all pertinent response items (treatment options) were presented.

10.3.1.6 Considerations within Total Survey Error framework

A summary of design considerations within the total study error framework are presented in Table 12.

Domain	Subdomain	How addressed in this study
Respondent selection	Sample size	Appropriate sample size calculated with reference to workforce data. Trade-off in power for attainable sample size made.
	Sample coverage	No access to trainee networks across all regions, therefore recruitment achieved through national meetings. Convenience sampling strategy used.
	Non-response at unit level	Questionnaires were delivered through personal approach and responses were anonymous. Both intended to improve response rates.
Response accuracy	Non-response at item level	Clear rubric developed through pilot phase and anonymity in response to encourage responses which may not match practice norms. Limited length of questionnaire to avoid fatigue.
	Measurement error due to respondents	Anonymity in response to encourage responses which may not match practice norms. Limited length of questionnaire to avoid fatigue.
	Measurement error due to interviewers	N/A
Survey administration	Post-survey error	Administrative plans for handling data made. Included recording of first response only if multiple responses given to single response question.
	Mode error	Anonymous paper-based survey selected as considered more likely to be completed than web survey.
	Comparison error	No comparisons planned.

Table 12 Study considerations with reference to Total Study Error framework.

10.3.2 Eligibility criteria

Eligibility criteria for participation in the study was set as consultant gastroenterologist with a UK practice.

10.3.3 Questionnaire validation

The questionnaire underwent a pilot at the British Society of Gastroenterology Inflammatory Bowel Disease Clinical Research Group meeting in November 2015. This meeting was attended by consultant gastroenterologists. Meeting participants were invited to opt in to the pilot and provide anonymous feedback on the questionnaire. The questionnaire was accompanied by additional rubric inviting participants to offer feedback on questionnaire design.

Face validity was assessed by participants through completion of questionnaire with annotation of forms, or opportunity to provide verbal feedback to the investigator present at the meeting. Participants were asked specifically to comment on the wording of questions and applicability to real world experience. Participants were also asked to comment on any questions which were not relevant to the scenarios under discussion, providing a form of content validity. Written and verbal feedback was collated and presented to the clinical expert panel. Criterion validity was not assessed as there were no related validated questionnaires. Construct validity was not assessed as the questionnaire did not assess abstract concepts (table 13).

Type of validity	How assessed in this study	Reason
Face validity	Verbal feedback from steering group and mix of written/verbal feedback from pilot group.	
Content validity	Informally assessed by steering group which included experts in the field.	
Construct validity	Not assessed.	No relevant validated questionnaires identified.
Criterion validity	Not assessed.	No abstract concepts assessed.

Table 13 Assessment of validity of questionnaire

9.3.3 Questionnaire reliability

Test- retest reliability was considered as an option for this study. In a survey such as this where clinical practice is being assessed, a respondent might wish to avoid being seen as an outlier in their clinical practice. It is possible that respondents may review guidelines in the period between repeat testing. This could significantly change responses in a survey of practice, and therefore this form of reliability was not considered appropriate. A summary of reliability assessment is presented in table 14.

Type of reliability	How assessed in this study	Reason
Test-retest (stability)	Not assessed	Concerns over changing responses as respondents may review guidelines or refine answers to avoid appearing as outliers.
Alternate form (equivalence)	Not assessed	Rewording of questions and scales would require generation of a significant question bank, outwith resource of the study.
Internal consistency	Intra-class correlation of Likert scales in pilot study.	-

Table 14 Assessment of reliability of questionnaire

10.3.4 Data capture

The survey was opened to recruitment at specialist postgraduate gastroenterology meetings (British Society of Gastroenterology annual conference and Sheffield Gastroenterology Symposium). As there is no corresponding medical trainee research network to facilitate delivery, participants were invited to participate by collaborators at these meetings.

10.3.5 Pilot responses & Face Validity

Overall, feedback showed questions had face validity. Respondents did not raise concerns over any of the aspects of care addressed by the questionnaire, supporting validity of content. Respondents suggested additional questions or additional response options. These were:

- The question addressing typical route of access to healthcare in acute perianal sepsis was removed as all options were frequently selected and this did not offer any discriminatory value.
- Addition of question on investigations for a patient with known Crohn's disease of a patient with a new fistula were converted from frequency, to 'select all that apply'.
- Conversion of 'selected cases' option to 'frequently' and 'occasionally' in questions on use of immunosuppressant drugs.
- Questions on the selection of first line drugs were reformatted to allow respondents to select single or multiple agents as required.
- Two questions were added to identify whether or not the presence of proctitis or complex fistula anatomy altered choice of treatment.
- The question on timing of immunosuppression/modulation after sepsis clearance was reworded to remove the implication that anti-TNF agents were expected to be used.
- Responses on evidence of sepsis resolution were converted to 'select all that apply'.
- An additional item related to drug dose optimisation was added.
- A free-text item was added to describe second and third line therapeutic strategies.

Internal consistency of Likert scales was assessed using intra-class correlation.

The final questionnaire is presented in Appendix H.

10.3.6 Sample size calculation

The Royal College of Physicians census in 2014 reported approximately 1,100 practicing consultant gastroenterologists[271]. This means that 89 responses were required to achieve a 10% margin of error with a 95% confidence interval. With an estimated response rate of 60%[272], this required 148 questionnaires to be distributed.

10.3.7 Analysis

Numerical data from the questionnaire was collated and presented in a descriptive manner only. Free text data on indications for stoma and proctectomy were collated and representative statements reported. Intra class correlation for internal consistency was calculated using a two-way random effect model in SPSS (IBM, Armonk NY).

10.3.8 Ethical approval

The questionnaire was approved by the University of Sheffield Research Ethics Committee (UREC:7595)(Appendix I). Participation was done so on an 'opt in' basis, with completion of the questionnaire taken as consent to participate.

10.4 Results

10.4.1 Pilot

A total of 19 responses were captured during the pilot study. Intraclass correlation was 0.804 (95% CI 0.562-0.942) showing a high degree of internal consistency of scales.

10.4.2 Full study

A total of 202 questionnaires were distributed and 111 responses were obtained through the various conferences. The overall response rate was 55%. Response rates to questionnaire items ranged from 79.2-100.0%. This was an anonymous survey with no demographic data captured.

10.4.3 Initial Management and Assessment

At initial presentation of a symptomatic fistula, 91 of 111 (81.9%) of respondents would undertake imaging as their first action. If imaging was required, 108 of 111 (97.2%) of respondents would obtain MRI pelvis and 1/111 (0.9%) endoanal ultrasound. Eighteen of 111 (16.5%) would refer directly to a surgeon. If referral for urgent sepsis management was required; 102 of 111 (93.5%) of respondents would refer to a named surgeon, with the remaining 7 (6.5%) referring patients to the emergency surgery team.

Respondents indicated that they would ‘Always’ (60/107 (56.0%)) or ‘Frequently’ (45/107 (42.0%)) use antibiotics in the acutely symptomatic fistula. Only 2/107 (1.8%) indicated they would never use antibiotics in this setting. The antibiotic of choice was metronidazole for 91/107 respondents (85.0%), ciprofloxacin for 67 (62.6%), and co-amoxiclav for 27 (24.2%).

Respondents were asked to indicate the minimum set of investigations for a patient with an existing diagnosis of Crohn's disease who presents with a new perianal fistula. MRI pelvis would be required by 92/111 (82.9%) of respondents, flexible sigmoidoscopy by 48 (43.2%), faecal calprotectin by 35 (31.5%), and colonoscopy by 33 (29.7%). Rigid sigmoidoscopy would be requested by 1 (0.9%), barium enema by 1 (0.9%) and examination under anaesthetic by 9 (8.1%).

A further scenario was described of a patient with a perianal fistula and clinical suspicion of underlying Crohn's disease. Colonoscopy was the preferred investigation in this setting, with 88/107 respondents indicating they would always request this (figure 21).

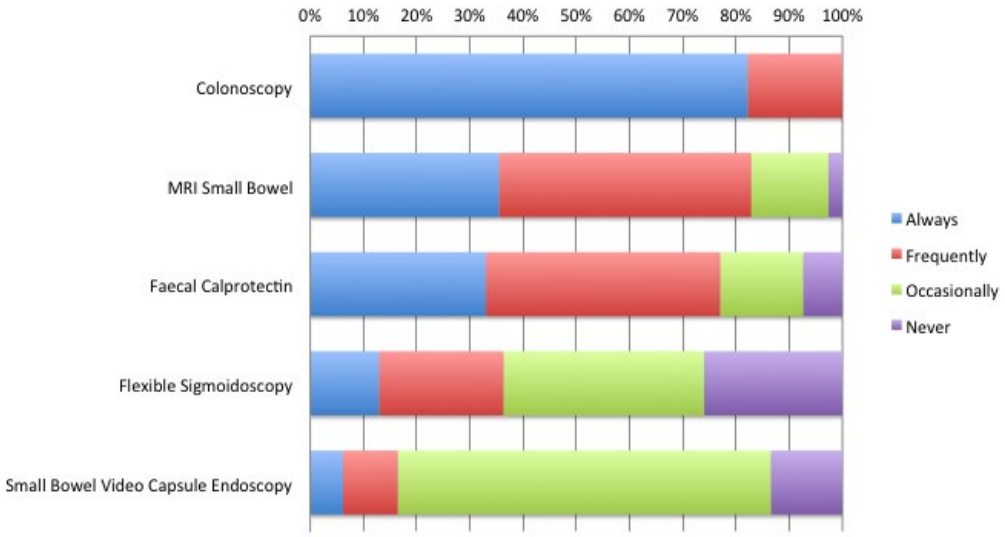

Figure 21 Use of investigations by gastroenterologists in patients with fistula who are suspected to have Crohn's disease.

10.4.4 Management following clearance of sepsis

Respondents were asked to describe the interval they would normally leave between the clearance of perianal sepsis and the commencement of medical therapy (excluding antibiotics). This interval was two weeks for 41/103 respondents (39.8%), four weeks for 39 (37.8%) respondents, 6 weeks for 18 (17.4%) respondents, and eight weeks for 4 (3.8%) respondents. One response (0.9%) indicated an interval of more than nine weeks before commencing medical therapy (figure 22)

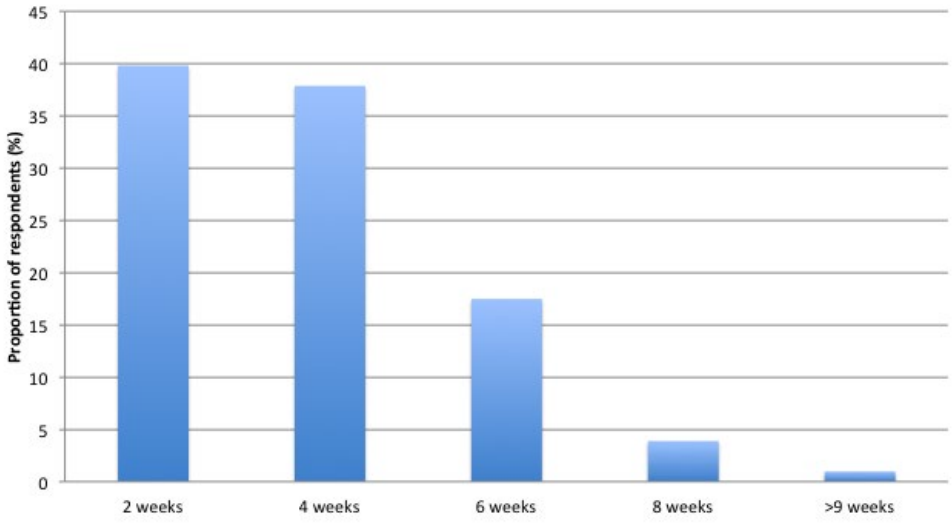

Figure 22 Timing between clearance of sepsis and commencement of medical therapy.

When asked if respondents required evidence of sepsis clearance prior to medical therapy, 25/106 (23.6%) indicated they always required evidence, 54 (51%) frequently asked for evidence and 27 (25.4%) occasionally asked for evidence. The evidence taken into account was surgeons' report from EUA 80/106 (75.5%), patient symptoms by 74 (69.8%), repeat imaging by 76 (71.7%) and overall disease activity by 44 (41.5%).

An IBD multidisciplinary team (MDT) was accessible to 106/108 respondents (98.1%). Of these, 25 (23.6%) of respondents indicated they always discuss patients with Crohn's anal fistula in this setting. This was done 'frequently' by 54 (51.0%) of respondents and

'occasionally' by 27 (25.4%). No respondents with access to an MDT reported a practice of not discussing these patients in the MDT.

10.4.5 First line medical therapy

Initial medical therapy was reported by 93 respondents. Of these, fifty-four (48.6%) respondents would use thiopurines as first line agent, and 56 (50.4%) anti-TNF-α agents. Twenty-seven (29.0%) and 16 (17.2%) would add antibiotics to thiopurine and anti-TNF therapy respectively. Thirty-one (33.3%) would combine antibiotics, thiopurines and anti-TNF-α therapy, and 9 (9.7%) would use thiopurines and anti-TNF-α therapy alone (figure 23).

Respondents were asked to define their first line anti-TNF-α agent, if appropriate. Of 85 responses, 74 (87.1%) use infliximab as their first-choice agent, with 11 (12.9%) using adalimumab. Free text comments indicated that this reflected clinician preference, but that patient choice was often important to this decision.

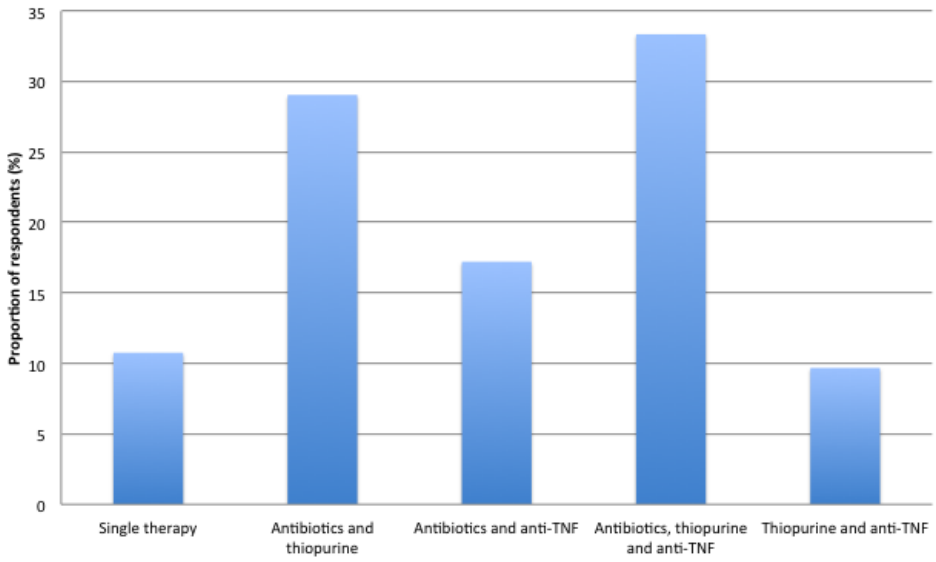

Figure 23 Combinations of first line medical therapy used.

Where antibiotic therapy was considered, 89 respondents offered a preference. Of these, 49 (55.0%) would use ciprofloxacin and 39 (43.8%) would use metronidazole. Co-amoxiclav was the preferred agent of one respondent. The typical period of antibiotic therapy was described as one week by 2/89 respondents (2.2%), two weeks by 37 (41.5%), one month by 35 (39.3%), two months by 10 (11.2%) and more than two months by 5 (5.6%).

When asked if the presence of proctitis altered therapeutic strategy, 70 (68%) indicated that it did alter management and 33 (32%) indicated that it did not. Of the 70 where proctitis altered management, 21 (30%) said it altered surveillance strategies, 21 (30%) said it altered duration of therapy, 56 (80%) would use medications administered per rectum, and 26 (37%) said it would change the choice of medical agent.

10.4.6 Monitoring and escalation

Following initiation of therapy, 26/87 (29.9%) of respondents would assess response to therapy at one month, 52 (59.8%) would assess at three months, 6 (6.9%) at six months, and 3 (3.4%) indicated variation in follow-up based upon severity of disease. Respondents were then asked to define the interval between commencing a drug and escalating therapy. Of the 108 respondents, one (0.9%) would escalate after one month of therapy, 26 (42.6%) would escalate after three months of therapy, 40 (37.0%) would escalate after six months of therapy and one each (0.9%) after twelve and twenty-four months (Figure 24). This decision was based on clinical symptoms (rather than time bound) by 19 respondents (17.6%).

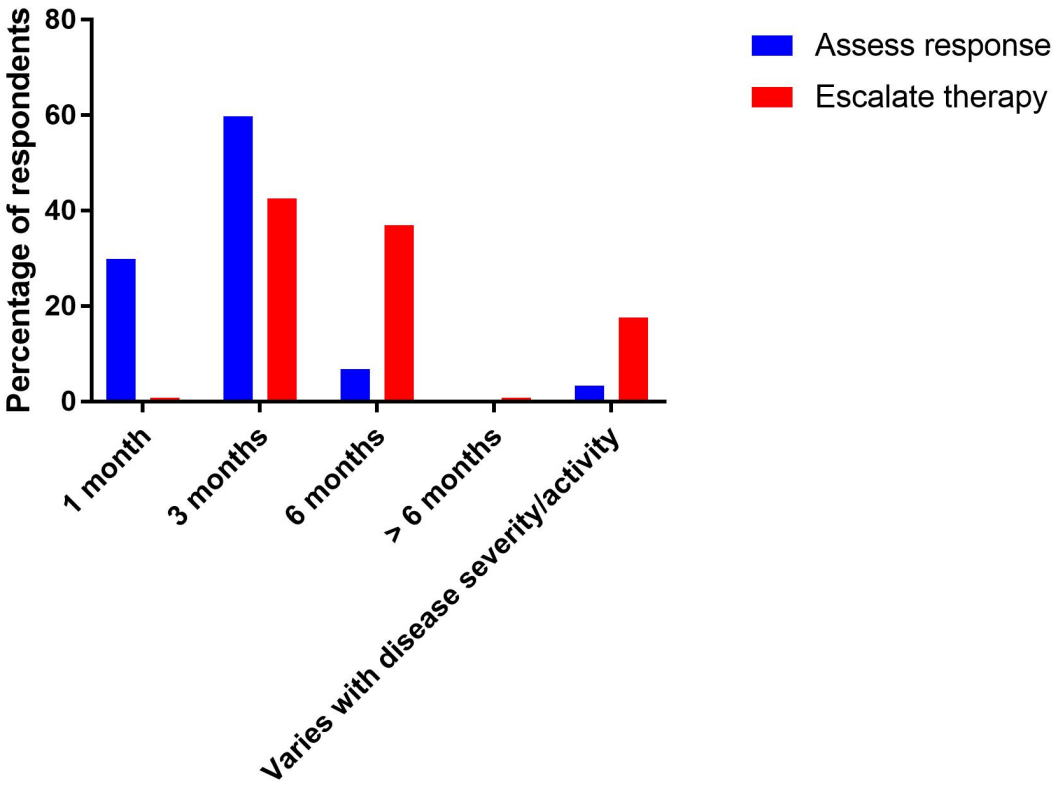

Figure 24 Duration of therapy before reassessment and escalation of treatment.

To monitor response to treatment after commencement of medical therapy, 66/111 (59.4%) of respondents would do so on a clinical basis, and 53 (47.7%) indicated they would usually ask for repeat imaging .

In a patient who was stable or improving on first line therapy, 2/107 (1.9%) would stop medical therapy, 14 (13.1%) would step-down medical therapy, and 91 (85.0%) would continue current therapy (figure 25 a). Thirty respondents offered a choice of step-down medical agent: 1 (3.3%) to aminosalicylates (from azathioprine), 16 (53.3%) to thiopurine agents (from dual therapy with antibiotic/anti-TNF agents), two to methotrexate (6.6%) (from anti-TNF agents), 4 (13.3%) to infliximab (from dual therapy with azathioprine or reduction of dose in two cases), and 7 (23.3%) to adalimumab (monotherapy from dual therapy with azathioprine). In free text comments on second and third line escalation therapies,

Adalimumab was well represented. Vedolizumab was reported as a second or third line option by five respondents. A small number of respondents including surgical therapy as a second or third line intervention in a deteriorating patient.

In the context of a patient with deteriorating fistulating disease, 32/111 respondents (28.8%) would change medical therapy, 56 (50.5%) would undertake further pelvic imaging and 23 (20.7%) would refer to a surgeon for further assessment (figure 25 b). These categories were mutually exclusive.

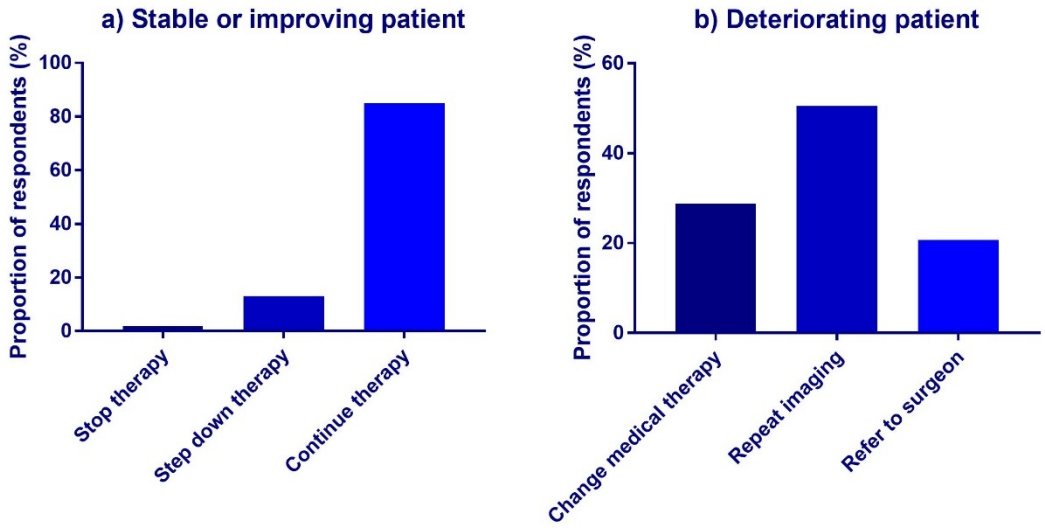

Figure 25 Clinical actions when faced with a) stable or improving fistula b) deteriorating fistula.

Of the 77 respondents who offered a choice of escalation medical therapy, 2 (2.6%) would convert to azathioprine (from aminosalicylates or steroids), 41 (53.2%) to infliximab (from thiopurines) and 25 (32.5%) to adalimumab (from thiopurines or infliximab). Alternate

strategies were proposed by 9 (11.7%) of respondents and were typically escalating doses of anti-TNF-α therapy.

When asked about strategies to optimise drug dosages, 78/111 (70.2%) indicated that they checked thiopurine blood levels, 78 (70.2%) checked blood anti-TNF-α drug levels, and 61 (54.9%) screened for anti-TNF antibodies.

10.4.7 Involvement of surgeons

Respondents were asked to indicate reasons for surgical referral. Long duration on immunosuppressant agents was the indication for 17/111 (15.3%), loss of response to drugs in 82/111 (73.9%), and impact of fistula on quality of life in 59/111 (53.2%).

Free-text responses were sought on reasons for consideration of stoma. These were typically intractable sepsis, fistula refractory to medical therapy, negative impact of disease on quality of life and patient choice. One respondent indicated they would refer only if advised by the MDT. A second question asked about reasons for referral for proctectomy. The answers to this question were virtually identical to consideration of stoma, except for the addition of proctitis as an indication.

10.4.8 Synthesis of pathway

A summary of the preferred process related to flow through a patient pathway is presented in figure 26.

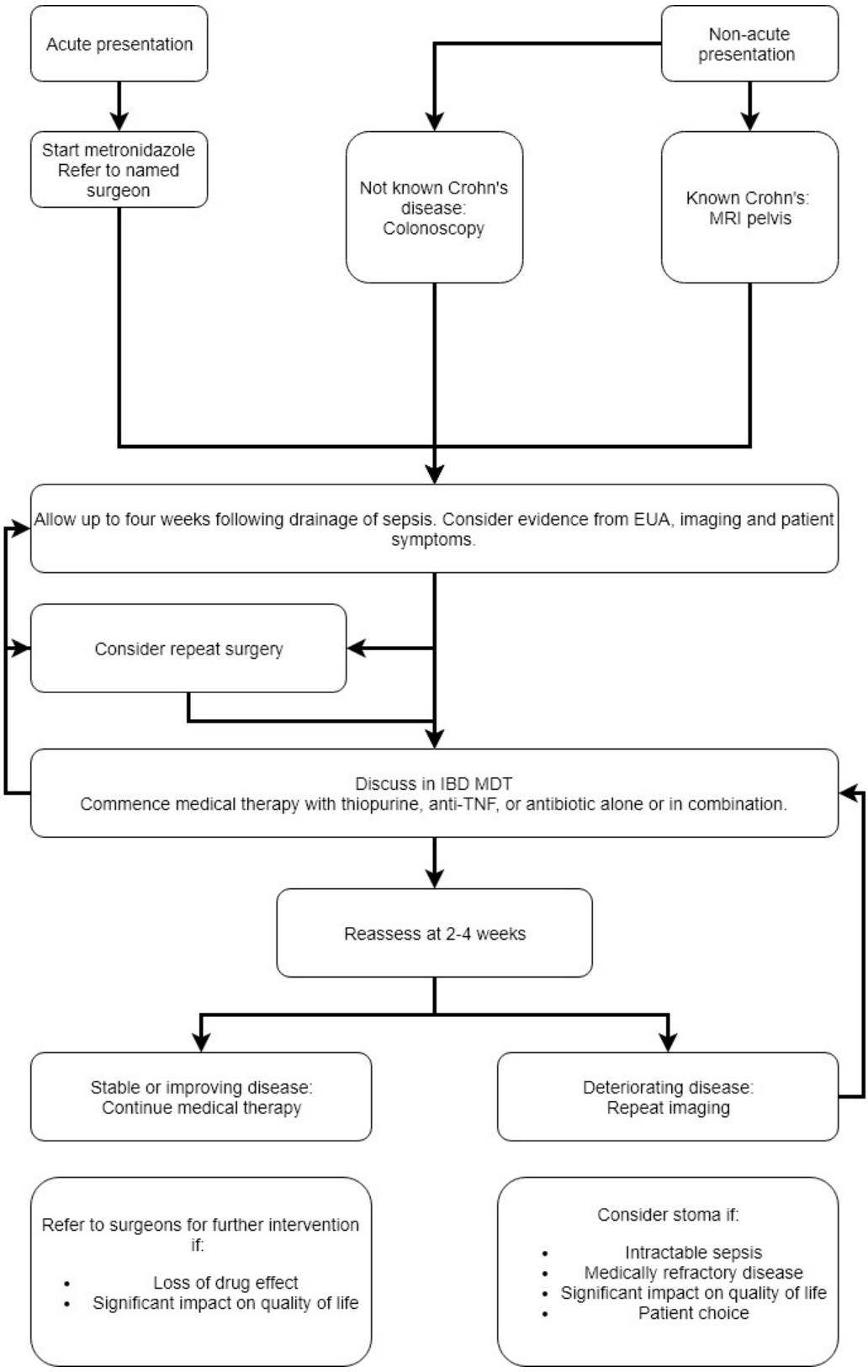

Figure 26 Flowchart with preferences for medical management of Crohn's anal fistula

10.5 Discussion

10.5.1 Summary

This exploratory survey of UK consultant gastroenterologists suggests considerable variation in management strategies for fistulating perianal Crohn's disease. There is notable variation in the choice of first line medical therapies and reassessment strategies. Perhaps reassuringly, there was wide access to an IBD MDT, and consensus on indications for surgical intervention.

10.5.2 Findings in context

Current guidance from the European Crohn's and Colitis Organisation (ECCO) advocates early sepsis control and assessment of anatomy, treatment with metronidazole, anti-TNF with or without thiopurine, with clinical assessment at least every three months. Reassessment of fistula and consideration of stoma is advised in persistent symptomatic disease [111]. British Society of Gastroenterology (BSG) guidelines advocate antibiotics and thiopurine agents as early therapy, with anti-TNF agents used in severe fistulating disease[268]. Results from this survey do not show strict adherence to either one of these approaches, with a clear split between thiopurine first and anti-TNF first. This survey also shows wide variation in how and when clinicians escalate therapy; this indirectly suggests that the more complex or difficult to manage the fistulating disease is, the less certainty there is on subsequent management steps.

The variation identified may reflect a number of issues; limited evidence base upon which to formulate guidance, or limited awareness of guidelines. For example, the use of aminosalicylates and corticosteroids reported here is not supported by current evidence [176] [273]. This variation might also be attributed to clinician factors, such as disagreement with the guidelines, systemic factors, or consideration of guidelines as a suggestion rather than requiring strict adherence [274] [275]. It is also important not to underestimate the clinician's

experience of the local population and their preferences. Patients may disagree with treatment strategies in other settings, and omit drugs to avoid side-effects[276].

The survey also highlights variation around the timings in the management pathway, including intervals between commencing therapy, reassessment, and escalation. There was disparity in the suggested interval from drainage of sepsis to commencement of medical therapy, with many clinicians expecting an interval of a month or more. It is not entirely clear whether this reflects clinician preference or factors related to healthcare system pressures. In addition, responses did not reflect a need for a more aggressive medical approach in those with proctitis [176], with about a third of respondents indicating that it did not alter their management. The described indications for stoma and proctectomy agree with published consensus [176].

It has not been possible to identify corresponding work from other countries. A recent cohort demonstrated that 60% of patients with perianal fistula were treated using anti-TNF-α therapy. The same study noted wide variation in the use of antibiotics[277]. A retrospective cohort also found variation in the use of medical therapies aside from biologics[73]. Notably, both of these studies were performed in centres with a developed IBD service. The study reported here did not ask respondents to state whether they worked within a specialist IBD centre, or provided services within a more general gastroenterology setting.

10.5.3 Strengths and limitations

There are limitations to survey-based research, specifically responder bias and questionnaire utility. The response rate of 55% compares favourably with other surveys of gastroenterologists [254 278 279]. Despite this, the results provide a reflection of variation in UK medical management of this condition. Free-text responses confirmed that respondents were not only IBD sub-specialists, with a number of respondents indicating that they did not regard themselves as IBD experts and would seek advice at second or third line therapy (or earlier).

The spread of recruitment across national meetings limits responders to those engaging with professional development or research activities, but avoids issues of geographic clustering through dissemination in a single hospital.

The decision to include clinicians with specialist and non-specialist practice was an active one – the study aimed to record a reflection of 'real world' clinical practice. It is recognised that the development of subspecialisation will vary across differing units, meaning that non-specialists may provide care to patients. Despite this, it was judged that the description of variation in practice and uncertainty will help identify potential improvements that are widely applicable. Whilst our response rate was 55%, this is favourable compared to other recent clinician surveys, with response rates of up to 30%[255 280]. Our corresponding surgical survey achieved a response rate in excess of 70%, although this is unusual and probably related to trainee driven recruitment at centre level[22]. Reasons for non-completion might be related to unfamiliarity with the condition, or perceived length of the questionnaire. Surgeons were not included in this survey as we have previously undertaken a similar assessment of their practice[177]. In that study, 64% of surgeons would ask for anti-TNF therapy as first line treatment, and that indicated that proctitis had an impact on their treatment strategies.

10.5.4 Implications for practice

Medical therapy is just one component of a complex stepwise treatment pathway for patients with Crohn's disease and perianal fistulae, and physicians work together with surgeons, radiologists and specialist nurses to deliver this. Existing studies suggest benefit of this model[112 281]. It is therefore important that the therapeutic strategy and goal are shared by physician, surgeon and patient to help reconcile complex medical and surgical pathways which helps ensure timely investigation and intervention. MDT meetings are clearly central to this but other steps to facilitate the patients flow between medical and surgical services are needed – for example protocols to allow direct referral from IBD specialist nurses to specialist

surgical teams. Joint medical and surgical IBD clinics may help, not only in initial assessment, but also after an emergency admission and examination under anaesthetic to agree and plan anti-TNF therapy.

This survey was intended to provide insight into clinician level management of patients with Crohn's anal fistula as a starting point for work to standardise care. Areas of practice with significant variation are presented in table 15. Areas for further assessment include timing of assessment following initiation of medical therapy, and subsequent escalation of medical therapy. With the need for strong antibiotic stewardship, the type and duration of antibiotic treatment also needs clarifying. It would also be prudent to explore patient experience around the treatment of perianal Crohn's fistula. In the meantime, it is important that UK specialty associations recognise and address variation in management through further research, educational outreach, audit and guidelines.

Domain	Variation	Relevant Research Questions
Initial Management and Assessment	Use of endoscopic examination Impact of proctitis on medical management Use of pelvic imaging	What clinicopathologic features affect initial management of Crohn's anal fistula?
First line medical therapy	Biologic first vs thiopurine first therapy Use of antibiotics	Does combination of anti-TNF, thiopurine and antibiotic offer treatment benefit vs other drug combinations?
Monitoring and escalation	Time to commencement of immunosuppression Time to assessment of clinical response	Can immunosuppression be started safely immediately following drainage of sepsis? What is the appropriate time to wait for assessment of clinical response/escalation of therapy?
Involvement of surgeons	Indications for referral for surgical input	When does surgical treatment offer benefit to patients, including improvement in symptoms or quality of life?

Table 15 Summary of areas of variation in practice and potential research questions

10.6 Conclusion

There is variation in the choice and timing of medical therapies for perianal Crohn's fistula. This may reflect a limited and uncertain evidence base, rejection of guidelines by clinicians, or an absence of national guidelines. Management delays resulting from this variation are likely to contribute to the significant debility experienced by patients with this condition.

11 Survey of Colorectal Surgeon Clinical Practice

Data from this chapter has been published following peer review:

Lee MJ, Heywood N, Sagar PM, Brown SR, Fearnhead NS and pCD collaborators. *Surgical Management of Fistulating Perianal Crohn's Disease - A UK Survey*. Colorectal Dis. 2017;19(3)266-273 doi: 10.1111/codi.13462.

My role in this study included design of questionnaire, pilot and initial analysis. Amendments to questionnaire, data-collection and analysis, preparation of manuscript.

All co-authors provided input on design, analysis and interpretation of data, and preparation of the manuscript. Nicola Fearnhead and Steven Brown provided oversight of the study.

Permission to reproduce from co-authors and the publisher have been obtained.

11.1 Background

11.1.1 Variation in surgical practice

It is recognised that there is a variation in surgical practice, this can occur across nations, small geographical areas, or even within the same hospital unit[282]. The reasons for this are related to the fundamental complexity of clinical decision-making, demands and expectations of patients and physicians, and the supporting evidence base. Variation in surgical practice does not necessarily equate to the volume of procedures being offered, but may also affect the type and timing of procedure.

11.1.2 A framework for understanding variation in surgical practice.

Variation in surgical practice is a subject of interest, and the topic of several publications[283]. In order to understand variation in surgical practice, Wennberg *et al* have proposed a theoretical framework[284]. This framework categorises procedures into three groups:

- **Effective care** – those procedures that are effective with no significant trade-offs, and no conflict between physician and patient on the value of the procedure.
- **Preference-sensitive care** – those procedures which require trade-offs around a patient's needs and values e.g. breast reconstruction after breast cancer surgery.
- **Supply-sensitive care** – procedures provided in the absence of data or theory guiding frequency or timing of use, where those hospitals with a plentiful resource will offer the procedure more frequently than those with limited resource e.g use of endoscopy to monitor inflammatory bowel disease.

Wennberg also proposes four main factors that affect the use of each of these modes of healthcare. These are medical theory, medical evidence, per capita supply of resources, and patient preferences[284]. Medical theory and evidence play a strong role in effective care. Medical theory and patient preferences tend to be most important in preference sensitive

care, and per capita supply of resources is the most important in supply sensitive care. Correspondingly, there is good quality evidence that the use of clinical guidelines and patient decision aids reduces variation in volume of surgical procedures[283].

11.1.3 Describing variation in the management of Crohn's anal fistula

As discussed in chapter 8, the evidence for specific surgical procedures is limited. Surgical management of this condition is also likely to be 'preference sensitive'. Coupled with the sparse guidance offered in clinical guidelines, it is not clear how surgeons are currently managing patients with Crohn's anal fistula. The first step to address clinical variation is to explore current practice, and explore whether there is variation and in which aspects of care it occurs.

11.2 Aim

To report current colorectal practice in the surgical management Crohn's anal fistula in the United Kingdom (UK).

11.3 Method

11.3.1 Questionnaire design

11.3.1.1 Item generation

The aim of the item generation phase was to develop a list of areas where variation in surgical practice might occur. The items were generated using three sources: 1) systematic review, 2) panel of clinicians, 3) expert patient input.

11.3.1.2 Systematic review

The systematic review of surgical therapies (chapter 8) reports a range of surgical options for definitive treatment of fistula. This supports the inclusion definitive therapies as a theme. This review also reports stoma and proctectomy as late stage treatments, the theme 'consideration of stoma' was added.

The assessment of the clinical pathways presented in chapter 12 supports the inclusion of diagnostic tools and acute surgical management as themes. The systematic review of medical therapies identifies candidate medical therapies, therefore adjunctive medical management was added as a theme.

11.3.1.3 Clinician panel

An expert clinician panel including three colorectal surgeons and two gastroenterologists, all with IBD focused practice, reviewed the themes identified from the systematic review.

11.3.1.4 Expert patient input

Patient input on the questionnaire design was solicited from members of the standing 'patient engagement' panel for the ENiGMA collaboration. This is panel involves patients who have been treated for Crohn's anal fistula. A representative from this group was asked to provide an opinion on areas where variation was suspected from the patient perspective.

Domain	Theme	Source
Initial management/assessment	Use of antibiotics Investigation to identify Crohn's disease or fistula,	Systematic review, expert panel, patient panel
Acute management	Who performs procedure Strategies for acute sepsis control	Systematic review, expert panel, patient panel
Elective management	Procedure at first planned EUA Additional imaging	Pathway assessment, expert panel, patient panel
Multidisciplinary management	Access to MDT Preferred adjunct agents	Expert panel, systematic review
Definitive surgical therapy	Surgical interventions for fistula closure Effect of fistula location on strategy Indications for diversion or proctectomy	Systematic review, expert panel, pathway patient panel

Table 16 Domains and themes identified for inclusion in the questionnaire.

The expert clinical panel collated these themes and proposed a set of fields to include in the study:

Initial management and assessment

- Use of antibiotics at first presentation
- Additional diagnostic tests required

Acute management

- Respondents practice in acute perianal sepsis
- Respondents recommendations to others treating acute perianal sepsis

Elective management

- Choice of interventions at first planned examination under anaesthesia
- Further investigations required
- Additional medical therapy offered

Multidisciplinary management

- Access to IBD MDT
- Preferred drugs to support fistula treatment

Definitive surgical therapy

- Procedures offered as definitive surgical treatment of anal fistula
- Procedures offered as definitive surgical treatment of rectovaginal fistula
- Indications for stoma and proctectomy

It is recommended that questionnaires begin their design with questions that neither address sensitive areas nor challenge the respondent [256]. Given this, each section began with questions that were felt likely to fall into common or uncontroversial areas of practice (e.g. use of antibiotics in acute perianal sepsis). The section then moved into more in depth questions on specific aspects of management.

There were no validated questionnaires available to assess the topics of interest. The questionnaire was therefore developed using bespoke items, with validity of questions assessed during the pilot phase. The items generated included closed questions with binary answers or selections from lists, Likert scales, and free-text boxes.

Closed questions were used where a binary answer (yes/no) was appropriate. These were used to establish fact (e.g. whether the respondent had access to an IBD MDT). It was anticipated that respondents might have varying opinions or practice. Where this was the case, a list of potential responses was offered (e.g. choice of first line drug), with an 'other' option available. The list of options was generated based upon the literature reviews, pathway assessment and the clinical expert panel input. Some questions asked for clinicians to indicate the relative frequency of an event in an ordinal manner. A Likert scale was used to capture this data. As in the previous chapter, a forced Likert scale was used.

The questionnaire was intended for paper completion and electronic return by local collaborators. The cover of the questionnaire included the title, an explanation of the aims of the questionnaire, a statement that responses were anonymous and contact details of the research team in case of query.

11.3.1.5 Questionnaire pre-pilot

The questionnaire was subjected to iterative review by the expert clinical group. The group ensured revision of questions to be neutral in form, and that all pertinent response items (treatment options) were presented.

11.3.1.6 Considerations within Total Survey Error framework

A summary of design considerations within the total study error framework are presented in Table 17.

Domain	Subdomain	How addressed in this study
Respondent selection	Sample size	Appropriate sample size calculated with reference to workforce data. Trade-off in power for attainable sample size made.
	Sample coverage	Trainee networks provide coverage across UK in general surgery[285].
	Non-response at unit level	Questionnaires were delivered through personal approach and responses were anonymous. Both intended to improve response rates.
Response accuracy	Non-response at item level	Clear rubric developed through pilot phase and anonymity in response to encourage responses which may not match practice norms. Limited length of questionnaire to avoid fatigue.
	Measurement error due to respondents	Anonymity in response to encourage responses which may not match practice norms. Limited length of questionnaire to avoid fatigue.
	Measurement error due to interviewers	N/A
Survey administration	Post-survey error	Administrative plans for handling data made. Included recording of first response only if multiple responses given to single response question.
	Mode error	Anonymous paper-based survey selected as considered more likely to be completed than web survey.
	Comparison error	No comparisons planned.

Table 17 Study considerations with reference to Total Study Error framework.

11.3.2 Eligibility criteria

Eligibility criteria for participation in the study was set as consultant colorectal surgeon with a UK practice.

11.3.3 Questionnaire validation

The questionnaire underwent a pilot at the Digestive Diseases Federation meeting in June 2015. This meeting was attended by a range of clinicians providing care for gastrointestinal disease, including surgeons. Meeting participants were invited to opt in to the pilot and provide anonymous feedback on the questionnaire by researchers attending the event. The questionnaire was accompanied by additional rubric inviting participants to offer feedback on questionnaire design.

Face validity was assessed by participants through completion of questionnaire with annotation of forms, or opportunity to provide verbal feedback to the investigator present at the meeting. Participants were asked specifically to comment on the wording of questions and applicability to real world experience. Participants were also asked to comment on any questions which were not relevant to the scenarios under discussion, providing a form of content validity. Written and verbal feedback was collated and presented to the clinical expert panel. Criterion validity was not assessed as there were no related validated questionnaires. Construct validity was not assessed as the questionnaire did not assess abstract concepts. This is summarised in table 18.

Type of validity	How assessed in this study	Reason
Face validity	Verbal feedback from steering group and mix of written/verbal feedback from pilot group.	
Content validity	Informally assessed by steering group which included experts in the field.	
Construct validity	Not assessed.	No relevant validated questionnaires identified.
Criterion validity	Not assessed.	No abstract concepts assessed.

Table 18 Assessment of validity of questionnaire

11.3.3 Questionnaire reliability

Test- retest reliability was considered as an option for this study. In a survey such as this where clinical practice is being assessed, a respondent might wish to avoid being identified as an outlier in their clinical practice. It is possible that respondents may review guidelines in the period between repeat testing. This could significantly change responses in a survey of practice, and therefore this form of reliability was not considered appropriate (table 19).

Type of reliability	How assessed in this study	Reason
Test-retest (stability)	Not assessed	Concerns over changing responses as respondents may review guidelines or refine answers to avoid appearing as outliers.
Alternate form (equivalence)	Not assessed	Rewording of questions and scales would require generation of a significant question bank, outwith resource of the study.
Internal consistency	Intra-class correlation of Likert scales in pilot study.	-

Table 19 Assessment of reliability of questionnaire

11.3.4 Pilot responses & Face Validity

In the pilot phase, 20 questionnaires were distributed and 15 were returned (response rate 75%). Feedback showed questions had face validity. Respondents did not raise concerns over any of the aspects of care addressed by the questionnaire, supporting validity of content. Respondents suggested additional questions or additional response options. These were:

- Endoanal ultrasound was added as a response option for all items discussing imaging.
- Addition of question item on frequency of post-operative imaging
- Additional question on modality of choice
- Addition of item on frequency of repeat EUA in elective setting
- Conversion of binary answer on use of imaging to four-point Likert scale.

The final questionnaire is presented in Appendix J.

11.3.4 Data capture

The full questionnaire was run through the UK surgical trainee research collaboratives, led jointly by the South Yorkshire Surgical Research Group (SYSuRG) and the North-West Research Collaborative (NWRC). There are fifteen general surgery research collaboratives which are organised on a regional basis (e.g. South Yorkshire, West Midlands, Wales, London) and have potential for wide delivery of surveys. Collaborators were asked to deliver the questionnaire to consultant colorectal surgeons in their units. Initial contact was made via the National Research Collaborative email lists and electronic contact made to local collaborative leads and cascaded locally. Collaborators were asked to support delivery of hard-copy questionnaires locally to Consultants and return at least three completed questionnaires to the Research Electronic Data Capture™ (REDCap) system, hosted by the University of Sheffield[286]. Although questionnaires were anonymous at respondent level, the number of centres and participants included was recorded by collaborators.

11.3.5 Sample size calculation

ACPGBI reports 1,000 consultant members. This means that 88 responses were required to achieve a 10% margin of error with a 95% confidence interval. With an estimated response rate of 60%[272], this required 146 questionnaires to be distributed. Sampling was undertaken using a convenience approach, with hospital participation defined by trainees responding to invitation to participate.

11.3.6 Analysis

Numerical data from the questionnaire was collated and presented in a descriptive manner only. Where binary answers were changed to four-point answers for the final study, yes and no options were analysed as ‘always’ and ‘never’ responses respectively. Free text data on

indications for stoma and proctectomy were collated and representative statements reported. Intra class correlation for internal consistency was calculated using a two-way random effect model in SPSS (IBM, Armonk NY).

11.3.7 Ethical approval

The questionnaire was approved by the University of Sheffield Research Ethics Committee (UREC:7386)(Appendix K). Participation was done so on an 'opt in' basis, with completion of the questionnaire taken as consent to participate.

11.4 Results

11.4.1 Pilot of survey & reliability

In the pilot, twenty questionnaires were distributed to eligible participants and fifteen were returned (75% response rate). Inter-rater reliability for Likert-based tools was assessed using intra-class coefficient 'good' correlation across average measures at 0.830 (95% CI 0.701-0.920).

11.4.2 Full survey

In the full review phase, 133 responses were received from 179 distributed questionnaires (74.3% response rate). Of these, 70 respondents practised in district general hospitals and 63 in teaching hospitals. This accounted for 32 different centres across the UK, including centres in Wales and Scotland according to collaborator location. Location is not reported here as responses were anonymous. For final analysis, both phases were pooled, giving a total of 154 responses of 214 (71.9% of all distributed questionnaires).

11.4.3 Acute management of perianal sepsis

This section addressed patients admitted acutely with perianal symptoms. There was variation in the use of perioperative antibiotics in the acute setting, with 39.6% of respondents always using them and 5.8% never using them. Most respondents (42.2%) would start antibiotic therapy pre-operatively on the ward or in clinic, with 40.9% starting therapy at induction of anaesthesia. The antibiotic of choice was metronidazole (77.9%), followed by co-amoxiclav (35.1%) and ciprofloxacin (20.1%). Few respondents would always ask for pre-operative imaging in the acute setting (7.1%), but the majority would seek imaging frequently (37.0%) or occasionally (51.9%). Where imaging was used, magnetic resonance imaging (MRI) of the pelvis was the preferred modality (96.1%), with a small minority using endo-anal ultrasound (2.5%) or CT (1.9%) (table 20).

Where the diagnosis of Crohn's disease was suspected but not yet established, respondents were asked to report which investigations they would use to confirm or refute this. Faecal calprotectin was routinely used by 22.9%, colonoscopy always used by 57.1%, flexible sigmoidoscopy always used by 16.8% and MR small bowel by 9.7%. Conversely, 25% of respondents would never use faecal calprotectin to aid diagnosis, 3.2% would not use colonoscopy, 18% would not use flexible sigmoidoscopy, and 13.6% would not use MR of small bowel. No respondents routinely used video capsule endoscopy (VCE) to confirm diagnosis of Crohn's disease, and 40.2% would never use VCE in this setting (Figure 27).

	Response (%)				
In the acute setting:	**Always**	**Frequently**	**Occasionally**	**Never**	**Missing**
Would you use antibiotics?	61 (39.6%)	45 (29.2%)	43 (27.9%)	2 (1.3%)	3 (1.9%)
	Pre-operatively	**Anaesthetic induction**	**Post-operatively**	**Other**	**Missing**
When would you start them?	65 (42.2%)	63 (40.9%)	10 (6.5%)	7 (4.5%)	9 (5.8%)
List	**Ciprofloxacin**	**Metronidazole**	**Co-amoxiclav**	**Gentamicin**	
What antibiotics would you use?	31 (20.1%)	121 (78.5%)	54 (35.1%)	22 (14.2%)	-
	Always	**Frequently**	**Occasionally**	**Never**	**Missing**
Would you obtain pre-operative imaging?	11 (7.1%)	57 (37.0%)	80 (51.9%)	5 (3.2%)	1 (0.6%)

Table 20 Summary of antibiotic & imaging use at initial presentation

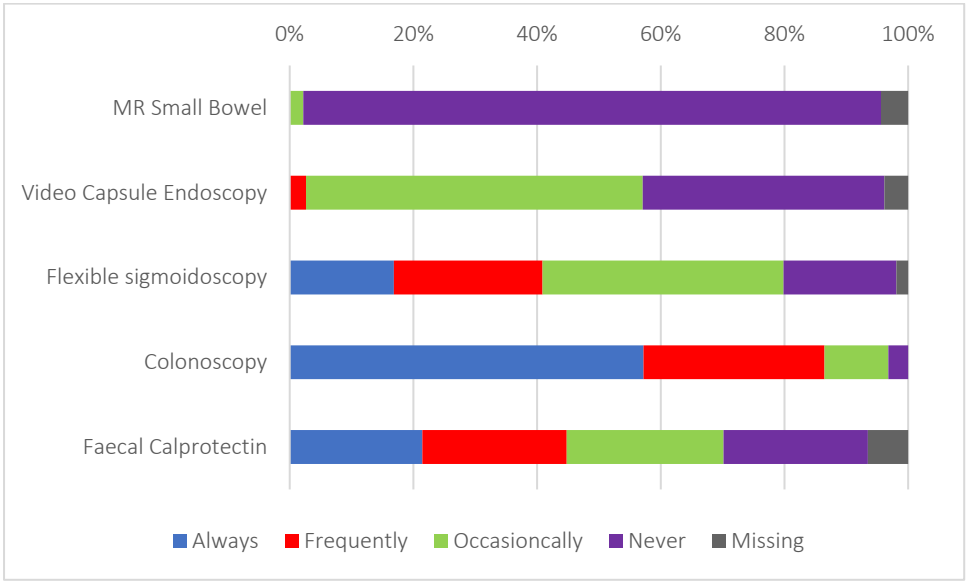

Figure 27 Investigations used where a new diagnosis of Crohn's anal fistula is suspected

11.4.4 Crohn's fistula in acute setting

Respondents were asked to identify which procedures they would routinely consider in an operation for an acutely symptomatic/emergency presentation of Crohn's anal fistula; 32% would drain sepsis, 31.1% would consider placement of a draining seton if appropriate, and 0.6% would consider excision of fistula track. The majority of respondents (89.6%) indicated that they would never consider a cutting seton in this setting (Table 21).

Respondents reported on what advice they would give to a less experienced surgeon (a general surgical colleague or registrar) undertaking surgery in this setting. Responses tended to recommend a more conservative approach with 43.5% advocating drainage of sepsis 19.5% advocating placement of a draining seton, and 94.8% advising against a cutting seton. Free text comments from two respondents indicated a feeling that only an experienced colorectal surgeon should be undertaking these procedures.

	Response (%)				
If you were doing the case, would you consider:	**Always**	**Frequently**	**Occasionally**	**Never**	**Missing**
Incision and drainage of abscess	50 (32.4%)	48 (31.1%)	44 (28.6%)	8 (5.1%)	4 (2.5%)
Insertion of draining seton	48 (31.1%)	61 (43.5%)	35 (22.7%)	1 (0.6%)	10 (6.4%)
Insertion of cutting seton	0	0	13 (8.4%)	138 (89.6%)	4 (2.5%)
Excision of track	1 (0.6%)	0	45 (29.2%)	104 (67.5%)	4 (2.5%)
If you were advising a colleague or registrar, would you advise:	**Always**	**Frequently**	**Occasionally**	**Never**	**Missing**
Incision and drainage of abscess	67 (43.5%)	46 (29.8%)	31 (20.1%)	7 (4.5%)	3 (1.9%)
Insertion of draining seton	30 (19.4%)	50 (32.4%)	60 (38.9%)	11 (7.1%)	3 (1.9%)
Insertion of cutting seton	0	0	4 (2.5%)	146 (94.8%)	4 (2.5%)
Excision of track	0	0	23 (14.9%)	125 (81.1%)	6 (3.8%)

Table 21 Practice around surgery in the acute/urgent setting.

11.4.5 Subsequent elective surgery

The survey elicited procedure preferences for the first subsequent elective examination under anaesthetic (EUA). As in the acute setting, draining seton was routinely considered (66.6%) and cutting seton was avoided (84.4%). Where preferences were indicated, Ethibond ® (Ethicon) was the preferred seton material for 41.5%, silastic slings for 24.6% and comfort drains ® (Agency for Medical Innovation) in 3.2%. Other procedures such as excision of track, fistulotomy and faecal diversion were not considered options in this context by 62.9%, 35.7% and 33.1% of surgeons respectively.

If a fistula was found at EUA, 30.6% would routinely undertake post-operative MRI. If a fistula was not identified, but suspected, 63.9% would routinely undertake post-operative MRI. Routine repeat EUA would be performed by 16.5% of respondents, although 75.9% of respondents indicated that they would frequently or occasionally undertake repeated EUA, suggesting a 'selected case' approach. Post-operative antibiotics were routinely used by 11.2% of respondents, and in selected cases (frequently/occasionally) by 75.0% (Table 22).

	Response (%)				
At first planned EUA, would you consider	**Always**	**Frequently**	**Occasionally**	**Never**	**Missing**
Insertion of draining seton	48 (31.1%)	61 (43.5%)	35 (22.7%)	1 (0.6%)	10 (6.4%)
Insertion of cutting seton	0	0	13 (8.4%)	138 (89.6%)	4 (2.5%)
Excision of track	1 (0.6%)	0	45 (29.2%)	104 (67.5%)	4 (2.5%)
Fistulotomy	0	5 (3.2%)	88 (57.1%)	55 (35.7%)	6 (3.8%)
Faecal diversion	0	0	54 (35.0%)	53 (34.4%)	47 (30.5%)
After first elective procedure, would you routinely plan for:	**Always**	**Frequently**	**Occasionally**	**Never**	**Missing**
Post-operative antibiotics†	15 (11.2%)	21 (15.7%)	79 (59.3%)	13 (9.7%)	5 (3.7%)
Post-operative imaging if fistula found†	48 (36.0%)	48 (36.0%)	32 (24.0%)	1 (0.7%)	4 (3.0%)
Post-operative imaging if no-fistula found†	85 (63.9%)	33 (24.8%)	9 (6.7%)	2 (1.5%)	4 (3.0%)
Repeat EUA †	22 (16.5%)	47 (35.3%)	54 (40.6%)	6 (4.5%)	4 (3.0%)

Table 22 Summary of management around first planned examination under anaesthetic.

†Percentage based on 133 respondents from full survey as no equivalent response options used in pilot.

11.4.6 Medical and multi-modal management of Crohn's anal fistula.

An inflammatory bowel disease multi-disciplinary team was available to 87.6% of respondents. Of these, 25.1% routinely discussed all cases of Crohn's anal fistula in this setting and only 0.7% of respondents never discussed patients. A multi-modal approach utilising joint medical and surgical therapy was routinely used by 28.6% of respondents, with just 1.9% not using a combined approach (table 23).

Gastroenterology follow-up was arranged for all patients by 71.4% of respondents. Immunosuppressant therapy was routinely used in treatment of this condition by 32.8% of respondents, with 58.8% indicating a selected-case approach. Eight responses were excluded from this analysis as their response from the pilot survey could not be mapped to the final questionnaire.

Surgeons were asked to identify which drug(s) they would prefer a patient to receive as part of multi-modal care. Anti-TNF-α therapy was most frequently preferred (64.2%), followed by azathioprine (33.7%). Despite expressing preferences, the final decision on medical management was left with a gastroenterologist by 42.2% of surgeons (table 23).

The decision on seton removal was made by surgeons in 64.2% of cases, the multidisciplinary team in 33.7% of cases and by gastroenterologists in 5.8% of cases. The patient made the decision for seton removal in 4.5% of responses. A free-text option was available to report timing of seton removal. Responses indicated that this was highly variable and tailored to the patient. In some cases, timings were related to surgery e.g. 3 months post-op, and in others related to biologic therapy e.g. after third dose. Respondents also indicated that it might be left in-situ indefinitely.

	Yes		No		Missing
Do you have access to an IBD MDT?	135 (87.6%)		14 (9.1%)		5 (3.2%)
	Always	**Frequently**	**Occasionally**	**Never**	**Missing**
Do you routinely discuss CAF patients in an IBD MDT?†	39 (25.1%)	58 (41.7%)	45 (32.3%)	1 (0.7%)	0
Do you arrange follow up for patients with gastroenterology?	110 (71.4%)	31 (22.3%)	9 (6.4%)	0	4 (2.6%)
Do you use multimodal approach?	44 (28.5%)	70 (45.5%)	19 (12.3%)	3 (1.9%)	18 (11.6%)
Do you use immunosuppressant drugs?††	48 (32.8%)	58 (39.7%)	28 (19.1%)	8 (5.4%)	4 (2.7%)
What drugs would you ask for to complement surgical therapy?				*n*	*%*
			Glucocorticoid steroids	34	22.0
			Aminosalicylates	24	15.5
			Azathioprine	52	33.7
			6-Mercaptopurine	16	10.3
			Methotrexate	23	14.9
			Anti-TNF-α therapy	99	64.2
			Gastroenterology decide	65	42.2

Table 23 Summary responses and multimodal management approaches used.

**Selected cases group was split into Frequently and Occasionally after pilot. †Percentage based on 143 respondents who replied 'Yes' to IBD MDT or missing responses (i.e. excludes those with no MDT). †† 8 patients excluded as option 'selected cases' removed in full version. IBD=Inflammatory bowel disease, MDT = multidisciplinary team, CAF = Crohn's anal fistula*

11.4.7 Definitive Surgical Management of Crohn's anal fistula

Eleven surgical procedures were considered as options by respondents as options to facilitate definitive closure of a fistula. The most frequently considered options were removal of seton only (70.7%), fistulotomy (57.1%), advancement flap (38.9%), fistula plug (36.4%) and ligation of intersphincteric track (LIFT) procedure (31.8%). Fistulectomy (27.9%), fibrin glue (12.9%) and local perineal flaps (7.8%) were used by fewer respondents. Early adopters of technology indicated use of over the scope clip (OTSC) (1.2%), video assisted fistula closure (VAAFT) (1.9%) and fistula-assisted laser closure (FiLaC™) (0.6%) (Table 24).

Most respondents used diverting stoma and proctectomy on a selected case basis, with only 12.3% of respondents never using a stoma and 12.9% never considering proctectomy. Free-text responses defining indications for these were similar with the phrase 'failed bottom' used by many respondents. This was defined as recurrent or chronic perianal sepsis, incontinence, and symptoms or proctitis refractory to medical therapy. Dysplasia and malignancy were reported as specific indications for proctectomy. Patient choice was identified by several respondents as a factor in their decision to undertake these procedures. Where proctectomy was performed, a small perineal defect would be primarily closed, but respondents preferred flap-based perineal reconstruction if a large defect remained.

A significant minority (41.5%) of respondents indicated that they would treat rectovaginal fistula. This group of respondents would use definitive procedures including advancement flap (21.5%), fistula plug (10.9%), Martius flap (9.3%), omental interposition (6.2%) and LIFT procedure (4.6%) to treat recto-vaginal fistula. A diverting stoma would be used by 6.2% of respondents. A summary of definitive options used in perianal and rectovaginal fistulae are presented in Table 24. Respondents were asked to select all that applied.

Which of the following procedures would you offer in the treatment of Crohn's anal fistula?	Perianal Fistula (n=154)	Rectovaginal fistula (n=64)
Removal of Seton only	109 (70.7%)	-
Fistulotomy	88 (57.1%)	-
Fistulectomy	43 (27.9%)	-
Fistula Plug	56 (36.4%)	7 (10.9%)
Advancement flap	60 (38.9%)	14 (21.5%)
Fibrin Glue	20 (12.9%)	-
LIFT	46 (29.8%)	3 (4.6%)
OTSC	2 (1.2%)	-
VAAFT	3 (1.9%)	-
FiLaC	1 (0.6%)	-
Local (Perineal) Flap	12 (7.8%)	-
Martius Flap	-	6 (9.3%)
Omental interposition	-	4 (6.2%)
Diverting stoma	-	4 (6.2%)

Table 24 Definitive surgical procedures and their use in perianal and rectovaginal fistula.

LIFT=Ligation of intersphincteric tract, OTSC = over the scope clip, VAAFT=Video assisted anal fistula treatment, FiLAC = fistula laser assisted closure.

11.4.8 Synthesis of pathway

A summary of the preferred items related to flow through a patient pathway is presented in figure 28.

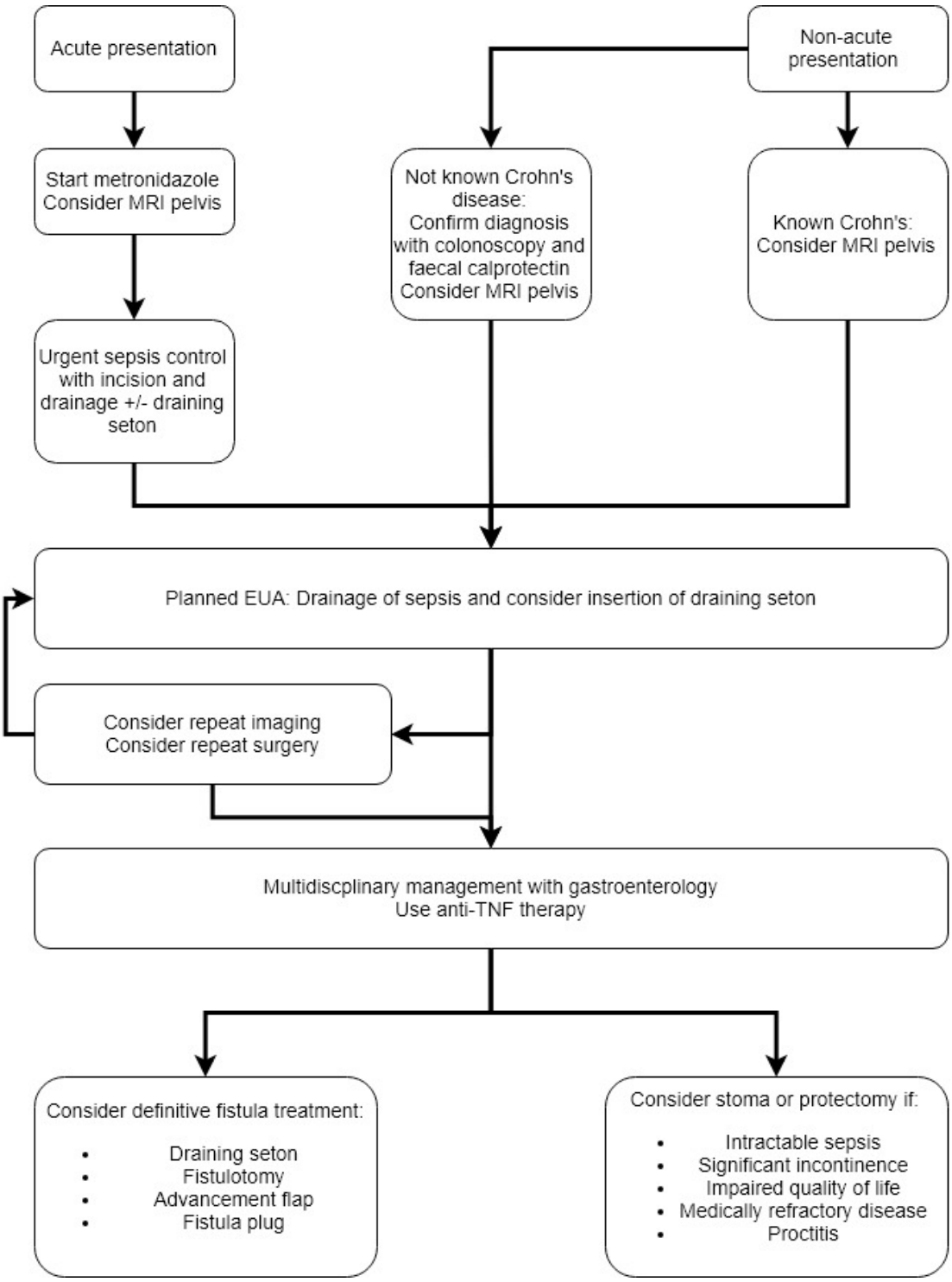

Figure 28 Flowchart with preferences for surgical management of Crohn's anal fistula

11.5 Discussion

11.5.1 Summary

This study has used a collaborative approach to assess current UK surgical practice in fistulating perianal Crohn's disease. It has identified areas of common practice, including choice of imaging modality, antibiotics and avoidance of sphincter-disrupting treatments such as cutting seton. The survey has clearly exposed variation in practice including choice of operative intervention, timing of seton removal and optimal use of multimodal therapy.

11.5.2 Strengths and limitations

There are limitations associated with survey-based research including responder bias. We attempted to address these in the study design by using personal contacts and trainee-consultant relationships with the opportunity for case-based discussions over impersonal electronic surveys with attendant poor response rates. Mitigation against survey fatigue due to length of questionnaire was also evident in engagement of local collaborators to deliver and complete the questionnaire. Anonymous participation in the survey may also have helped improve response rates, as there was no concern about identification or challenge related to practice. The high response rate was achieved with the support of the trainee collaborative networks.

Management of a condition with variable presentations and degrees of severity such as fistulating perianal Crohn's disease, will inevitably lead to some difficulties in achieving clear agreement around routine practice as management is rightly tailored to each case. This is reflected by the high proportion of respondents who selected 'frequently' or 'occasionally' as options.

11.5.3 Findings in context

There is little evidence on the use of antibiotics alone in the treatment of perianal Crohn's disease, with meta-analyses on the use of ciprofloxacin suggesting a marginal effect in remission of Crohn's anal fistula [287] [288]. In combination with Adalimumab, it may offer additional benefit in healing [289]. Recent American guidelines suggest that antibiotics in perianal sepsis might be of benefit only in the immunosuppressed, or where there is systemic upset or cellulitis [290].

Magnetic resonance imaging is well established as the imaging modality of choice in perianal Crohn's disease, and has been used to guide therapy in one study [86]. Endo-anal ultrasound is not yet a widely used technology. It has a niche role here as a diagnostic adjunct in specialist hands [291],but has limitations depending on the type of fistula present [292].

Surgeons used a variety of investigations for establishing the diagnosis of Crohn's disease. Faecal calprotectin is a sensitive marker of mucosal inflammation, so may be raised in a number of non-Crohn's related scenarios [293] [294]. Endoscopic assessment allows visual and histologic assessment of the colon. The split between colonoscopy and flexible sigmoidoscopy may be associated with surgeons ruling out proctitis only rather than assessing the whole colon, as proctitis is a prognostic factor in mucosal healing [176] and also in persistence of fistula.

The roles of anti-TNF-α therapy and azathioprine are well established in this setting, so their positions as drugs of choice are merited [74] [86] [289]. Previous work has demonstrated that steroids should not be used for Crohn's anal fistula alone, and their use in this setting runs counter to current guidelines [176] [273]. The use of steroids to treat associated luminal disease may be appropriate, and it is possible that this factor was considered when responding to questions about best medical therapy [273].

In both acute and initial elective settings, the survey shows a tendency towards conservative and sphincter-preserving procedures, in the form of drainage of sepsis and use of draining seton. Respondents widely rejected the use of cutting setons in this group of patients. Patients with Crohn's anal fistula tend to follow a chronic and recurrent disease course necessitating multiple interventions, and therefore efforts should be made to preserve continence where possible [295]. The conservative advice given to less experienced surgeons suggests UK practice is aimed at avoiding iatrogenic exacerbation of fistulating disease and tends to favour management by experienced colorectal surgeons.

The removal of seton timing varied with treatment intent, although in free text comments, respondents indicated that they tended to follow one of two published UK practices [86 296]. The perceived advantage of early removal of a seton is the removal of a 'splint' maintaining patency of a fistula and allowing it to heal. The trade off is that removal too early in the treatment process might promote recurrent perianal sepsis.

There is a wide range of procedures offered as definitive surgical options for patients with Crohn's anal fistula. Draining seton alone, fistulotomy, fistula plug and LIFT have been described in the literature, with varying outcomes, although this is mostly observational and not trial based data[98 102 295]. The variety of choice in definitive surgery may reflect in part a lack of consensus and limited evidence for the surgical management of Crohn's anal fistula but may also be influenced by individual surgeon expertise. Many of the respondents will refer on to specialists. This study did not record the subspecialisation of the respondent, so it is possible that variation is in part due to response from non-specialists.

Much of the recent literature has focussed on a multimodal approach to Crohn's anal fistula, with emphasis on sepsis control and institution of medical therapy (e.g. biologics) to aid fistula closure showing benefit over surgery alone [112] [281]. Current trials are investigating various permutations of this approach [94]. It is encouraging that most respondents have access to an IBD MDT and utilise immunosuppressant drugs as part of their therapy, although only 28% routinely employ this approach. This study did not explore make-up of the IBD MDT or whether it was supported at a local or regional level.

11.5.4 Specialist practice

There is a group of surgeons who do not undertake proctectomy or stoma formation, or manage Crohn's rectovaginal fistula. In light of the varied definitive options described, it is possible that a number of surgeons will simply place a seton and not offer any surgical options beyond that, perhaps preferring to refer on to specialist colleagues. Single centre experience with rectovaginal fistula, even in tertiary or quaternary centres comes from small cohorts [297] [298]. As volume is associated with outcome in some aspects of colorectal surgery [299], perhaps centralisation of definitive surgery for Crohn's anal fistula should be considered. This might offer better outcomes, but risks losing local expertise in peripheral hospitals [300]. Those who do undertake proctectomy or stoma formation broadly agreed on indications for these procedures. It is of note that patient preference or request was a recognised indication, as quality of life in patients with Crohn's anal fistula has been found to be improved in patients who have a stoma [50].

11.6 Conclusion

This study provides a current understanding of individual surgical approaches to Crohn's anal fistula in the context of trends in national practice. Variation in practice will have implications for design of and implementation of future research interventions in Crohn's anal fistula. Further work is required to reach consensus on standardisation of the Crohn's anal fistula management pathway. In the interim, early and efficient control of sepsis, multimodal Crohn's anal fistula management, and an emphasis on sphincter-preserving surgical techniques are the current foundations of managing Crohn's anal fistula in the UK.

12 Multicentre Pathway Mapping Exercise

Data from this chapter has been published following peer review:

Lee MJ, Freer C, Adegbola S, Elkady S, Parkes M, Hart AL, Fearnhead NS, Lobo AJ, Brown SR. Patients with perianal Crohn's fistulae experience delays in accessing anti-TNF therapy due to slow recognition, diagnosis and integration of specialist services: lessons learned from three referral centres. Colorectal Diseases 2018 Mar 22. doi: 10.1111/codi.14102. [Epub ahead of print]

My role in this study included study design, securing local approvals, data collection and analysis, preparation of manuscript.

Clare Freer, Sam Adegbola and Soad Elkady undertook data collection at their respective hospitals.

The remaining authors provided oversight and contributed to analysis and preparation of manuscript.

Permission to reproduce from co-authors and the publisher have been obtained.

12.1 Background

12.1.1 Local factors related to treatment

Whilst a patient and clinician may be responsible for making decisions about investigations and treatment, the ability to implement these decisions is reliant upon a number of factors. Firstly, there is the recognition or suspicion of a diagnosis which leads to a decision to investigate or treat. The time interval from requesting an investigation to completion of the investigation will be dependent upon the available resource for the test, both in terms of number of appointments available for the resource, and the number of competing referrals for the resource. This is similar for the institution of a treatment strategy, although there may be additional safety tests such as blood tests or pre-operative assessment. This suggests that treatment strategies may also be 'supply sensitive'.

12.1.2 Patient pathway

A patient pathway is a process or sequence of events where a patient is taken from referral or first related clinical activity, through to treatment[301]. These have been used in settings such as laparoscopic cholecystectomy[302], complex biliary disease[303], and oesophageal cancer[304], and achieve more efficient use of resources with lower costs of care.

Pathways are typically time bound. In the assessment of suspected cancer, a '31/62' limit is used – 31 days to diagnosis, 62 days to first treatment[305]. Due to the tight time bounds on this pathway, there is a push to complete their treatment pathway as soon as possible. This may lead to prioritization of this group of patients over groups competing for the same resource. There is no pathway equivalent to this in the management of inflammatory bowel disease. This may be associated with variation in the investigation and treatment of Crohn's anal fistula. Delays within this pathway may affect quality of life and may also influence the efficacy

of therapy. The pathway may be subject to variation due to individual clinician practice as demonstrated in chapters 10 and 11.

12.1.3 Complexity in healthcare

As outlined in previous chapters, the management of Crohn's anal fistula is a complex intervention. This process requires input from multiple clinical teams, offering several different interventions according to different disease states of the patient. The Medical Research Council (MRC) has identified characteristics related to complexity in healthcare interventions[306]. These include number and type of interventions, the interaction of multiple groups and variability in outcomes and intervention types. A summary of these characteristics is shown in table 25.

Component of complexity	Explanation
Number of interacting components within experimental and control interventions	Decisions about treatment made by a common team
Number and difficulty of behaviours required by those delivering or receiving the intervention	Behaviour of staff within assessment may affect outcome. For example where behaviours related to health promotion behavior are required at each clinical contact, this may reflect excessive number of new behaviours for an intervention to be consistent.
Number of groups or organisational levels targeted by the intervention	Where only one group e.g. surgeons require behavior or practice modification for an intervention, this is more likely to be achievable than modifying practice or behaviours of several groups.
Number and variability of outcomes	Assessment of an outcome is difficult where outcomes are non-binary and associated with multilple health states. This makes measurement more challenging.
Degree of flexibility or tailoring of the intervention permitted	A complex intervention may be more than administration of a single intervention or drug. It may require tailoring of the intervention to patient factors including disease states.

Table 25 Summary of components of complexity as defined in the Medical Research Council 2008 framework.

These contributors to complexity arise from an evaluation perspective and are thought to exert direct and indirect influences on outcomes[307]. The MRC recognises that for these interventions, causation cannot always be definitively proven in standard randomised trials[306]. The MRC proposes that alternate methods of evaluation should be considered.

A related system for assessing outcomes lies in 'realist evaluation'; a branch of social science research concerned with complex evaluations which asks '*what works, for whom and in what setting*?'. It is based upon the assumption that each intervention has a context and mechanism arrangement that explains outcomes (Figure 29)[308]. Context refers to the setting of the intervention and includes resource and behavioural factors associated with the intervention. This may explain why rates of MRI imaging may be high in a centre with easy access to an MRI scanner compared to lower rates in a centre with limited access to this modality. Resource availability may modify behaviours meaning that use declines in a centre with limited access. Mechanism refers to how an intervention works. For example, an intervention where patients had to undergo drainage of perianal sepsis within 24 hours of presentation may be achieved differently in different units. One hospital might place all patients on the emergency list to undergo sepsis drainage by a junior surgeon with limited experience, others may provide access to a consultant theatre list for expert management. It is possible to imagine how this might affect outcomes; those undergoing procedures by less experienced surgeons might have recurrent episodes of sepsis or need further procedures before moving onto further interventions.

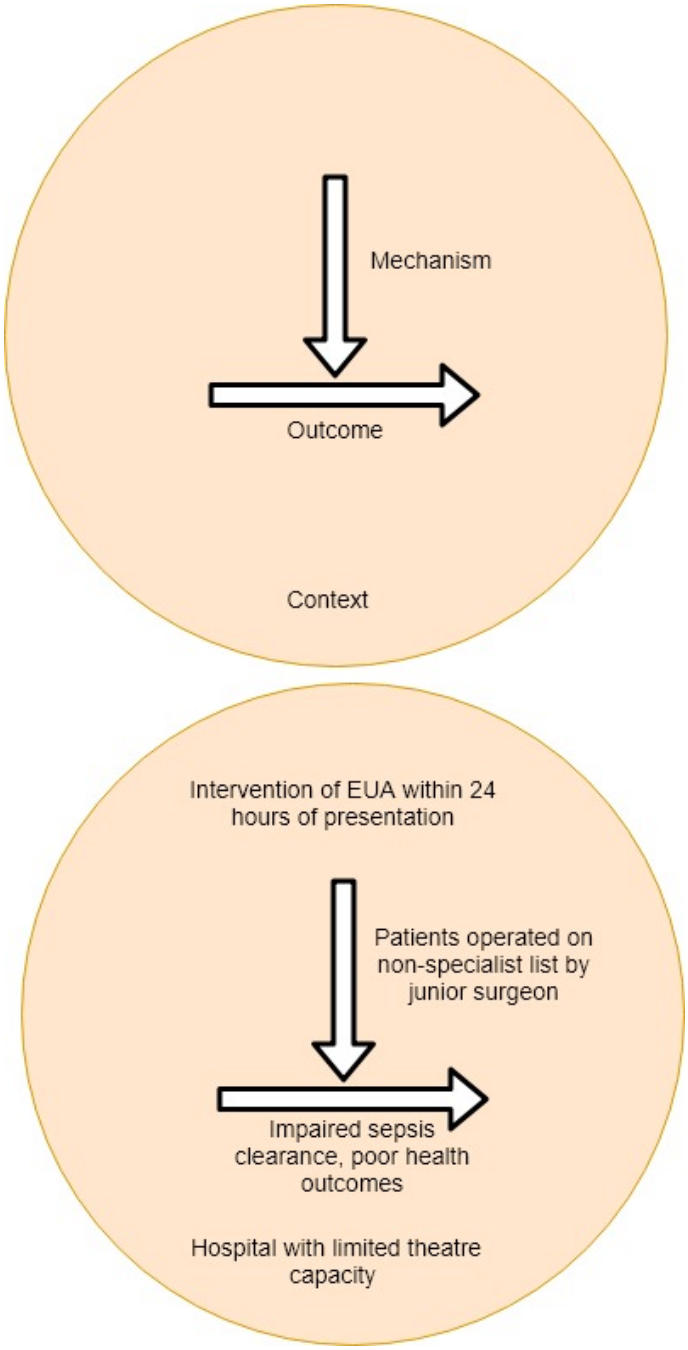

Figure 29 Summary of context-mechanism-outcome model and example of intervention described in this format.

Both of these methods for evaluation are designed to be used in prospective evaluation of a complex intervention. That is not possible within the context of this study, although principles from these systems have been incorporated into the methodology.

12.2 Aim

The primary aim of the study was to explore the pathway from presentation with symptomatic Crohn's anal fistula to treatment with anti-TNF therapy in specialist hospitals with the secondary aim of identifying areas for pathway improvement.

12.3 Method

12.3.1 Pathway start and end point

The start-point of the patient pathway was selected as the point of presentation with a symptomatic fistula, in any clinical setting. Guidelines state that initial treatment should be control of sepsis and use of anti-TNF-α therapy[111]. As outlined in the previous chapters, patients would often undergo multiple assessments and interventions along this pathway, and there is relative agreement on how an initial presentation should be managed. Given this, and the variation in treatment options, it was determined that the end of the patient pathway should be first treatment with anti-TNF-α therapy. Patient pathways may diverge at this point to include other medical therapies or operations, but all should pass through this treatment node.

12.3.2 Pathway nodes of interest

A patient pathway includes key steps. Working with a group of gastroenterologists and surgeons, it was expected that a patient pathway might reasonably include one or more of:

- Surgical outpatient appointment
- Gastroenterology outpatient appointment
- Inflammatory Bowel Disease Clinical Nurse Specialist outpatient appointment
- Magnetic resonance imaging scan of the pelvis
- Examination under anaesthesia or other planned surgical procedure
- Emergency surgical procedure to assess or treat perianal sepsis or pain

12.3.3 Retrospective design

A prospective cohort design was not feasible for this study. There is a lack of data on the UK incidence of Crohn's anal fistula, and have no benchmark upon which to base estimates of pathway length. This means that estimation of sample sizes, and costing of a research project

to pathway completion was not possible. This study has been reported in line with the 'strengthening reporting in observational studies' (STROBE) guideline[309].

Whilst surgical research is derided for use of retrospective data[178], it serves an important purpose here: it allows exploration of readily available data to inform any prospective study design. As this study uses primarily administrative data, there should be low levels of missing data in the study design. A further consideration is that a prospective study with active observation might introduce observer bias.

12.3.3.1 Approvals

The data collected for this study is routinely collected, and forms part of an assessment of practice. As such, it falls under the remit of service evaluation. This means that authorisation to conduct this work is given by local clinical governance teams, rather than the NHS research and ethics committee. Local approvals were secured for each participating site. The approval documents for the Sheffield site are shown in appendix L. Outside governance approvals, each site was required to have approval of a gastroenterologist and surgeon as data related to both departments would be under review.

12.3.3.2 Participating sites

Three centres were selected to participate in this study. These centres are recognised as having well developed IBD services, with access to all relevant investigative and therapeutic options. The participating centres were Sheffield Teaching Hospitals NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust, St Mark's Hospital, London Northwest Healthcare NHS Trust. These sites were selected as they provide a comparable context[308] for comparison and aggregation of data.

12.3.4 Case identification

Cases were identified using a convenience strategy with no formal power calculation. Cases were identified through administrative clinical coding. The International Classification of Diseases (ICD) published by the World Health Organisation provides a standardized method for reporting diseases and comorbidity by disease system. This system identifies Crohn's disease using the reference K60.x and perianal diagnoses as K61.x . At the time of writing, the 10th revision of this document was in use[310]. Hospital administrative databases were searched using ICD-10 clinical codes K50.x (Crohn's disease) AND K60.x OR K61.x (anal fistula), for events between 2010 and 2015. Identified cases were cross-checked against local biologic therapy databases to confirm which patients had received anti-TNF treatment. Patient records were retrieved for identified cases.

12.3.5 Inclusion Criteria

Adults with newly symptomatic Crohn's anal fistula not on anti-TNF therapy at the start of the study period, and who had received anti-TNF therapy by the end of the study period, were included. Those with non-fistulating perianal manifestations of disease, those who declined anti-TNF therapy, and those who transferred care from one hospital to another during the study, were excluded.

Demographic and clinical data extracted from clinical records included: time since diagnosis of Crohn's disease at beginning of pathway, and prior anti-TNFα, thiopurine or methotrexate use. Crohn's disease phenotype was classified according to Montreal criteria[10].

12.3.6 Data extraction

Data extraction was performed by a collaborator at each site. Pathway data extracted included: date of first presentation with symptomatic fistula within the study period, date of first anti-TNFα dose, date, location and specialty of all IBD-related documented clinical interactions (outpatient/inpatient), timing of MRI scans, and visits to operating theatre (planned and unplanned). All data were anonymised prior to transfer to the lead side through a secure email system (nhs.net).

12.3.7 Analysis

Overall pathway length was calculated as time from first presentation to time of first dose of anti-TNF in days. Clinical events identified included attendance at surgical and medical outpatient clinics, MRI scans, admissions, and surgical procedures. Time to transition from each care event (i.e. medical outpatients, surgical outpatients, medical admissions, radiology (MRI), elective theatre) was for each event in days. Mean number of events per pathway was calculated, as was the rate of care events and unplanned readmission per 30 days of pathway (care events/(pathway length/30). These values were plotted following log transformation to normalise the distribution.

Comparison of medians between groups was performed using Mann-Whitney U-test. Other statistical tests used are indicated in parenthesis. A p value of <0.05 was set as the threshold for statistical significance *a priori.* This study was registered as a service evaluation with audit departments at respective hospitals.

12.4 Results

12.4.1 Summary of included cases

Clinical coding identified a total of 311 cases across all sites. Following removal of duplicates and excluded cases, a total of 79 (25.4%) of patients were eligible for the study. These were split 24/23/32 across the three sites. Case flow and reasons for exclusion are presented in Figure 30.

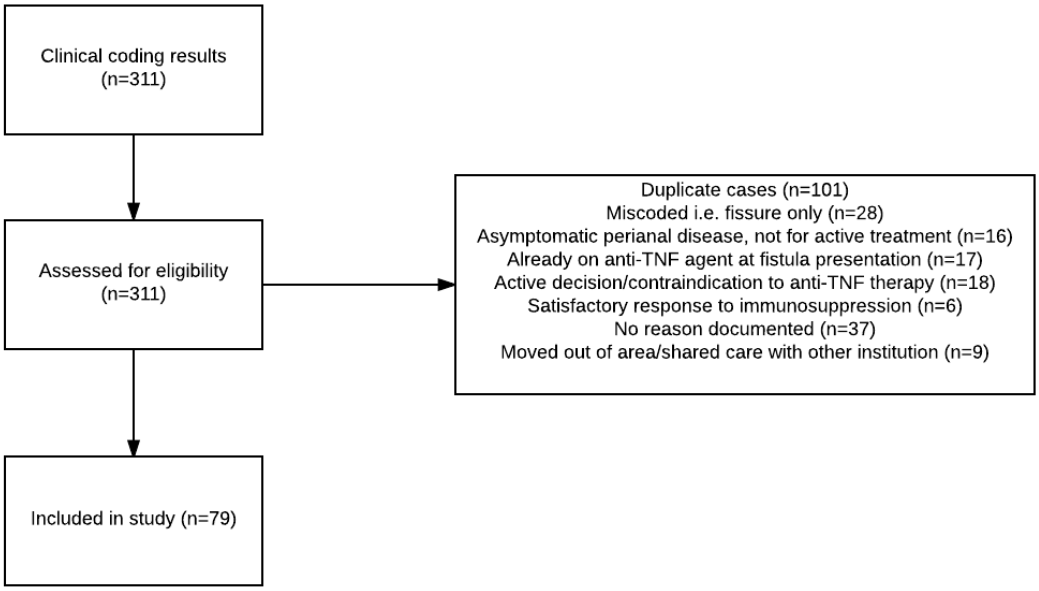

Figure 30 Case flow of patients included in the study and reasons for exclusion

12.4.2 Clinical characteristics

54 patients (68%) had a pre-existing diagnosis of Crohn's disease (CD). The date of diagnosis was confirmed from clinical records. In these patients, the mean time from diagnosis of CD to presentation in this study was 9.5 years (S.D.+/-7.2). Patient phenotype is presented in table 1. Of the 54 patients with a prior diagnosis of CD, 14 (25.9%) had previously received anti-TNFα therapy, 27 (50.0%) had previously received thiopurine agents, and 1 (1.8%) methotrexate. The Montreal classification of included patients is presented in table 26.

	A1			A2			A3		
	L1	**L2**	**L3**	**L1**	**L2**	**L3**	**L1**	**L2**	**L3**
B1	1	1	2	5	14	13	1	2	2
B2	0	2	0	1	0	4	0	0	0
B3	0	1	4	2	11	10	0	1	2

Table 26 Montreal Classification of Included Patients.

This defines phenotype of disease by age at diagnosis (A1= less than 16 years old, A2 = between 17 and 40 years old, A3 = more than 40 years old), location of disease (L1 = ileal, L2 = colonic, L3 = ileocolonic) and behavior of disease (B1 = non-stricturing, non-penetrating B2 = structuring, B3 = penetrating (all would have prefix of 'p' for perianal disease)). This table shows that most patients in this study had A2 L2/3 B1/3 disease behaviours.

12.4.3 Interval between presentation and anti-TNF treatment

The median time from presentation of a symptomatic Crohn's fistula to receiving the first dose of anti-TNF therapy was 204 days (almost seven months)(IQR 113-453 days) (Figure 31) across the whole cohort. The median interval for patients with existing CD was 174 days compared to 365 days for those with a new diagnosis of CD (p=0.019). There was no significant difference in the median length of the pathway in those patients with a pre-existing diagnosis of CD according to whether they had or had not received anti-TNF in the past (136 vs 199 days, p=0.29).

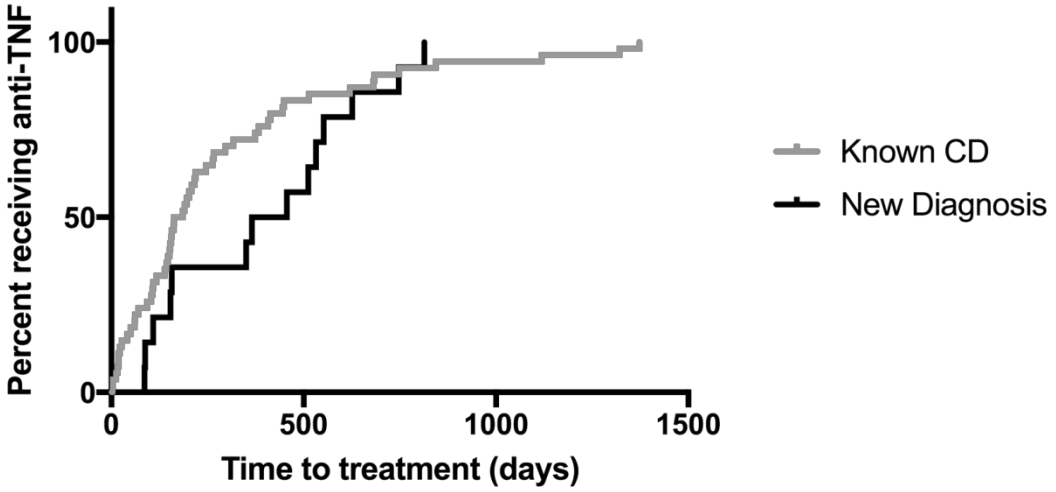

Figure 31 Kaplan Meier chart showing time from entry into pathway to receiving anti-TNF. Time to treatment split by new and existing diagnoses of Crohn's disease.

Number of care events per 30 days underwent log transformation. Longer pathways showed a negative correlation with the number of clinical events per 30 days of the pathway (Spearman r = -0.87, ((-0.91 to -0.79) p<0.01) and with unplanned readmissions Spearman r = -0.95 ((-0.97 to -0.91) p<0.01) (figure 32). This suggests that longer pathways are not associated with increased clinical activity, which might suggest underlying difficult to treat disease. Similarly, the longer pathways are not associated with increased rates of emergency admissions, which may reflect underlying symptom control.

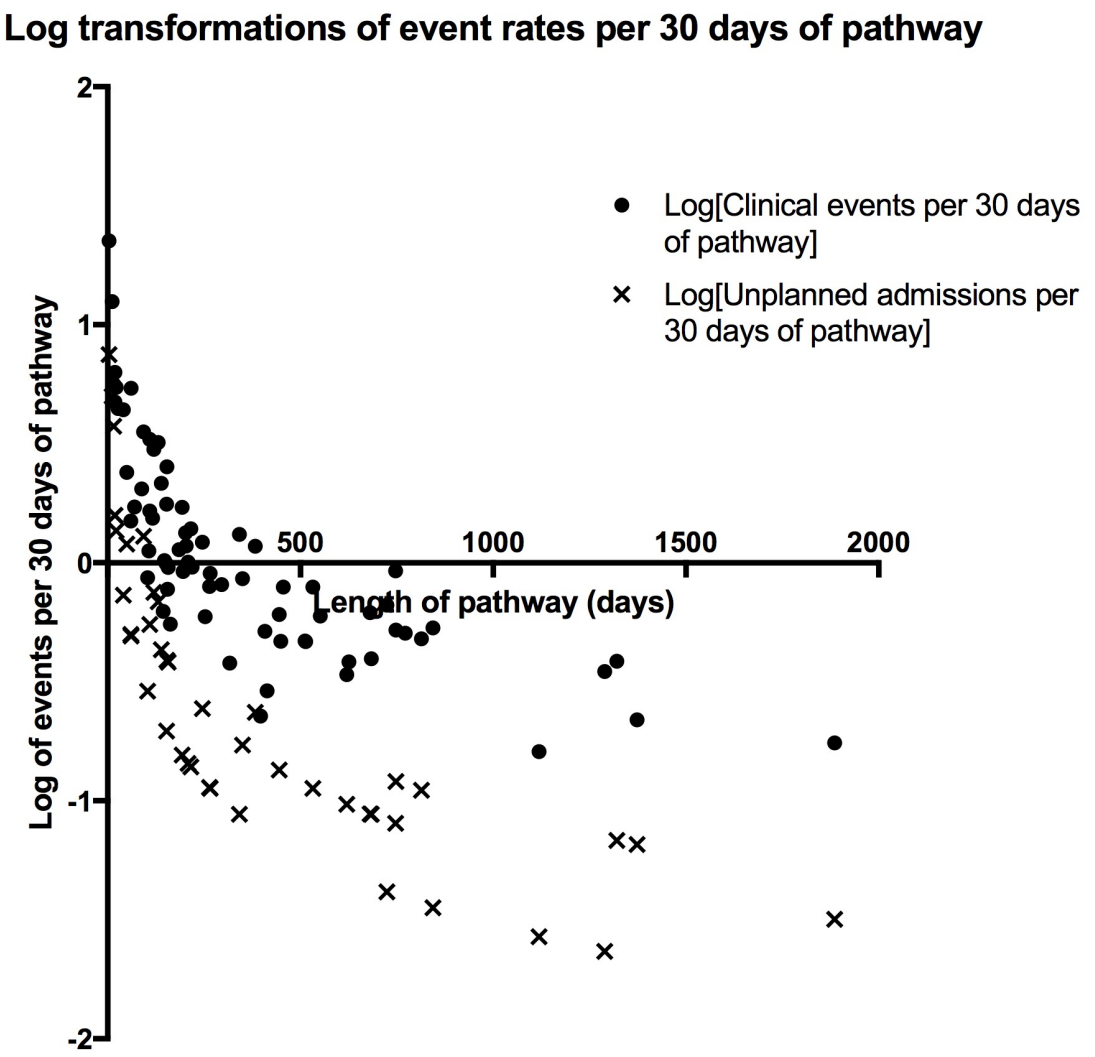

Figure 32 Log transformation of rates per 30 days of pathway for any clinical event, and unplanned admission by length of pathway (days).

Both show significant negative correlation of rates with pathway length. (Clinical event Spearman r = -0.87, (-0.91 to -0.79) p<0.01; Unplanned readmission Spearman r = -0.95 (-0.97 to -0.91) p<0.01.

12.4.4 Route of access and outpatient use

Overall, 29(36.7%) of 79 patients initially presented via an acute surgical route, 5(6.3%) presented via a medical admissions unit, 21(26.6%) and 22(27.8%) via surgical outpatients and medical outpatients respectively, and 2(2.5%) presented through contact with an IBD

specialist nurse. For those 25 patients with no prior diagnosis of CD, 9(36.0%) presented via surgical outpatients and 9(36.0%) as an acute surgical admission. 7 (28.0%) patients presented through medical outpatients. The distribution of point of access by diagnosis is detailed in Table 27. The mean number of surgical outpatient events per patient was 1.10, and the mean number of medical outpatient events per patient was 1.49.

	New CD (n=25)	Known CD (n=54)	Overall (n=79)
Medical Outpatients	7 (28%)	15 (27.8%)	22 (27.8%)
Acute medical admission	0	5 (9.3%)	5 (6.3%)
Surgical Outpatients	9 (36.0%)	12 (22.9%)	21 (26.6%)
Acute surgical admission	9 (36.0%)	20 (37.0%)	29 (36.7%)
IBD Specialist Nurse	0	2 (3.7%)	2 (2.5%)

Table 27 Point of access to pathway split by whether patient had new or existing diagnosis of Crohn's disease.

Numbers denote number of patient accessing through each route, with percentage of study population in brackets

12.4.5 Frequency of MRI scanning

An MRI was performed in 59 (74.6%) of patients during the pathway. Of those undergoing MRI, 42 (71.1%) underwent one scan, 15 (25.4%) patients underwent two MRI scans. One patient each (1.69%) underwent three and six MRI scans. The mean number of MRI was 1.03 per patient.

12.4.6 Frequency of surgical interventions

Of the 79 patients, 72 (91.0%) underwent a total of 140 surgical procedures, including examination under anaesthetic, seton insertion, drainage of sepsis, or other fistula procedures (see Table 28 for breakdown). Of these, 36 (50.0%) had a single procedure, 17 (23.6%) had two procedures, 6 (8.3%) had three procedures, 13 (18.0%) had four procedures. The mean number of operations was 1.9 per patient.

Procedure performed	Number (percentage of all procedures)
Examination under anaesthetic	14 (10.0%)
Drainage of abscess	39 (27.8%)
Insertion of seton	67 (47.8%)
Lay open of fistula	10 (7.1%)
Anal fistula plug	1 (0.7%)
Video assisted anal fistula treatment (VAAFT)	1 (0.7%)
Seton removal	5 (3.5%)
Stoma formation	2 (1.4%)
Proctectomy	1 (0.7%)

Table 28 Procedures performed during patient pathway.

12.4.7 Time to transition

Time to and from each point of care (medical or surgical outpatients, medical or surgical admission, nurse specialist appointments, MRI scans and elective theatres) was calculated. Transition from medical outpatients or admission to surgical outpatients tended to be shorter than transition from surgical admission or outpatients to medical outpatients (32.0 vs 56.5 days; p = 0.08) (Table 29). The median time to commencement of anti-TNF from last clinic appointment was 77 days (IQR 27.5-225.5 days).

From \ To	MRI	SOPD	MOPD	MAU	SAU	CNS	Elective Theatre
MRI	-	42	29	-	19	-	-
SOPD	24	51.5	56	-	59	-	22
MOPD	34	35	89.5	16	70	43	35
MAU	24	11	26	-	18	-	-
SAU	29.5	45	75	60	61	-	0
CNS	16	40	39	18	-	-	-
Elective Theatre	-	59	48.5	55.5	38	25	73.5

Table 29 Table showing median time to move from one part of the pathway to the next.

Point of origin is in the left column, and destination is in the horizontal column. '–' indicates no data available. MRI = Magnetic Resonance Imaging, SOPD = Surgical Outpatient Department, MOPD = Medical Outpatient Department, MAU = Medical Admissions Unit, SAU = Surgical Admissions Unit, CNS = Clinical Nurse Specialist.

12.4.8 Establishing Current Pathways

Based upon this data, there are 3 potential clinical pathways from presentation of perianal Crohn's disease to anti-TNF therapy. The pathways are essentially determined by mode of presentation.

Surgical outpatient presentation

Patients presenting to surgical outpatients tend to undergo elective surgery (median wait 22 days), followed by attendance at medical outpatients (median wait 48.5 days). Most then undergo an MRI (median wait of 34 days) then return to medical outpatients (median wait 29 days). After this, they will be started on anti-TNF therapy (median wait 77 days).

Emergency surgery presentation

Patients entering the pathway via acute surgical admission will undergo MRI (median wait 29.5 days), before attending for surgical follow up (median wait 42 days) and undergoing elective surgery (median wait 22 days), and then attending medical outpatients (median wait 48.5 days) and accessing anti-TNF therapy (median wait 77 days).

Medical outpatient presentation

Finally, patients may present to medical outpatients and be referred for an MRI (median wait 34 days), before referral for a surgical opinion (median wait 42 days) and undergoing elective surgery (median wait 22 days). They may then proceed to anti-TNF therapy (median wait 77 days) (see figure 33).

It is important to note that these reflect frequently represented pathways for the whole cohort. As suggested by above findings, some patients will have multiple clinic appointments and multiple MRI scans. Patients presenting to the surgeons as an emergency typically

underwent outpatient MRI scan, although a small number underwent emergency examination under anaesthesia, with same day discharge and outpatient imaging.

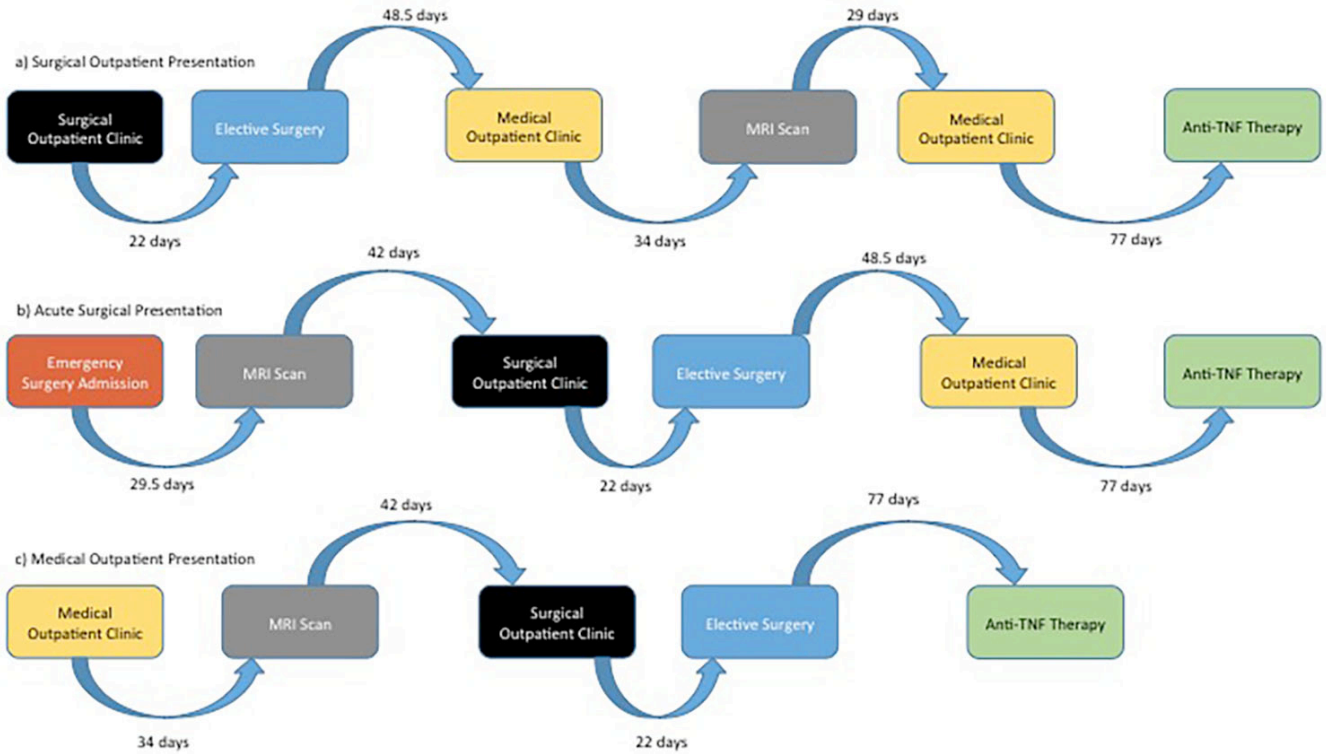

Figure 33 Typical pathways of patients from presentation with Crohn's anal fistula to commencement of anti-TNF therapy

a) for patients presenting to surgical outpatients, b) for patients presented acutely to the surgical team and c) for patients presenting initially to the medical outpatient team. Curved arrows are labelled with median waiting times (in days) between sequential steps in the pathways described. NB not to scale.

12.5 Discussion

This is the first study to assess the delays between presentation of perianal Crohn's disease and initiation of biological treatment. It has shown that the median pathway length is substantial, even in centres with an established IBD service. There is median delay of 204 days. In one case, the delay extended to over five years. This study identifies two particular barriers to a shorter patient pathway: establishing the initial diagnosis of Crohn's disease in a patient with newly diagnosed fistula, and referral or access to medical services by surgeons.

12.5.1 Barriers to diagnosis

Perianal fistula may be the first presentation of Crohn's disease in 15% of patients[32]. Some presentations of perianal disease may be immediately apparent as Crohn's disease. There may be clinical features typical of Crohn's disease such as florid oedematous skin tags, multiple fistulae and proctitis. In others without these pathognomic features, patients may be treated initially as having cryptoglandular disease. There is currently no other diagnostic tool allowing early identification of disease Crohn's disease. In addition, acute perianal abscesses, presenting as an emergency, may be treated by a less experienced junior surgeon, possibly with limited senior input and sometimes minimal follow up again contributing to appropriate management delay

12.5.2 Complexity in the patient pathway

Patients with suspected Crohn's disease do not qualify for enhanced pathways available to patients with suspected cancer, and yet the unrelenting disease process may mean that by the time of clinical review, disease progression may necessitate a return to an earlier point in the pathway. For example, further urgent surgery to drain recurrent infection, or repeat MRI

scan to assess newly arising fistula tracks. Even if the patient has an uncomplicated disease pathway, the wait for medical, radiological and surgical review or intervention lead to substantial delay in treatment with a consequent impact on quality of life and potentially on long-term outcomes and likelihood of successful treatment.

Options to reduce the delays at each of these steps should be considered, and could include agreed fast track referral pathways between medical and surgical arms of the IBD service – including directly into surgical admissions units and back to receive anti-TNF-α infusions. Combined in-patient rounds and out-patient clinics are likely to help the rapidity of diagnostic clarity and appropriate decision-making with respect to appropriate treatment. Even more than this may be required – an open door policy with the multidisciplinary team interacting on a daily basis rather than just meeting periodically may facilitate the interdisciplinary clinical conversations that potentially smooth a patient's journey with a difficult and complex condition.

12.5.3 Basis for time driven pathway

This work is driven by the view that earlier anti-TNFα is better than later anti-TNFα for both clinical outcome and quality of life benefits. No trial has tested this hypothesis. Evidence suggests that duration of fistula presence is a poor prognostic factor indirectly suggests benefit of a time-based approach[311 312]. However, given the impact of fistula symptoms on quality of life and the common situation where disease deteriorates whilst waiting for the next step in the pathway, a streamlined pathway would seem sensible.

12.5.4 Limitations

There are limitations to this study, particularly its retrospective nature. We have only captured the timing of events, not the intention that lead to the event (e.g. routine vs urgent

follow-up), nor have we captured factors related to patient choice. We have also defined the pathway as terminating only when anti-TNF therapy has been commenced. Nevertheless we feel that focusing on this element of the treatment pathway is relevant as both a surrogate for i) the experience of these patients in terms of symptomatic debility[43 313], and ii) because of the perception that delays in treatment may be associated with a poorer outcome – a finding replicated in other aspects of Crohn's disease[314 315].

There is a high level of variation in pathways to anti-TNF therapy for patients with perianal Crohn's fistula disease. In most cases the delay to treatment is substantial. It is very likely that such delays affect both quality of life and overall outcome. These findings could be used to test strategies to reduce delay, or to understand barriers to implementation of effective treatments from randomised trials into clinical practice.

12.6 Conclusion

There is delay in many of the elements of the pathway in patients with Crohn's anal fistula. In particular, commencement of anti-TNF therapy is often delayed with new diagnoses of Crohn's disease waiting 365 days and patients with established CD waiting 174 days. Diagnosis is a challenge in patients with first presentation of Crohn's disease. Resolving these delays is important to reduce the debility associated with perianal Crohn's disease.

13 Consensus on Surgical Management of Crohn's Anal Fistula

Citation: Lee MJ, Heywood N, Sagar PM, Brown SR, Fearnhead NS. ACPGBI Consensus Statement on the management of Fistulating Perianal Crohn's disease. Colorectal Dis 2017;19(5):418-429

I was involved in study design, generation of voting items, invitation of participants, conduct of the consensus meeting and collation of results.

Co-authors were involved in the conduct of the exercise and preparation of the manuscript. Steven Brown and Nicola Fearnhead were involved with the preparation of statements, conduct of event, analysis of results and preparations of manuscript.

Permission to reproduce from co-authors and the publisher have been obtained.

13.1 Background

13.1.1 Variation in management

Crohn's disease has been associated with perianal fistulation since the condition was first described, with around 33% of Crohn's patients affected [316]. Management of Crohn's anal fistula presents particular challenges related to heterogeneity in presentation and disease course, and the need for long-term immunosuppressive medical therapy and multiple surgical interventions[138 174]. As outlined in previous chapters, there are a several different surgical treatments available for Crohn's anal fistula and in outcomes following surgery.

The previously reported survey of surgical management of Crohn's anal fistula indicated that some areas of practice showed variation, including antibiotic choice, imaging modalities and use of draining setons. There was also variation in other aspects of management such as optimisation of multimodal care and selection of definitive surgical procedures[317].

13.1.2 Guidelines to inform practice

A guideline provides recommendations on a set of clinical actions or processes, summarising best practice for a given condition. There are broadly speaking three types of guideline – evidence based, evidence-based consensus, consensus without evidence base. Evidence based guidelines are considered the most robust and reliable form of guideline, although they require significant time and resource to develop[318]. An evidence-based consensus guideline is 'a public statement on a particular aspect of medical knowledge that is generally agreed upon as an evidence-based, state of the art knowledge by a representative group of experts in that area'[319]. Where evidence is lacking, it might be appropriate to undertake a non-evidence based consensus, for example in the adoption of a novel technology or technique.

13.2 Delphi methodology

13.2.1 Background to the Delphi Process

The Delphi process was conceived by the RAND corporation in the 1950s[320]. It was originally used as a forecasting method for the likelihood of Russian bombing attacks on the USA. It was subsequently policy makers, and recognised for its role in facilitating group communication around complex situations[321]. In recent years, it has been adopted as a method to achieve consensus in health-related matters. It broadly uses method of item generation, followed by prioritisation through iterative voting, with a final consensus (figure 34). Those participants informing the consensus are typically invited experts or other stakeholders. The use of experts in this process gives rise to the name of the process, referring to the Oracle at Delphi in Greek history[322].

13.2.3 Method of Delphi consensus

Study design

Prior to beginning the study, it is important to define the aim of the exercise. A short, open question may be posed to address the question, or a set of statements may be proposed, with the facility for participants to add their own statements for discussion[321].

Panel selection

It is important that a panel includes a broad selection of participants representing a range of views, not just those the organiser wishes to endorse. Some methodologists consider a Delphi consensus to be a jury of peers[323], therefore the jury should be representative. This can be achieved through diversity in aspects such as age and geographic location.

Round 1: Item generation

In the first round, items for inclusion are drawn from different sources. These include those identified through systematic review of the literature, through supporting qualitative or quantitative work, or those identified by an expert panel as being of relevance. Participants in this round can add additional items for voting[321 324]. The process of voting is summarised in figure 34.

Subsequent rounds: Iterative voting and ranking of items

During subsequent rounds, each item undergoes further votes. Responses from previous rounds are presented to participants to allow interpretation of the group consensus. The number of items may be reduced where agreement cannot be reached after rounds of voting[321 324]. Voting is anonymous and ensures that all participants voices are valued equally.

Final round: Agreement of consensus

The final round of voting may occur as early as round two[322]. Where consensus is reached, participants should be willing to commit to and support the resulting statements[324].

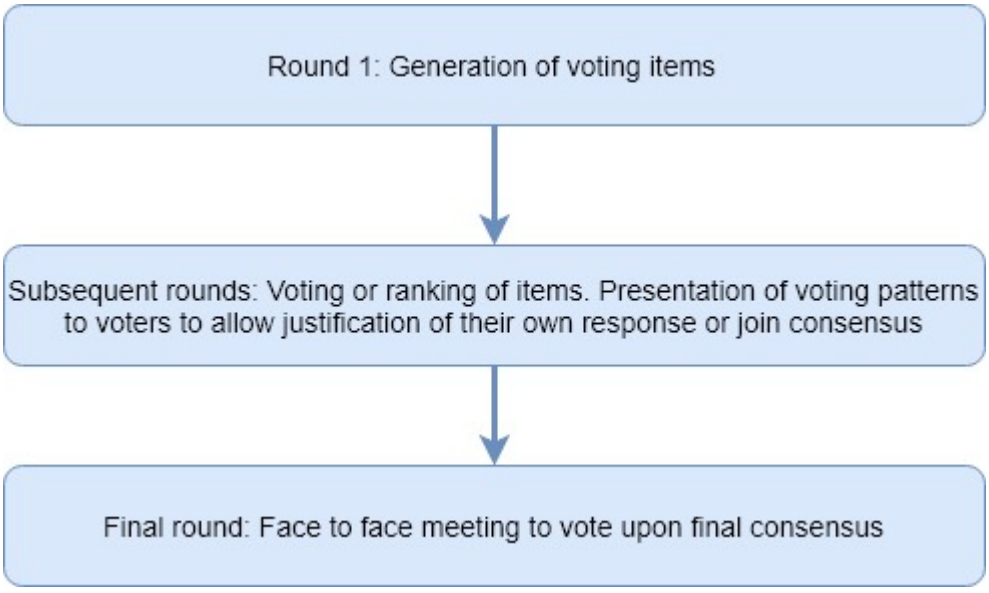

Figure 34 Summary of Delphi methodology

Modifications of Delphi methodology

The key principles of Delphi are anonymous and iterative voting. This means that rather than being held remotely, a consensus exercise can be held in one location providing anonymity can be achieved. Similarly, it is possible to use a quasi mixed-method approach to predetermine statements for voting[324]. Both strategies may be employed to reduce the time taken to achieve consensus.

13.2.2 Strengths and limitations of the Delphi process

Unlike other methods of prioritisation such as nominal group or Q sort, Delphi is designed to achieve consensus[324]. Iterative voting and discussion allows experts on the panel to understand point of view of others to achieve consensus. It also fosters collaboration amongst the group of experts; this is the same group likely to be responsible for implementing any findings[321 324].

These strengths can also be considered a weakness, as the desire to achieve consensus can lead to a central tendency, avoiding extreme statements. This may lead to the group agreeing a position that does not provide new information[324]. This is a particular problem when expert groups provide generic statements to avoid areas of disagreement, meaning that statements have no significant influence upon practice[323]. The method can also require a significant period of time to complete and reach consensus[322]. Improper selection of the panel can also lead to bias due to inadequately representation of belief or opinion.

13.3 Aim

The aim of this exercise was to establish UK evidence-based consensus on surgical management of Crohn's anal fistula.

13.4 Method

13.4.1 Justification of consensus methodology

To establish consensus amongst UK colorectal surgeons, a pragmatic approach to consensus methodology had to be taken. An electronic Delphi approach would be conducted over a long period of time and may lead to attrition from an already small pool of participants. Alternative methods such as nominal group technique would require long periods of time with intense negotiation, limiting the number of items that could be addressed in available time.

With these considerations, it was decided that generation of evidence-based items prior to voting, voting without discussion, time for discussion, and a second vote, would be the appropriate approach. This means that the methodology used took the form of a modified Delphi Technique. This method has been used as an accepted variant[324].

13.4.2 Item generation

Potential statements for inclusion in the consensus were developed by an expert group of colorectal surgeons and gastroenterologists with specialist interest in managing inflammatory bowel disease (IBD). All statements were based on systematic literature review, and current practice based on responses to the survey of surgical practice described in previous chapters.

Statements were prepared in five principal areas of practice: i) context, ii) assessment and management of an acute presentation of Crohn's anal fistula, iii) operative and perioperative practice in the elective setting, iv) multidisciplinary management and v) definitive surgical management.

13.4.2 Participants

Participants in the consensus were invited as they had indicated interest in contributing through completion of the questionnaire, or following advertisement of the exercise by the Association of Coloproctology of Great Britain and Ireland (ACPGBI), the UK colorectal specialty association

13.4.2 Voting

Each statement was presented to the group of experts, and an initial vote undertaken electronically using ResponseCard® (Turning Technologies, UK), allowing contemporaneous and anonymous recording of votes, with responses visible to participants.

The initial vote was followed by debate amongst experts and refinement of the wording of the consensus statement prior to a reiterative second vote. Voting was undertaken using a five-point Likert scale, ranging from 'strongly disagree' to 'strongly agree'.

Consensus was defined a priori as ≥80% of respondents voting in agreement (either agree or strongly agree). Participants could change their final vote until closing of that vote, once all votes were cast.

Weighting was attached to each statement based on the available evidence and strength of recommendation. This classification was based upon modified GRADE criteria, as used in other consensus documents [176 325]. In summary, this method ranks recommendations as '1' (strong) or '2' (weak). These are modified with a letter to indicate the level of evidence supporting this. 'A' denotes high quality evidence such as a well-conducted randomised controlled trial or meta-analysis. 'B' identifies moderate quality evidence such as a non-randomised trial or

prospective study. ‘C’ identifies low quality evidence such as retrospective studies or case series. ‘D’ is used where expert opinion supports the recommendation. Grading was carried out by the steering group. The consensus process is summarised in Figure 35. This exercise was registered with the University of Sheffield ethics committee (UREC:007371) (Appendix M).

Figure 35 Summary of method of consensus exercise

13.3 Results

The consensus group consisted of 17 Consultant Colorectal surgeons and two patient representatives. The colorectal surgeons all had a declared interest in inflammatory bowel disease. The patient representatives had engaged with the ACPGBI Delphi process and regularly shared experiences of patients treated for aspects of inflammatory bowel disease, including Crohn's anal fistula. A total of 51 statements were considered. Responses to accepted statements are presented below, along with the results of the final vote (SA – Strongly Agree, A – Agree, N – Neutral, D – Disagree, SD – Strongly Disagree). Rejected statements are summarised after each section, along with reasons for rejection.

13.3.1 Context – Accepted Statements

Fistulating perianal Crohn's disease is frequently a chronic condition. 1A

It is recognised that patients with fistulating perianal Crohn's disease may heal, although the majority of patients will have recurrent or non-healing fistulating disease[174]. This typically requires long-term medical therapy and repeated surgical procedures[138].

Management of fistulating Crohn's anal fistula should take a patient-centred approach. 1C

The preferences of surgeons and patients in surgical treatments have been shown not to align in some aspects of Crohn's disease [326]. Due to the chronic nature of the disease, treatments should be tailored to the needs and goals of each patient. Some patients may prefer symptom palliation while others may aim for definitive management aimed at fistula eradication. These choices and patient-selected outcomes should be respected and addressed using shared decision-making [48].

Prognostic factors for successful healing include:

Absence of proctitis. 1A.

Short duration of fistulating disease. 1C.

Non-Smoking status. 1C.

'Simple' fistula. 1C.

Prognostic factors for failure of healing include:

Proctitis. 1A.

Active Smoking status. 1C

'Complex' fistula. 1C.

Prognostic factors for healing and failure of healing have been identified in studies ranging from retrospective cohorts to prospective trials. Proctitis is a predictor for proctectomy in a number of retrospective studies [248 327]. Complex fistulae (i.e. those which are **not** short, low tracks as per the American Gastroenterology Association classification) [216] are associated with poor healing rates. Smoking status has an impact on the overall activity of Crohn's disease, increasing the rate of relapse [328]. The duration of fistulating disease reflects the perception that it may be easier to manage a 'fresh' fistula rather than a well-established, fully epithelialized fistula. This has been identified as a significant prognostic factor in an open label study, where it was treated as a continuous variable with no predictive cut-off reported[329]. Despite the importance of these factors in response to treatment, randomised controlled trials have not undertaken adequate stratification to mitigate effects across treatment arms [76 93]. It is worth noting that the ongoing PISA trial has specifically included early seton removal in both interventional arms[94]again suggesting that clinicians place importance on likelihood of successful treatment if fistulae are of relatively recent onset. Voting results for accepted statements are shown in figure 36.

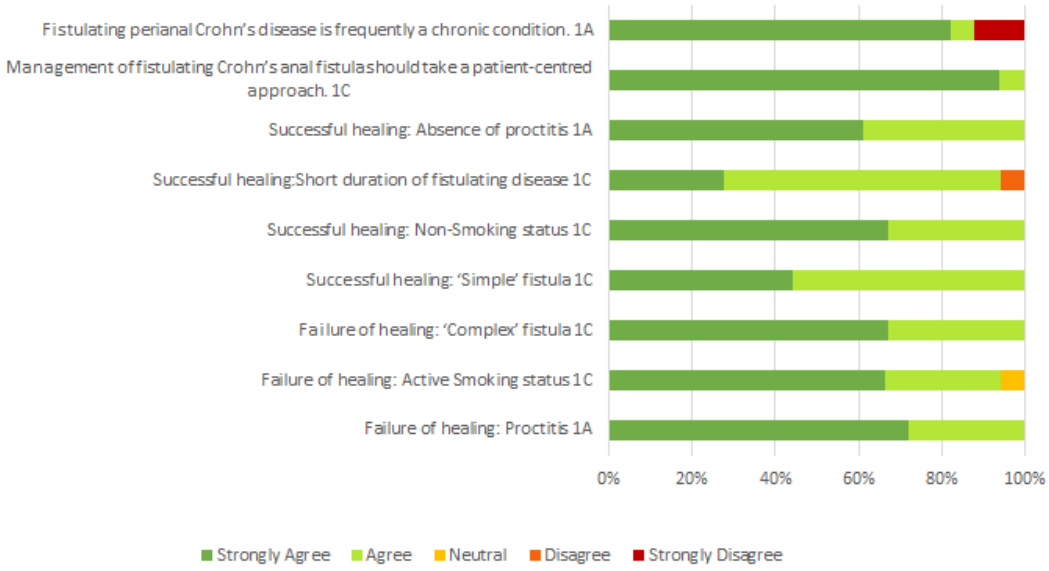

Figure 36 voting results for context statements

13.3.2 Acute Management – Accepted Statements

Perioperative metronidazole should be used in selected cases in the acute setting. 1B

The majority of the literature assesses both ciprofloxacin and metronidazole [287]. The consensus group preferred to use metronidazole, in line with survey results[177]. This may reflect UK antibiotic practice and avoidance of ciprofloxacin due to its causative link with *Clostridium difficile* infection[330], although this is thought to be lower in CD populations than other populations [331]. Ciprofloxacin has been used in the longer term as an adjunct to anti-TNF therapy in Crohn's anal fistula, although this has had varied results [88 289]. The consensus group did not advocate antibiotics in all patients presenting acutely with Crohn's anal fistula. The specific circumstances where the consensus group would recommend antibiotics were in the presence of local cellulitis or induration, systemic sepsis, immunosuppression, or where there might be a delay before drainage of sepsis.

Acute operative management should involve drainage of any abscess. 1B

An experienced colorectal surgeon should consider placing draining seton(s) in readily identifiable fistulae. 1B

Sepsis control is the principal aim of surgical drainage in the acute setting, and therefore drainage of any abscess is advised. If fistulae are readily identifiable, then a seton should be placed acutely at the time of abscess drainage[332]. In this setting, tissue is potentially friable and oedematous and there is an increased risk of creating false tracks [333]. Given this, the expert agreement was that only those with appropriate experience should place a seton in this setting.

Cutting setons should not be used in perianal Crohn's disease. 1D

Historically prevalent, and occasionally still used in fistula surgery, the cutting seton was rejected for use in Crohn's anal fistula by the consensus group. This corresponds with current UK practice;90% of surgeons would never consider a cutting seton in this setting [177]. Due to the nature of the disease and recurrent procedures, cutting setons were felt to carry unacceptably high risk of future incontinence[334]. Voting results for accepted acute management statements are presented in figure 37.

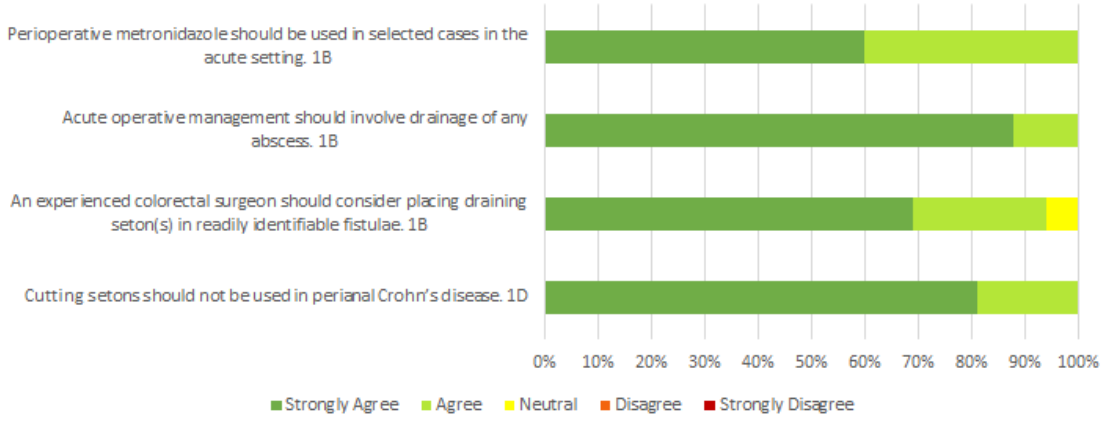

Figure 37 Voting results for accepted acute management statements

13.3.3 Acute Management - Rejected statements

Selected patients should undergo an MRI scan preoperatively

SA: 0% A: 63% N: 19% D: 13% SD: 6%

The seton material of choice is a silastic sling

SA: 13% A: 13% N: 31% D: 38% SD: 6%

The consensus group felt that whilst a 'road-map' MRI might be useful, the primary aim in this setting was control of sepsis and that this should not be delayed. Responses to seton choice in the survey were heterogenous. Participants in the consensus indicated use of Ethibond®, silastic slings and Comfort drains™ (CJ Medical, Truro, UK)[177].

13.3.4 Initial Elective management – Accepted Statements

Draining setons should be placed in fistula tracks at first elective Examination Under Anaesthesia*. 1A*

The use of draining setons in this setting is well described. This allows ongoing drainage of a track as a bridge to immunomodulatory therapy [281]. It may not be technically possible to insert a seton in every case.

Selected patients will require MRI of the perineum. 1C

MRI of the perineum is the most commonly used imaging modality in UK Crohn's anal fistula practice [177]. Precise indications for MRI did not emerge from discussions but it was apparent that not all surgeons would request MRI in all patients. Some surgeons would prefer to have imaging before undertaking an elective examination under anaesthetic, to aid localisation of fistula openings and any residual sepsis. Other surgeons indicated that they would use MRI post-operatively to assess resolution of fistula-related sepsis after placement of setons [86].

Selected patients will require repeat examination of rectum under anaesthetic. 1D

A second examination may be of benefit in a patient with on-going symptoms, or those where it was not possible to place draining setons at first operation. An experienced colorectal surgeon is usually able to define fistulae and control sepsis, a pre-requisite to biologic therapy [335 336].

Presence or absence of proctitis should be established with diagnosis of perianal Crohn's fistula. 1B

Proctitis is felt to be a prognostic indicator for successful management of Crohn's anal fistula and presence of proctitis requires focus of attention on disease control with

immunomodulation [337-339]. As such, presence or absence of proctitis should be confirmed at the first opportunity following diagnosis.

If Crohn's disease is suspected, then diagnostic confirmation should be sought with colonoscopy and/or imaging 1B

Colonoscopy can be used to assess for proctitis, and also the terminal ileum for evidence of Crohn's disease. This may be useful in cases where perianal fistula is the first presentation of IBD. Choices for cross-sectional imaging typically include CT to assess for terminal ileal pathology, or MRI small bowel series to confirm the phenotype of disease [340]. Despite the reported performance of faecal calprotectin [61], variation in levels based on location of disease [341] and the reported sensitivity to other causes of inflammation in the gut meant that it was not recommended in this setting. Voting results for accepted initial elective management statements are presented in figure 38.

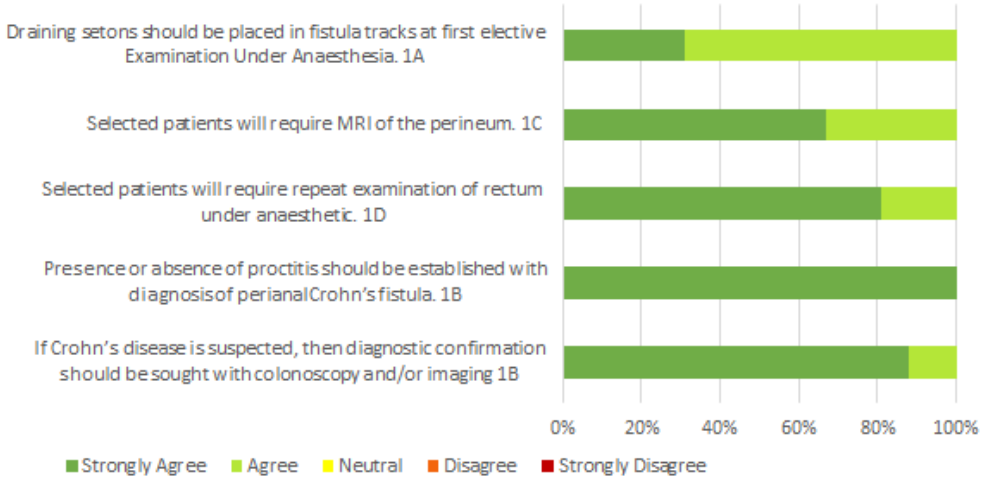

Figure 38 Voting results for accepted initial elective management statements

13.3.5 Multidisciplinary management

All patients with perianal Crohn's disease should be discussed in a multidisciplinary setting. 1D

All surgeons managing perianal Crohn's disease should use a multidisciplinary approach. 1A

Current best practice in Crohn's anal fistula management uses both medicine and surgery to achieve fistula closure [95 112 281]. In order to achieve this, it requires surgeon and physician to work together, along with the wider multidisciplinary team (MDT) including clinical nurse specialists, pathologists and gastrointestinal radiologists. Although there is evidence for multimodal (multidisciplinary) management, there is, at present, no evidence for a formal MDT meeting in the management of these patients [112]. However, it is recommended as an IBD service standard by the Royal College of Physicians[342].

Medical therapy is best directed by a gastroenterologist. 1D

Surgical opinion is important in decisions about medical therapy. 1D

In keeping with the multidisciplinary approach, medical therapy should be directed by a gastroenterologist. The surgeon may be able to offer insight on operative findings that could influence multimodal management. These should be taken into account when considering modification of therapy [112].

Steroids should not be used in isolated perianal Crohn's disease. 1B

There is no evidence for the use of systemic steroid therapy in the treatment of Crohn's anal fistula alone. Steroids may be useful to treat other sites of luminal inflammation in these patients [343].

Multidisciplinary discussion about anti-tumour necrosis factor-α therapy should occur promptly after sepsis control. 1B

Whilst there is no body of evidence on timing of biologic therapy, use of biological agents including anti-TNF-α agents, is considered to be an important aspect of successful symptom control in Crohn's anal fistula [75 77 79]. This is already recognised by the majority of surgeons managing this condition [177]. Biological therapy should be addressed soon after control of sepsis and may avoid unnecessary delay in healing.

Timing of removal of a seton should be a multidisciplinary decision involving the patient. 1D

Optimal timing of seton removal after induction with anti-TNF-α therapy has not yet been established. 1A

A number of factors may influence seton use including the anatomy of the track, patient symptoms and therapeutic intent (palliation of symptoms vs. closure of fistula tracks). At present, the evidence base has not defined the optimum time for seton removal. Previous work has discussed the timing of seton removal in relation to induction with biologic therapy [86 344]. Typically reported management in the surgical survey[177] preferred the previously reported strategy of seton removal around the second dose of anti-TNF therapy[296]. Given the degree of uncertainty, decision-making should be guided by clinicians, but shared with the patient. Voting results for accepted multidisciplinary management statements are presented in figure 39.

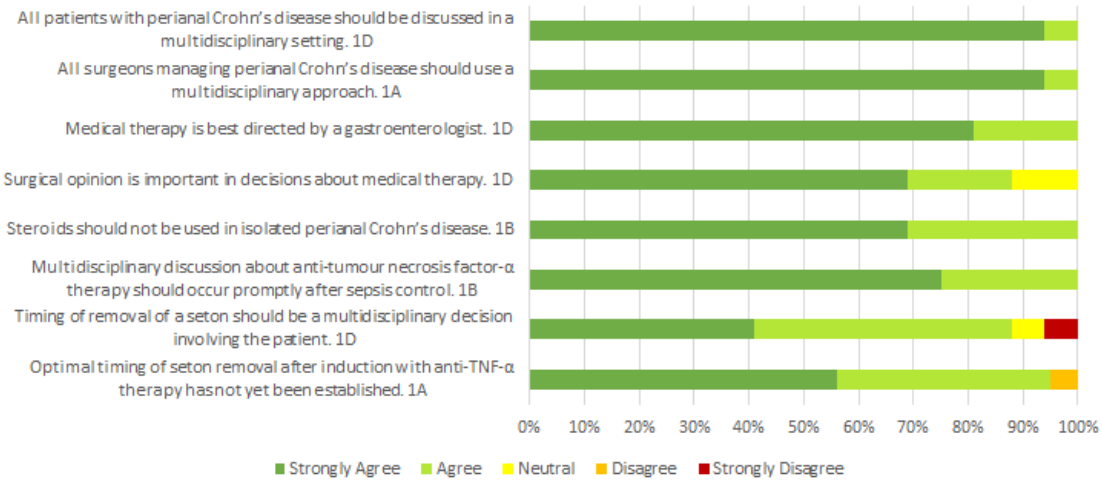

Figure 39 Voting results for accepted multidisciplinary management statements

13.3.6 Multidisciplinary Management - Rejected statements

Further surgical management should be undertaken by a core member of the IBD multidisciplinary team. *SA: 13% A: 38% N: 6% D: 25% SD: 19%*

The definition of an IBD MDT was felt to be inadequately established, such that defining a 'core member' would be problematic.

13.3.7 Definitive Surgical Management – accepted statements

Sphincter preserving techniques should be used in a stepwise fashion based on functional risk. 1C *SA: 61% A: 39% N: 0% D: 0% SD: 0%*

With repeated surgical procedures and metachronous fistulae, options for surgical management should be considered in light of their likelihood of success and impact on immediate and future continence. Selection of initial procedures aimed at healing should weigh up success rate against risk of incontinence in the context of patient preference, with individual patient trade-off preferences guiding therapy, rather than clinician selection [326].

In many patients, long-term management with a seton may be an acceptable option [281]. This provides symptomatic relief and carries little risk to continence. It may avoid repeated surgery in up to 90% of patients [345].

Secondary tracks should be successfully treated before definitive surgical management of primary tracks. 1D.

For the purposes of this consensus, the following definitions were used: a primary track has an internal opening in anorectum and an external opening on the perineum; a secondary track has an external opening on the perineum but does not have an opening into the anorectum but rather communicates indirectly via a primary track; a secondary tract is the blind sinus or sideways branch off either. Closure of a primary track may impede drainage of a secondary tract, leading to further abscess formation and recurrent symptoms. Secondary tracks should be addressed prior to closure of the primary or 'feeding' track. This will ensure clearance of residual sepsis and diminish chances of failure in treating the primary track[346]. In some cases, treatment of the secondary track may be as simple as seton removal in a patient on biological therapy. It was also emphasised that surgery for the secondary track could be carried out immediately prior (ie under the same anaesthetic) to surgery on the primary track, and may include procedures such as drainage, laying open, seton removal or insertion of anal fistula plug.

Fistula plug is a continence preserving option in perianal Crohn's disease. 1B

Fistula plug (AFP) for Crohn's anal fistula has been described in several papers. A recent meta-analysis reported complete closure in 58.3% of patients, with little change in continence [347]. A subsequent RCT was performed using this therapy in Crohn's anal fistula and achieved

closure in 31.5% of patients at 12 weeks[93]. In this study 54 Crohn's patients underwent an anal fistula plug, with fistula closure at 12 weeks achieved in 31.5%. The closure rate was similar to that achieved with seton removal alone (RR 1.31 95% CI 0.59-4.02; p=0.19). This study excluded patients with proctitis but included both complex and simple fistula treated. Complexity of fistula was not associated with outcome. In review of source material, abscess formation occurred in 3.7-53.8% of patients[208 213 214 348]. Additional complications included one wound dehiscence[214], five plug extrusions and two episodes of significant perianal pain[348].

There is a conflict between the meta-analysis and RCT data, that is reflected in the acceptance of the consensus agreement that the anal fistula plug may still have a role. The meta-analysis included both prospective non-randomised cohorts and retrospective cohort data. It is likely that these patients were entered based on clinician preference and reflect 'real world' data, although results may be affected by the relatively small sample sizes, and bias towards reporting favourable results. There is also limited data on the co-incident medical therapy in these studies. The RCT was selective in certain aspects (absence of rectal disease) and less prescriptive in others (fistula anatomy not standard). This could mean that patients were entered into the study who may not have received a fistula plug based on clinician preference. It is plausible that fistula plug offers benefit in some anatomical configurations, but not others (e.g. simple vs complex, long vs short track). Whilst the evidence for this intervention is not overwhelming, there are relatively few reports of complications. Coupled with the minimal invasiveness, a fistula plug may be considered an acceptable option for the treatment of this condition.

Permacol ™ paste (Covidien, Mansfield, MA), Over the scope clip (OTSC ®, Ovesco Endoscopy AG, Germany), FiLaC® (Fistula Laser assisted Closure Biolitec AG, Jena, Germany) and autologous stem cells may have potential as continence preserving techniques. 2C

These therapies have been used in Crohn's disease in small numbers, with success rates of 54%, 83%, 71% and 57% respectively, and little in the way of adverse outcomes [104 349 350]. As yet, no large randomised controlled trials have reported on their use in Crohn's anal fistula. Only a small number of UK surgeons regularly use these emerging technologies in clinical practice [177].

The results of a randomised controlled trial of autologous stem cells versus a control of physiological saline, both with sutured closure of the internal fistulous opening in patients maintained on biological therapy, has been published since the consensus, with results significantly favouring the use of autologous stem cells, even in the context of a high rate of fistula closure in the control arm[246].

Advancement flap is a treatment option in perianal Crohn's disease. 1C

Eight retrospective[185 198 217-222] and two prospective observational studies[223 224] reported the outcome of mucosal advancement flaps in both Crohn's and idiopathic perianal fistulous disease. Of the 624 reported procedures, 240 of these were performed for Crohn's fistula. Success in short term healing was seen in 50.0%-85.0% of patients. Where reported, recurrence at >1 year was 30.0%-50.0%[198 223]. Complications were reported in only one study, with occurrence of haemorrhage and flap retraction occurring in 6.6%[218]. The experience of endoanal advancement flap in CD was summarised by Soltani et al in 2010 [99]. They found a success rate of 64%, with incontinence rates at 9.4% in Crohn's anal fistula.

Selection criteria for these procedures typically avoided proctitis, but there was no consistent reporting on medical therapy required to induce favourable local conditions, nor was there reporting on the medical therapies required to maintain favourable conditions and support healing post-operatively. Therefore, consideration of this procedure should be tempered by

the potential impact of concomitant medical therapy and disease activity, as well as potential for impaired continence in a patient group who prioritise preservation of continence.

Further (high-quality) information may be gained from the current PISA trial, which incorporates endoanal advancement flap as one of the intervention arms [94]. On current evidence an advancement flap might be considered in the absence of proctitis, significant fibrosis or stricturing disease.

Ano/recto-vaginal fistulae will rarely heal on anti-TNF-α therapy alone. 1A

Definitive treatment of ano/recto-vaginal fistulae should be by specialist surgeons in specialist centres. 1D

Ano/Recto-vaginal fistula represents a unique challenge in Crohn's anal fistula. Genital fistulae in Crohn's will rarely heal with biologic therapy alone [76 351]. Not all UK surgeons will manage this condition, and consequently it is managed in fewer centres with expertise in a range of operative techniques [177 297 298]. Treatment of ano/rectovaginal fistulae should be under combined surgical and luminal gastroenterological care.

Diverting stoma may improve quality of life for patients with perianal Crohn's disease. 1B

Faecal diversion is indicated in uncontrollable sepsis. 1C

Faecal diversion may be considered for symptom control. 1C

Faecal diversion may be considered if proctitis cannot be medically managed. 1C

Use of a stoma is often considered a 'failure' by clinicians. Evidence highlights that patients affected by perianal Crohn's disease see improvement in some quality of life domains following formation of a stoma [50], and some patients have indicated that they would like to discuss this early in their treatment[313]. Therefore, quality of life as reported by the patient may be an indication for stoma. Both colostomy and ileostomy have been used for this indication. Selection of stoma location should take into account distribution of disease (i.e. rectal, colonic) and previous surgery[107]. Uncontrollable or recurrent sepsis, incontinence, or ongoing discharge are indications for faecal diversion, although up to two thirds of patients may subsequently require further surgery including proctectomy [107 352].

Proctectomy provides improved symptom control and quality of life in selected patients. 1D

This statement highlights the importance of patient priorities and their role in decision-making. As such, it might be considered early in the treatment process. Current UK practice would consider proctectomy in the face of recurrent or refractory perianal sepsis, rectal disease refractory to medical therapy, to improve quality of life or at patient request[177]. As well as the indications highlighted for stoma formation, proctectomy might also be considered in patients with strictures, and cancers forming in fistula tracks [353 354]. This is not an absolute panacea as a number of patients may still have perineal morbidity and altered pelvic function, including dyspareunia in 10%[110 355].

There may be a role for myo-cutaneous flap-based perineal reconstruction after proctectomy for perianal Crohn's disease. 2C

Proctectomy in the setting of severe Crohn's anal fistula is often associated with poor perineal healing, with delayed healing at or beyond 12 months in 58% of patients[355 356]. A retrospective

study of a cohort of 145 patients who had undergone proctectomy for Crohn's disease found persistent perianal sinus in 23% of patients, and was associated with rectal involvement and faecal contamination of the surgical field. Despite numerous interventions, closure was achieved in only 9 patients[357]. While a sinus may result in an occasional perineal discharge, in some the non-healing perineal wound may re-establish considerable discharge and sepsis. For this reason reconstruction with a rectus abdominis, gluteal or gracilis based myocutaneous flap should be considered [358 359]. Voting results for accepted definitive surgical treatment statements are presented in figure 40.

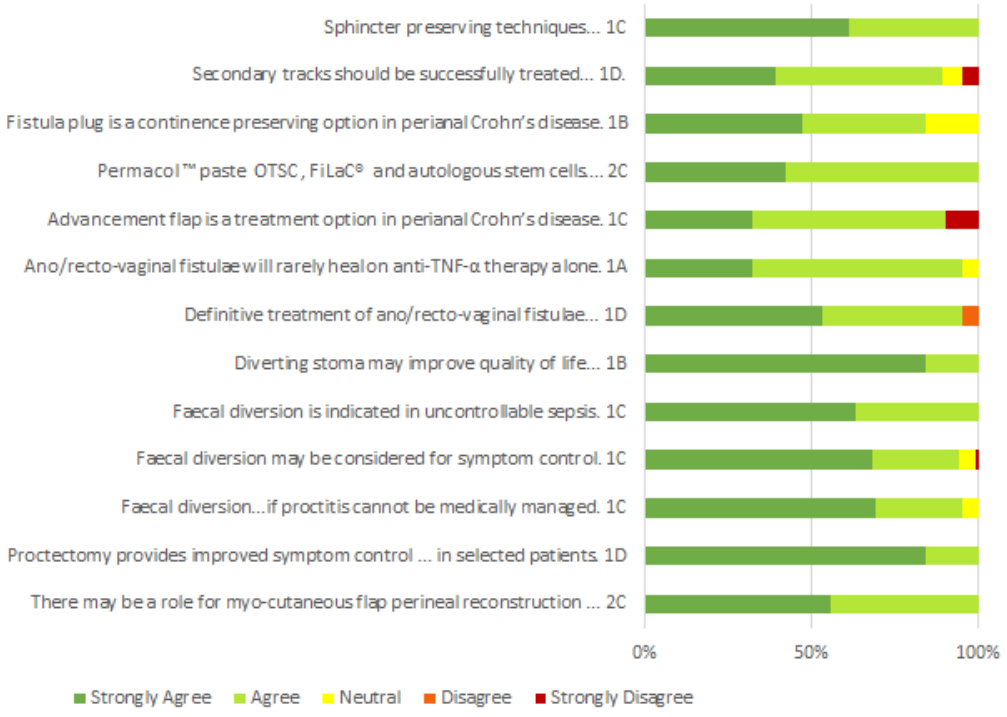

Figure 40 Voting results for accepted definitive surgical management statements

13.3.8 Definitive Surgical Management - Rejected statements:

Fistulotomy has a role in perianal Crohn's disease where there is minimal sphincter division.

SA: 17% A: 44% N: 17% D: 17% SD: 6%

Fibrin glue may be effective in long or complex tracks.

SA: 0% A: 0% N: 0% D: 56% SD: 44%

LIFT procedure is a continence preserving option in perianal Crohn's disease.

SA: 5% A: 42% N: 42% D: 11% SD: 0%

It should be noted that there is evidence to suggest laying open of a superficial fistula is not associated with problems of healing in the large majority of patients[360], although one third of patients may have long term incontinence [361].Various permutations of this statement were discussed including 'no' and 'minimal' sphincter division. The consensus group expressed concern that without clear indications and limits to what might be laid open, patients might come to harm from repeated fistulotomy.

The evidence for fibrin glue in Crohn's anal fistula arises from two small trials of patients with perianal Crohn's disease. One found that fistulae closed in 38% of those treated vs 16% of controls. The second study assessed outcomes in refractory Crohn's anal fistula (n=14) and achieved clinical improvement in 75% of patient at 3 months, with complete healing in 57% at two years. Poor results from studies in cryptoglandular disease have tempered the enthusiasm of the consensus group for this treatment [362].

The Ligation of the Inter-Sphincteric tract (LIFT) procedure was rejected as the evidence for its' use arises from a small single centre study, where 9/15 patients treated were healed at two months [102]. The consensus group felt that this was insufficient to recommend use in Crohn's anal fistula. Concerns were expressed around the conversion of anatomy to

intersphincteric fistula, precipitating subsequent fistulotomy. There was also concern that sphincter disruption and long-term incontinence with this procedure. Despite the fact that no sphincter is divided in this procedure, there is disruption of the intersphincteric space and significant traction on the sphincters.

13.4 Discussion

13.4.1 Summary

This paper reports on a consensus exercise, describing agreed practice in the treatment of fistulating perianal Crohn's disease. Due to the likelihood of repeated procedures, conservative or continence sparing procedures are preferred in the first instance. The role of the multidisciplinary team is reinforced and the need for adjuvant medical therapy highlighted. In contrast to other guidelines on the topic, this consensus has provided practical advice for surgeons managing this condition in the UK considering prevailing management trends. A summary of the recommended steps in management is shown in figure 41.

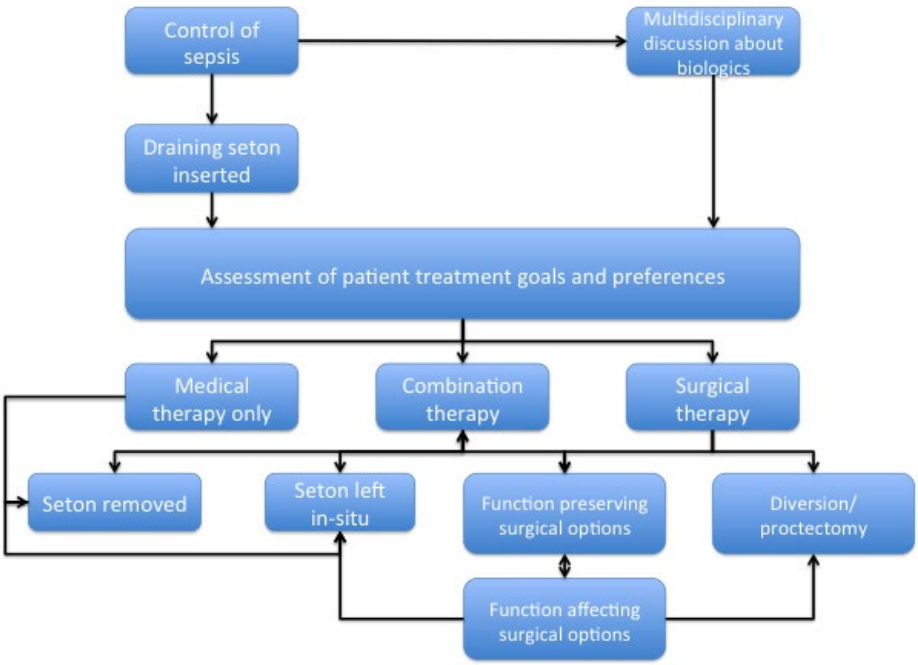

Figure 41 Summary of proposed patient pathway

13.4.2 Comparison with other guidelines

There are several contrasts and similarities with the two recent publications from the World Gastroenterology Organisation (WGO) and European Crohn's and Colitis Organisation (ECCO) [175] [176]. All papers agree on 'staging' the disease by assessment of the rectum for proctitis. The WGO publication further advocates assessment of the small bowel to complete staging. The ECCO paper was published in 2010, prior to a number of relevant publications on operative approaches to Crohn's anal fistula. Consequently, non-cutting fistulae and/or fistulotomy are recommended for simple fistulae. Surgical therapy is advocated for complex fistulating disease, but no specific procedures are mentioned. Ano/rectovaginal fistulae are discussed, and a combined medical and surgical approach (including stoma formation) is advocated [175]. The WGO consensus advocates the use of fistulotomy as a surgical procedure and suggests a number of treatments which may be considered in definitive surgical management including mucosal advancement flap, fistula plugs, LIFT and mesenchymal stem cells, and proposes a structured algorithmic approach[176]. In contrast, the UK-based consensus presented here advises that procedures are selected with patient aims in mind.

13.4.3 Strengths and limitations

The recommendations from this exercise have two key limitations or sources of bias: the participants and the information they used. The consensus group was by its nature self-selected and included surgeons with an interest in the condition. This has potential to skew results away from more nationally generalised recommendations. Despite this, none of the agreed statements show major conflict with the results of previous national survey of current practice [177]. Some recommendations were undoubtedly limited by the quality of available evidence. While large trials of medical therapy have been reported, there are fewer quality trials of surgical or multimodal therapies for this condition. Consequently recommendations

are based on either small trials or retrospective studies with inherent bias. These challenges have been identified in a recent review of guidelines for the management of anal fistula [363]. An ongoing trial aimed at improving outcomes for patients with perianal Crohn's disease has utilised best available evidence and guidelines to optimise the intervention arms, but also acknowledges the relatively poor evidence base for the selected components of each pathway[94].

In making recommendations, the consensus group considered both clinical outcomes and qualitative patient-reported outcomes. The body of literature on this condition reports widely on healing rates following use of setons and biologics [281], but limited focus on qualitative data following surgery. Quality of life data comparing Crohn's anal fistula patients with and without faecal diversion show that diverted patients have better quality of life [50]. There is a need to explore these aspects of care further to identify the patient benefits conferred by the various surgical options, and even consideration and discussion of diversion earlier in the patient journey than is currently offered. As highlighted following each recommendation, there is a limited evidence base from which we can draw strong recommendations and virtually no head to head comparisons of surgical therapies. It would not be appropriate to report economic data on these therapies as existent economic analyses consider 'mixed' fistula cohorts[364], ignoring the highly recurrent nature of these fistula. Surgical studies also fail to consistently report medical therapies associated with treatment, which are the main cost drivers in the treatment of perianal Crohn's disease[138].

One of the strengths of this exercise is that it recognises uncertainty and the need to involve patients in decisions about their care. Shared decision making has been investigated for patients undergoing surgery for breast and rectal cancer [365 366]. Following sepsis control, it would be appropriate to discuss the possible surgical options and relevant information to

patients to support decision making [367]. The management of Crohn's anal fistula should involve a multidisciplinary approach combining the knowledge of a gastroenterologist and colorectal surgeon who have appropriate experience. The use of best evidence should involve patients at the centre of their own care, with management of expectations considering the potential for chronicity and relapsing nature of the disease [368].

13.4.4 Implications for practice

This exercise has identified areas for further research, including work around optimum timing of seton removal and, by extension, timing of biologic therapy. The wide range of surgical procedures available reflects lack of evidence of their efficacy but may also reflect heterogeneity within the disease. There is a lack of data to enable robust judgements on the cost effectiveness of surgical options. Further work to understand this could take the form of clinical trials and should include assessment of patient preferences and choices in decision-making, quality of life and functional outcome at several time-points, as well as objective and subjective healing outcomes. This consensus exercise should be repeated at a future date when stronger prognostic data maybe available, as well as further information on the short and longer-term outcomes of novel therapies such as over the scope clip and stem cells, and trials using endorectal advancement flaps.

14 Mixed method approaches

14.1 What is mixed method research

Mixed method research is research that '*focuses on collecting, analysing, and mixing both quantitative and qualitative data in a single study or a series of studies*.'[369 370] It has been used in health research, and is becoming part of surgical research strategies[371].

As mixed method approaches have developed, there has been debate on the theoretical grounding of this research type[372]. Original proponents were described as either constructivist or positivist. Constructivism is an approach where no one source or method gives an answer, and that reflection on several methods or results can provide a reflection of reality. Positivism recognises only that which can be scientifically verified, or which is capable of logical or mathematical proof. Simplified, one group would prioritise qualitative data over quantitative data, and the other, the reverse. It is recognised that mixed methods have a tendency to favour certain forms of qualitative data (semi-structured interviews) and quantitative data (closed-question surveys), and this approach does not necessarily satisfy both philosophical groups[373].

As with most efforts to dichotomise complicated ideas, this left room between the two approaches for the emergence of the pragmatic paradigm. This asks 'what works?' for a specific research question, allowing adaptability of design, and for data types to be weighted in different ways[369 374]. This is important as the strengths and weaknesses of a data type may not become apparent until analysis is performed[375].

14.1.1 Benefits of mixed-method approaches

This mixing of data types provides several benefits[369 376]. These include:

- Complementarity: Data from one set of results can be used to illustrate points from another e.g. interview quotes may be used to explain or support discussion of a survey finding.
- Initiation: This is when the results of the two methods demonstrate divergence or incongruence and generate new hypotheses e.g. e.g. a survey of surgeons indicates their patients undergo frequent wound changes, but interviews with nurses reveal that these changes are infrequent and highlights potential barriers to frequent dressing changes.
- Expansion: This is where the methods are appropriately used to explore different aspects of a research question e.g. a clinical study to assess how many people attend a follow-up clinic appointment, and interviews with those who do not attend appointments to explore reasons for this.
- Triangulation: This involves the use of both studies to corroborate findings. The same (or similar) questions are asked using two different methodologies, with the findings from the two compared to assess where the 'real' answer lies. When triangulation is being undertaken, it is important to determine a priori which dataset will take priority when there is disagreement between the two[377 378].

The main disadvantage of a mixed method approach is that the study requires more time to design, and more resources to deliver, than delivering either a purely qualitative or quantitative study[372 375].

14.2 Design of a mixed methods study

There are five major designs of mixed method research. These are convergent, explanatory sequential, exploratory sequential, embedded, and mixed methods systematic review[376]. These use different data sources at difference stages in the study and apply different weighting to data according to the research question. The approach to survey-based research has already been outlined, and the approach to qualitative interviewing is described in the next chapter. Types of mixed-method design are presented in figure 42.

Convergent: Both qualitative and quantitative methods are used concurrently, and results are mixed at interpretation stage. Study design is suited to mapping process changes through capture of clinical data, mixed with interviews or focus groups of service users.

Explanatory sequential: This study design begins with a quantitative component which generates further questions. Qualitative methods are then employed to explore this.

Exploratory sequential: This study design uses qualitative data to generate research questions, which are then tested using quantitative methods such as a survey. This may be through exploration of experiences of a sample of patients, followed by a survey of a wider patient population.

Embedded: In this design, qualitative methods are embedded within a larger clinical study. This may be interviews or focus groups with study participants to explore outcomes or explore feasibility and acceptability of interventions.

Mixed methods systematic review: This is a form of systematic review which includes both quantitative and qualitative data in the synthesis of findings.

Figure 42 Types of mixed method study design

14.3 Selection of mixed method approach

The mixed method approach selected for this study was an exploratory sequential design. As there was no relevant data in the literature upon which to base a survey for this condition, it was decided to undertake a qualitative interview-based study to generate hypotheses to test in a quantitative survey. Themes emerging from the studies would undergo triangulation to identify areas of agreement and dissonance, validating or refuting findings[378]. This is particularly helpful where a population for research is potentially limited. The flow of data in this study is presented in figure 43. This study has taken a pragmatic approach.

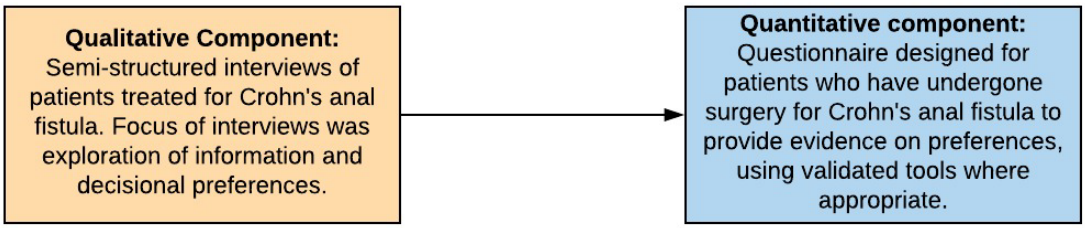

Figure 43 Design of mixed method study

15 Mixed Method I: Semi Structured Interviews - Patient experiences and preferences in receiving information on surgical interventions.

I was involved in study design, data collection and analysis. I prepared the manuscript with input from co-authors. Jack Marshall conducted interviews and supported analysis of data.

Oversight was provided by Georgina Jones, Alan Lobo and Steven Brown.

Permission to reproduce from co-authors has been obtained.

15.1 Background

The systematic review of surgical interventions did not identify a clear front running technique for the cure of Crohn's anal fistula. With the equivalence of outcomes, and subtle differences between interventions, selection of a procedure might be adjusted to account for patient preferences or values. This means that selection of a surgical procedure is a 'preference sensitive' decision[379].

The surveys of clinician preferences have given an indication of the treatments that tend to be offered to patients. The complementary data on patient information needs and preferences for this condition is not yet available. There are several ways to collect data from patients; qualitative interviewing is an approach that allows the generation of rich data that can be explored in a mixed-method study.

15.2 Interview based research

Qualitative research is an exploratory or hypothesis generating approach[380]. It assesses words and behaviours and the meaning behind them. In healthcare research, this commonly relates to the conduct of interviews and assessment of their content[381].

Interviews may be conducted in person or by telephone[256 321]. They may be designed to follow a strict protocol with no additional questions permitted (structured). Alternatively, they may provide a set of questions, but allow the interviewer scope to further investigate strands of interest arising during the investigation (semi-structured).

The content of interviews is typically transcribed and analysed. The approach to analysis can take several different forms[382 383]. It can focus upon language and how it is used (discourse analysis), interpretation to understand feelings and perceptions of events (phenomenological analysis). It can also be based more deeply in psychology research, with the interpretation of interviews within the context of existing theoretical models for example those describing grief processes or change models (grounded theory). Each of these has a setting in which it can be deployed.

15.3 Framework analysis

Framework analysis is a form of thematic analysis. In thematic analysis, transcripts of interviews or speech are analysed to identify themes. Themes may be proposed at the outset of the research project, or identified emergently during analysis. These themes can then be organised into over-arching or subthemes. Grouping of content is based upon themes only.

The same process is largely followed in Framework analysis, but data is coded on both a theme and case basis[384]. This allows generation of a coding matrix, permitting researchers to view content

according to both themes (what was said) and cases (who said what). This analytic approach was initially proposed for policy-based research, although has been used across healthcare.

15.4 Framework methodology

In brief, the framework methodology follows seven steps[383]:

1) Transcription of the interview. Verbatim transcription of the audio recording of an interview is standard practice. This transcription may be undertaken by the investigator who conducted the interview or by a researcher from their team. This allows familiarisation with the interview content. In some cases, this may be contracted to an outside service.
2) Familiarisation with the interview. Review of the interview transcript along with the audio recording and field notes allows the researcher to immerse themselves in the content of the interview, and to understand contextual content.
3) Coding. The research assesses the transcript line by line and codes any content within a phrase which might be important to any aspects of the research question.
4) Developing a working analytical framework. After coding 3-5 transcripts, the research team meets to discuss and agree a framework structure. This involves identification of over-arching (superordinate) themes, and sub- (subordinate) themes which address specific aspects of a theme.
5) Application of analytic framework. The refined analytic framework is then applied to the already coded transcripts, and to the remaining transcripts in a study.
6) Populating the framework matrix. The framework matrix is a summary table where each row represents a case, and each column represents a theme. The matrix is populated with appropriately coded text for each case and theme. This may be achieved using specialised computer software.

7) Interpreting data. The research team reviews the matrix to provide a narrative of the phenomenon under investigation.

15.5 Strengths and limitations of Framework Analysis

The main strength of framework analysis comes from the development of the analysis matrix[383]. The extraction of data into the framework facilitates the assessment of content presented in the participants own words and construction of a richer narrative than might be constructed from isolated themes. The systematic approach means that it can be used across teams with reproducible results[385].

The main limitation of framework analysis is the significant amount of time required to complete the analysis, especially where several different researchers are involved in coding. There is also the delay associated with the requisite training of researchers in the methodology[383 386].

15.6 Aim

To investigate informational preferences of patients related to surgical therapy of fistulating perianal Crohn's disease.

15.7 Method

This study received ethical approval from the Greater Manchester (South) NHS Research Ethics Committee (16/NW/0640) (Appendix N), and is reported in line with the Consolidated criteria for reporting qualitative research (COREQ) guidelines[387].

15.7.1 Research team and reflexivity

Interviews were carried out by JM or ML. JM was a male undergraduate medical student who undertook interviews as part of his Intercalated BMedSci studies. ML was a male clinical research fellow who undertook interviews as part of his PhD studies. ML has prior experience of conducting semi-structured research interviews. Both JM and ML undertook further interview training and feedback with GJ, a professor of health psychology. Interviewers were debriefed after initial interviews to ensure conduct of interviews was appropriate. Researchers established their relationship with participants at the point of recruitment, typically following a clinic appointment with another health professional. Where ML had reviewed the participant in a clinic appointment as part of routine care, JM undertook the interview. Participants were made aware of the clinical background of the interviewer, and of their interests in the topic. Reflexivity (the inherent bias carried by the conduct of the researcher in interviews or interpretation of transcripts) was addressed in two ways; interview training included efforts to avoid emotional reactions to responses and transcripts underwent dual review and coding by the investigators to address reflexivity related to interpretation. Transcripts were revisited later in the study to reassess findings in light of emerging themes.

15.7.2 Methodological Framework

A qualitative methodology was adopted using semi-structured interviews. Semi-structured interviews use a common framework or structure, but allow the researcher to explore ideas and concepts that arise through further prompts or questioning. A structured interview would allow only the questions

presented on the interview schedule. Qualitative methods were chosen to allow detailed exploration of patient experiences and preferences.

15.7.3 Participant Selection

The participant sample was selected through purposive sampling i.e sampling of the population to ensure variation amongst those interviewed by ensuring a mix of active and inactive fistula, and experience of different surgical procedures. Recruitment was targeted at biologic infusion clinics (nurse-led unit for ambulatory attendees receiving infusions of biologic therapy for Crohn's disease), and surgical-IBD clinics. Participants were eligible if they had undergone previous surgery for Crohn's anal fistula. Additional targeted recruitment was carried out during the study to balance the number of patients with a stoma against the number of patients treated with other surgical procedures as this group was under represented. Participants were identified through clinic attendance at one of two UK hospitals and approached following outpatient attendance. The approach included an introduction from one of the research team, and provision of an information leaflet with a tearable 'opt in' slip for return (Appendix O). When the patient indicated that they wished to participate, contact was made and a time for interview was agreed.

Participants were eligible to participate if they had undergone any surgical treatment for a Crohn's anal fistula at any point. If a potential participant did not have a conversational standard of English then they could not participate as the study was not funded to cover translator fees. Recruitment to the study ran from January 2017 to May 2018.

15.6.4 Setting

Research interviews were conducted in the education centre at Sheffield Teaching Hospitals, and the Clinical Research Facility at Blackpool Teaching Hospitals. The rooms selected were intended to be quiet and away from clinical areas.

As the interview might address sensitive issues, only the participant and interviewer were present during the interview. If a participant became distressed, the researcher would offer to suspend or terminate the interview and arrange for access to local IBD nurse specialists. Descriptors of participant age, sex, duration of Crohn's disease, prior fistula operations, and current fistula status were recorded.

15.6.5 Data Collection

An interview guide was prepared by ML and GJ based upon the previous reviews of the literature and with input from the research team (Appendix P). No pilot interviews were undertaken, although input from a patient representative was sought during the drafting of the interview guide. Each participant undertook a single interview, which was audio recorded. Supporting field notes were taken by the interviewer where appropriate. There is no consensus on the minimum number of interviews for adequate sampling in qualitative research[388]. As data saturation can occur with as few as twelve interviews[389], saturation was first assessed at this point, and then after each subsequent interview. Saturation was reached when five subsequent interviews did not reveal any new themes. Transcripts were not returned to participants for comment.

15.6.6 Data Analysis & Coding

Interviews were transcribed by their respective interviewer. Coding was undertaken independently by JM and ML using NVivo 11 Computer-Assisted Qualitative Data Analysis Software (QSR International, Australia). A screenshot of the NVivo coding interface is presented in appendix Q. Data analysis was undertaken using the framework methodology as described by Richie[384]. After five interviews, codes

were compared and discussed with the research team, and a coding framework was agreed. This framework was applied to subsequent transcripts. Participants did not provide feedback on the findings.

15.7 Results

A total of 17 people completed interviews, by which point saturation of themes was achieved. Of these, nine were male, 8 female and with a median age of 27 (range 19-71). Treatment experience included setons (thirteen cases), fistula plug (three patients), and stoma formation for fistula (four cases). Ten participants had an active fistula i.e. fistula with ongoing discharge requiring further treatment. Participants reported treatment experiences from four different hospitals, and ten different surgeons were named during interviews, showing a range of treatment experience. A summary of participant characteristics is shown in Table 30. Of those approached, 28 patients declined or did not contact the research team. No reasons were given. A sample transcript is presented in appendix R.

Case	Sex	Age (years)	Time since first fistula	Previous operations	Fistula status
I.1	M	19	15 years	Seton	Inactive
I.2	F	60	6 years	Seton	Active
I.3	F	45	14 years	Panproctocolectomy & ileoanal pouch	Inactive
I.4	M	23	9 years	Seton	Inactive
I.5	F	60	40 years	Seton, End Ileostomy	Active
I.6	M	25	7 years	Drainage of abscess	Active
I.7	F	26	7 years	Seton	Active
I.8	F	27	5 years	Seton, fistula plug, advancement flap	Active
I.9	M	56	20 years	Seton, fistula plug	Inactive
I.10	M	25	9 years	Seton, fistula plug,	Active
I.11	F	22	7 years	End Ileostomy	Inactive
I.12	M	31	1 year	Seton	Active
I.13	M	71	6 months	Seton, proctectomy	Inactive
I.14	M	22	6 months	Drainage of abscess, loop ileostomy	Inactive
I.15	F	24	3 years	EUA, seton, Loop colostomy	Active
I.16	M	67	15 years	EUA, seton	Active
I.17	F	35	10 years	Subtotal colectomy, temporary ileostomy, ileorectal anastomosis, EUA, drainage of abscess, seton	Active

Table 30 Summary of participant characteristics.

15.7.1 Coding hierarchy

The initial coding hierarchy contained four over-arching themes and 10 subthemes. These are summarised in table 31. Following discussion between the research team and following iterative review of all manuscripts, these were restructured into five over-arching themes: Experience of Crohn's disease, experience of receiving information, procedure specific comments, decision making and desired information. The final coding hierarchy, summary of themes and number of participants referencing them is shown in table 32. Saturation was assessed for following interview 12 and confirmed following interview 17. A graphic representation of themes and sub-themes is shown in figure 44.

Overarching theme	Sub-theme
Information	What the patient wants to know
	Information giving
	Information received
Living with a fistula	Impact on quality of life
	Fistula symptoms
Decision making	What factors affect decision making
	Patient involvement
	Shared decision making
Online health information	Patient use of internet
	Clinician views of online health information

Table 31 Initial proposed coding framework

Over-arching theme	Sub theme	Number of participants referencing subtheme (%)
Experience of Crohn's disease	Impact of disease	15 (88.2%)
	Quality of life	9 (52.9%)
	Effect of operation	12 (70.6%)
	Aftercare	10 (58.8%)
	Fistula expectations	9 (52.9%)
	Relationship with healthcare professionals	10 (58.8%)
Experience of receiving information	Delivery of information	8 (47.1%)
	Information from clinicians	15 (88.2%)
	The internet as an information source	15 (88.2%)
	Peer support	10 (58.8%)
	Written information	8 (47.1%)
	Conflicting information	4 (23.5%)
Procedure specific	Seton	12 (70.6%)
	Stoma	15 (88.2%)
Decision making	Trade-offs	14 (82.4%)
	Decision making preferences	15 (88.2%)
Desired information	Procedural information	9 (52.9%)
	Treatment goals	12 (70.6%)
	Sex and reproductive health	3 (17.6%)
	Aftercare	9 (52.9%)
	Delivery of information	8 (47.1%)

Table 32 Summary of emergent themes, subthemes and data saturation.

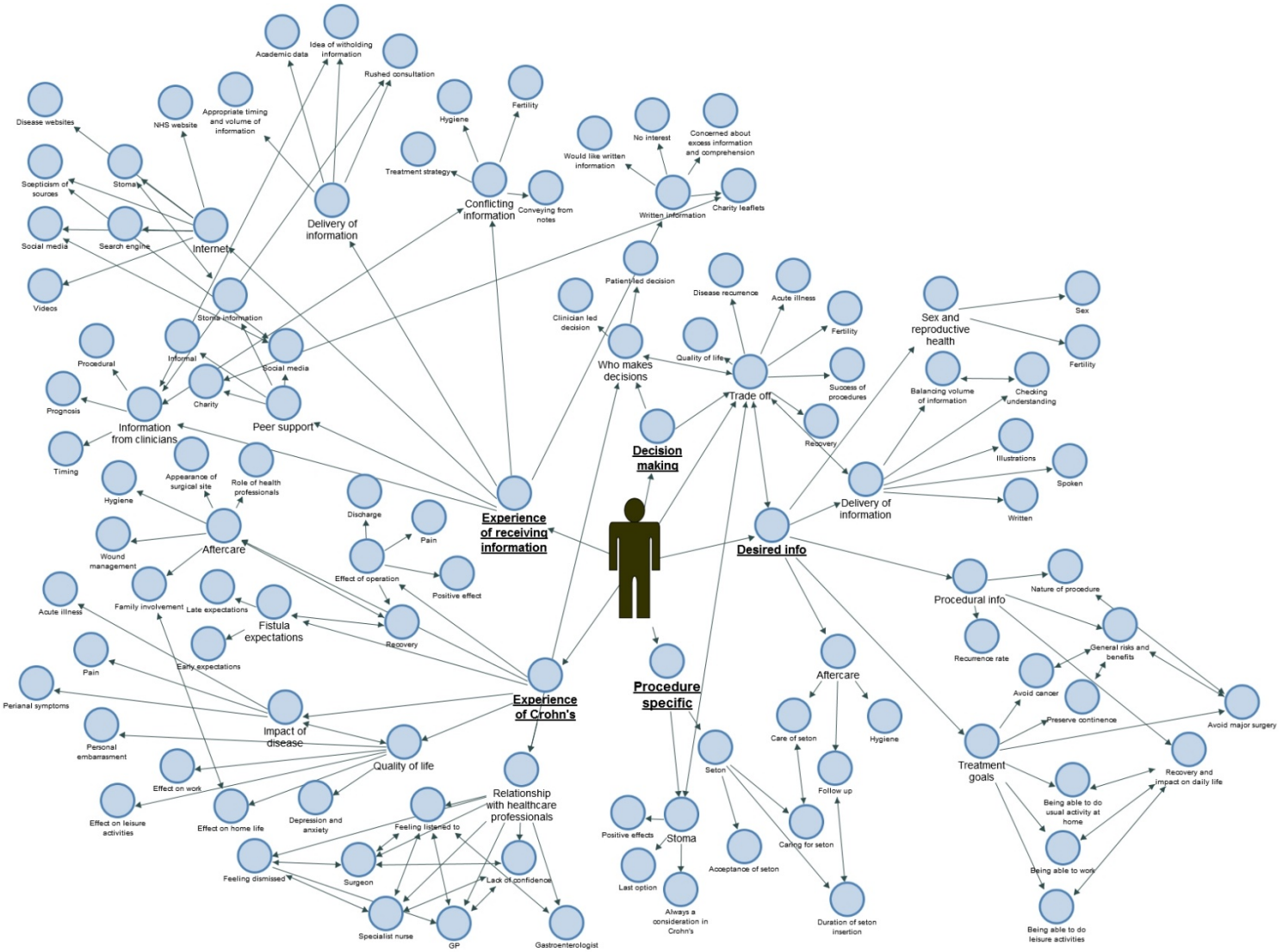

Figure 44 Concept map showing relationship of themes, sub-themes and third tier themes.

15.7.2 Experience of Crohn's disease

Six sub-themes were identified including impact of disease, quality of life, relationship with healthcare professionals, fistula expectations, effect of operation, and aftercare.

15.7.2.1 Impact of disease

All participants discussed their experience of Crohn's disease in general, and also specifically about their experience of fistulating disease. The experience was described in universally negative terms. This was often linked to aspects such as pain and the inability to undertake routine tasks.

> '… some of the nights I've had, when my bottom was bad, it was …honestly the pain was… it was terrible. Sitting on the toilet crying. And you shouldn't have to live your life like that should you?'
>
> I.14, M, Active fistula

15.7.2.2 Quality of life

The relationship between fistula and quality of life was explicitly mentioned by several participants. Both the condition and the drawn out investigative process were felt to have a negative impact on quality of life. Several participants discussed the odour related to discharge as having a significant negative impact on their quality of life as it affected their ability to go out in public and interact normally with others.

> '…it started to smell so it was like if I can smell it can other people smell it, I didn't wanna be near anyone in case it did.'
>
> I.1., M, Inactive fistula
>
> 'I'll suffer for another three months, but you just get used to living in this reduced state.'
>
> I.6., M, Active fistula
>
> 'Well, if I was in a queue in a shops or something, now and again I thought 'I can smell myself', and I'd walk away from the queue.'
>
> I.13. M, Inactive fistula

15.7.2.3 Effect of operation

Participants discussed their experiences of life after surgery. They reported experiences of pain which were worse than expected, and long recovery times, even after minor surgery.

> ‘I didn’t necessarily know it would maybe debilitate me that much for the period of time for recovery.’
>
> I.10, M, Active fistula
>
> ‘the first two weeks after it I thought I was dying. I’ve never been in so much pain’
>
> I.15, F, Active fistula

15.7.2.4 Aftercare

Aftercare was central to the experience of many participants. One aspect of this was what patients described as poor provision of information immediately following a procedure.

> ‘When I came out of theatre, all I know that I got these setons in and I didn’t know exactly, particularly what they were um you know I just, I were just sent home with them in and it was a bit frightening to be honest.’
>
> I.2, F, Active fistula

> ‘No. I wasn’t told anything when I was discharged. And, I was like…it was a cutting seton as well. So when I took the dressing off and looked in the mirror, I was like ‘Oh my god, there is a massive hole in my bum cheek’.
>
> I.15, F, Active fistula

15.7.2.5 Fistula expectations

Several participants discussed their expectations of fistula outcomes at the start of their experience. Across those interviewed, there was a tendency to desire a cure for fistula when it first appeared. Over time, many people accepted that as part of Crohn's disease, it was not a condition that could be cured, but could be managed.

> 'I thought there was a cure at first, so I was like 'ah so this is fine I don't care' and then they... explained more about it and I was like 'this is more serious than I thought'
>
> I.1., M, Inactive fistula

> 'I think that that is there focus when they come in, I want a cure, but you don't always cure, you can help you know and help it through life and living through life with it but you've got it and Crohns is a disease that isn't going to go away, not at this moment in time.'
>
> I.5, F, Active

15.7.2.6 Relationship with healthcare professionals

Both positive and negative relationships with healthcare professionals were described, and were often central to the patient experience of treatment and of receiving information. A number of patients reported dissatisfaction with aspects of their relationships with their surgeon. The varied opinions around clinician relationships seem to be related to patient opinions of treatment, whether they felt listened to by their clinician, and whether the clinician was able to offer advice or treatments which benefitted the patient.

‘In the end, um, I felt like I was being fobbed off to be honest…he washed his hands of me, he just said he was going to discharge me.’

I.2, F, Active fistula

‘The general care I got was kind of high and it maybe uh puts your trust more in what they're saying rather than being more critical of it.’

I.4, M, Inactive fistula

'The team of people who I can get hold of, who know me, who can explain things to me, who’ve looked after me with continuity, is the reason I don’t go anywhere else’

I.17, F, Active fistula

15.7.3 Experience of receiving information

Six subordinate themes were identified related to receiving information. These were information from clinicians, delivery of information, conflicting information, the internet as a source of information, peer support and written information.

15.7.3.1 Delivery of information

Many participants felt that the quality of counselling prior to surgery was poor, and could be delivered at a slower pace.

> ‘It just seems like everything is really rushed and they haven’t got time to really talk to you. They don’t actually sit down half of the time and it’s like duh, duh, duh, and they go into their offices, and it’s like…are we done?’
>
> I.5, F, Active fistula
>
> ‘It was quite rushed, and she sort of just gave me [leaflets] or whatever. I think I would have preferred someone to just sit down with me properly.’
>
> I.11, F, Inactive fistula

15.7.3.2 Information from clinicians

Information from clinicians typically focussed on short risks and outcomes of procedures and long-term outcomes of the condition.

> ‘At the time, that was sort of the thing that was most worrying to me…obviously I know it’s a small risk, of cutting your sphincter muscle…’
> I.6, M, Active fistula
>
> ‘Mr X said that he wants to take my seton out because it’s not working anymore, and was on about putting either a plug or a clip in. Try one of those he says, but there’s only a 50% chance that it works’
> I.7, F, Active fistula
>
> ‘I was always told it’s unlikely, well not unlikely, it’s never certain that a fistula is going to heal, and likewise, if someone has had fistulas from something like Crohn’s, it’s also likely that it recurs.’
> I.10, M, Active fistula

Two participants specifically mentioned a discussion of risk of incontinence prior to surgery, but other participants reported a focus on short term success and failure from surgical procedures.

15.7.3.3 The internet as a source of information

The internet was used by most participants to seek information on their condition and treatment options. Other information sources included discussion forums, written leaflets, and charity sources. Participants typically fell into those who found the internet useful, and those who did not.

'I looked on Google, and that made me even more scared.'

I.1, M, Inactive fistula

'I remember sitting in hospital, researching myself because I didn't get enough information….I would have liked to know more about the treatment itself.'

I.11, F, Inactive fistula

'On the stoma sites, a lot of people do Vlogs, so I've watched them before. There's some good ones that are helpful.'

I.15, F, Active fistula

15.7.3.4 Peer support

Peer support was often discussed as a way of finding out information which clinicians did not routinely offer. Internet peer support e.g. internet forums were typically considered to provide useful content. They also provided social support for participants as they reported feeling better after talking to others with similar problems.

> ‘You feel as if you’re not on your own, because other people are writing things.’
>
> I.2, F, Active fistula
>
> ‘Obviously, there’s forums and bits like that which you always seem to go to. People were great. Some people go…you get the odd horror story in here and there but you sort of expect [that].’
>
> I.6, M, Active fistula
>
> ‘I used the Crohn’s forum and there’s different sections for stuff. You can literally just click on one that’s about fistulas, and it will tell you loads of stuff. You can type in and message that I’d had one done, and can anyone offer some advices – loads of people come back and tell you stuff, it’s great.’
>
> I.7, F, Active fistula
>
> ‘I’m on so many support groups on Facebook…there’s so many people going through what I’m going through – it’s crazy.’
>
> I.15, F, Active fistula

15.7.3.5 Written information.

Written information, in the form of leaflets, was not seen as being a preferred format for delivery of information for many participants. It was felt to have a supporting role in the delivery of information.

> '[It's] secondary, supportive, rather than primary, because you can't ask questions of a piece of paper.'
>
> I.17, F, Active

15.7.3.6 Conflicting information

Participants reported receiving conflicting information from different sources. The areas where conflicting advice had been given around major implications of treatment decisions.

> 'I've seen different consultants, all lovely, but I felt like each person was telling me something different.'
>
> I.11, F, Inactive fistula
>
> 'Mr X tells me that it won't affect my fertility if I had the proctectomy. And when I went to [other hospital], they said it would massively affect me having children in the future.'
>
> I.15, F, Active fistula

15.7.4 Procedure specific comments

Two procedures had specific comments in the interviews. These were seton insertion, and stoma formation.

15.7.4.1 Seton insertion

The majority of participants specifically reported experiences of setons. These showed that setons generally improved symptoms, although participants did not like the experience.

> 'I've got this seton in and I feel fine, whereas before I hadn't got a seton in, but I felt horrific.'
>
> I.4, M, Inactive fistula
>
> 'Just having one with a seton in permanently is bearable'
>
> I.10, M, Active fistula
>
> 'I came out once and had a whole network of the things, and I couldn't figure out what was going where when and why. I was just desperate to get them out – they were horrid'
>
> I.17, F, Active fistula

Participants also expressed discomfort with the uncertainty related to the duration of seton placement.

> 'I had those setons in for about two years, and I remember thinking 'when are they coming out?'
>
> I.4, M, Inactive fistula
>
> 'I was told that they'd only need to be in there for a certain period of time, a certain number of weeks, then they could come out. I had some that were in for much longer!'
>
> I.17, F, Active fistula

15.7.4.2 Stoma formation

The demographics table shows that not all participants have direct experience of a stoma. Those who had discussed it with their surgeon had done so with it being considered an option of last resort. Opinions on stoma formation were both positive and negative. Both I.4 and I.17 had previously undergone temporary stoma formation and subsequent reversal for indications other than Crohn's disease in the past. Both expressed strong views on avoiding a stoma.

'I would see that as a last resort, I wouldn't want to have one'.

I.1, M, Inactive fistula

'I was reasonably happy to have it ….I was going through a 'no-life' situations, and I thought 'stoma bag can't be any worse than this is'….which as it's proving, it's not.'

I.13, M, Inactive fistula

15.7.5 Decision making

Two subthemes were identified: 'trade off' and 'who makes the decision'.

15.7.5.1 Trade off

Several participants alluded to trading off different aspects of treatment for different outcomes, referencing symptoms, quality of life, or repeated procedures as factors in their choices. Participants were typically willing to accept a procedure which limited disruption to their lives and achieved some symptomatic relief from the fistula compared to those which were intended to be curative but disruptive to life or associated with increased risks. Two participants had experienced medically refractory Crohn's disease and undergone stoma proctectomy or formation. Both indicated that trading-off a stoma for improved quality of life was worthwhile, despite the temporary impact on quality of life.

'I suppose I'd weigh up that against your success percentage and look at what suited me best. I obviously want the most successful treatment, but if it's going to be six months of to and fro between the hospital….'

I.6, M, Active fistula

'If…my quality of life was worse and that was a permanent state, then I would say yeah, the quality of life improvement would maybe be worth just having a stoma'

I.10, M, Active fistula

'I would guess I would probably opt for a less invasive procedure to start with and see how it goes. If it became really troublesome, we could do something more aggressive'.

I.17, F, Active fistula

15.7.5.2 Who makes the decision?

The process of decision-making was discussed by several participants. Several people indicated that they preferred a clinician-centred or clinician guided decision model. Others felt that they wanted a more active and decisive role in the process. Participants recognised the uncertainty associated with decisions, and this is perhaps why they willing to rely on clinician input.

'I'd take a professional opinion on that, I think. Take whatever the medical advice would say would be the best option for you'.

I.5, F, Active fistula

'I prefer for the doctor to be telling me what's best for me.'

I.16, M, Active fistula

'I like to be led by somebody who knows what they're on about. I like to make my own decision, but I like to be led in the right direction….as long as they're honest with me and lay all the information out, and not concentrating too much on worst and best. [Talk] about the middle ground where most people end up. I think I can make a pretty informed decision.'

I.9, M, Inactive fistula

'It's also been my choice as well – I'd say I've been quite involved in that'.

I.10, M, Inactive fistula

It was notable that many participants felt that they had not been offered a choice in the treatment of their fistula. They indicated that they felt that the surgical procedure on offer was the only option available to them. Some were aware of alternative options, but these were presented as an option if the proposed treatment failed.

‘They didn’t give me an option of what they were going to do. They were going to do this…but they didn’t go ‘there’s A,B,C and D’.’

I.6, M, Active fistula

‘They said they’d do whatever they felt was best if I was ok with that…’

I.7, F, Active fistula

‘They just give me one thing and say ‘We’ll try this’, so I’ve gone for that, not knowing there’s other possibilities.’

I.8, F, Active fistula

15.7.6 Desired information

Interviews explored the kind of information participants would like in order to make decisions about their care. This identified five sub themes; procedural information, treatment goals, sexual and reproductive health, aftercare, and delivery of information.

15.7.6.1 Procedural information

Participants broadly wanted to know about success and failure rates of fistula closure, and likelihood of fistula recurrence for specific procedures. They also wanted to know how likely it was that a treatment would improve their symptoms. There was a recognition that fistula can recur in the future, hence the focus on symptom control. Participants indicated that procedural information was widely covered by surgeons.

> 'It was useful knowing the percentages because I suppose you don't get your hopes as much then.'
>
> I.7, F, Active fistula
>
> 'Success rate is number one…what sort of percentage chance my surgery would succeed.'
>
> 'Because [recurrence] is sort of one thing you imagine…I don't have to worry about it, and then a few years down the line, you've got another one….is it worth actually going off and closing it at all?'
>
> I.10, M, Active fistula

15.7.6.2 Treatment goals

Participants discussed treatment objectives beyond fistula closure, including symptom improvement, and aspects related to daily activities and quality of life.

‘I think pain has to be number one. And the lack of itching or soreness.’

I.5, F, Active fistula

‘The success rate, probably followed by how invasive that procedure is….You don’t want to keep coming all the time. I’d rather go in and go ‘right, it should sort itself out now after a period of time’.

I.6, M, Active fistula

‘Recovery time. I want to know about aftercare and exactly what’s going to happen…..Speed and effectiveness really.’

I.14, M, Active fistula

‘I’d need to know that I can carry on doing the things that I do. I basically want to be able to sit on a bike seat for a start.’

I.16, M, Active Fistula

15.7.6.3 Sexual and reproductive health

Three participants (all female), raised concerns about the impact of treatments on sexual and reproductive health, and felt that this should be part of any discussion. During interviews with these participants, it was clear that information about fertility or sexual function had only been discussed because they had raised the topic.

‘They started mentioning fertility thing and I was like, oh, wow, wow, wow, what’s going on here?’

I.11, F, Inactive fistula

‘It obviously affects my sex life ‘cause it’s all closely linked isn’t it?’

‘Some people have said you can have children, some people have said you can’t so…’

I.15, F, Active fistula

‘I’m a female of child bearing age – is it going to have implications for that?’

I.17, F, Active fistula

15.7.6.4 Aftercare

Participants discussed the need for information about aftercare following treatment of their fistula.

> ‘The fact that they would always be draining and you would have to be wearing the pads.’
>
> I.5, F, Active fistula
>
> ‘If I was ever going for anything then [I’d ask] ‘What is your aftercare procedure?’
>
> I.6, M, Active fistula

15.7.6.5 Delivery of information

Several participants offered thoughts on the modality of sharing information. Many preferred a face to face discussion with a health care professional, typically a surgeon. They indicated that written information could be provided to take away and reinforce details from the consultation.

> ‘It’s just sitting down and taking the time….it would be helpful to give a leaflet…maybe even some pictures of stuff.’
>
> I.7, F, Active fistula
>
> 'Face to face, verbal. I like to ask a lot of questions, so to be able to have a dialogue has always been really useful.’
>
> I.17, F, Active fistula

15.8 Discussion

This study has explored patient experiences around receiving information and making decisions about surgery whilst being treated for Crohn's anal fistula. It suggests that information currently used to counsel patients before surgery on a fistula is not adequate in terms of format, delivery or content. It also demonstrates the significant negative effect of Crohn's anal fistula on quality of life across many domains, although the focus of the study is on how information was received.

15.8.1 Where do patients get information about treatment decisions?

Participants felt strongly that information about surgical treatments should be given verbally by their surgeon. They felt that the surgeon had the most appropriate knowledge to discuss treatments. Many patients also stated that satisfaction in their relationship with their surgeon was important when this information was being shared. The association between satisfaction and clinician relationship has previously been demonstrated in IBD[390].

The clinical encounter was not the only source of information for patients. In this study, participants accessed multiple sources for information about surgical treatments for Crohn's anal fistula. This is in keeping with the literature where patients use many different sources[253 390]. The use of internet forum is not a new finding, and, the reasons given for use of these websites are congruent with the literature[253]. Our review of internet based resources for patients undergoing surgery for Crohn's anal fistula found a limited number of resources, each of which discussed just one treatment. All sources achieved low scores using tools to assess decision support characteristics[125].

15.8.2 When should we give information?

In Elwyn's three talk model, the time to present options would be during the second phase[124]. Many participants felt uncomfortable with a discussion about a stoma at a point early in the disease process. Others felt that there was always a chance of a stoma when diagnosed with Crohn's disease and it was appropriate to have it as an option at any stage. Given that a shared decision paradigm requires

presentation of plausible options and elicitation of values, it should be appropriate to discuss all options prior to any planned procedure.

15.8.3 What should pre-operative information include?

Study participants expressed a list of informational items they would like to know when discussing a surgical treatment. These include items related to procedural conduct and high level outcomes of success and failure, impact of the procedure on quality of life and other functions, time needed to recover and aftercare considerations. These are summarised in figure 45. It is interesting that many patients were unable to recall the information shared with them during their consultations beyond the likelihood of success or failure of a treatment, and many expressed dissatisfaction with the amount of information given on non-technical features of procedures, including time to recover, impact on normal function, and in some cases sexual function. These experiences match with those reported in surveys of patients with IBD[390]. A study which included audio recordings of consultations about surgery for oesophago-gastric cancers found similar trends – surgeons focussed on technical factors and overall success (or mortality), whereas patients were more interested in time to recovery and impact on quality of life[391].

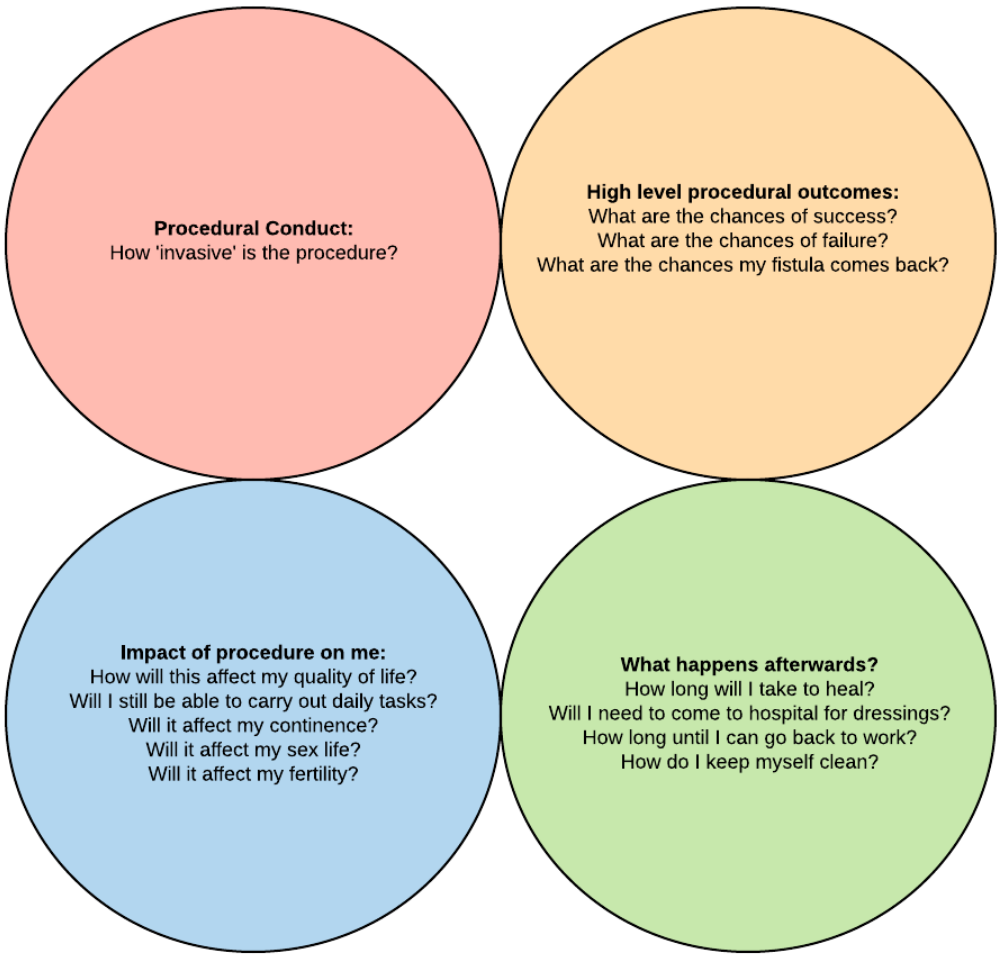

Figure 45 What do patients want to know when discussing fistula surgery?

15.8.4 Decision making

The interviews have clearly shown that patients can make trade-off decisions. Items which participants commonly valued included chance of procedure success, avoidance of repeat surgery, rapid return to normal function, avoidance of stoma formation. These were traded against costs including risk of procedure failure, risk of fistula recurrence, risk of stoma formation. Patients all reported that function or quality of life at the time of making a treatment decision could affect the balance of their decision. When discussing hypothetical choices, participants typically stated they would favour the least invasive and least disruptive intervention. This fits with the broader patterns seen in shared decision

making, where deployment of this approach tends to reduce the number of invasive tests or procedures[392].

Two previous studies have assessed trade-offs between treatment options in Crohn's disease and ulcerative colitis[326 393]. In order to understand the trade-off exercises, two key concepts are required: willingness to gamble, and willingness to trade. Willingness to gamble refers to the proportion of population who would risk a reduction of remaining life expectancy to avoid an alternate treatment. Willingness to trade describes the proportion of remaining life expectancy someone would risk to avoid an alternate treatment strategy[326 393]. In the study of preferences in Crohn's disease, patients were keen to avoid major surgery including proctectomy and permanent stoma formation[326]. There was a trend towards differing preferences in patients who had been managed surgically vs those who had been managed medically; for example 47% of patients treated medically would gamble to avoid a laparoscopic ileocolic resection compared to 29% of surgically managed patients. The same study found that surgeons and patients placed similar values on the options, but gastroenterologists had widely differing opinions. In a comparable study in ulcerative colitis, the same willingness to trade to avoid major surgery was seen, and trading preferences of gastroenterologists differed from the rest of the population[393]. Given the number of options available for treatment of Crohn's anal fistula, this exercise should be repeated in this setting.

15.8.5 Strengths and limitations

The main limitation of this study is that it was undertaken across just two NHS hospitals. This means that experiences reported reflect only those from these sites, and may not be directly extrapolated to those outside of these centres. As participants were recruited at different points in their treatment pathway, there is a risk of recall bias affecting the experience. There is also the risk of responder bias; this means that only those with strong positive or negative experiences of disease or treatment

participated, leading to reporting of only extreme experiences. The sample size was sufficient to reach saturation. This relatively low number may reflect the frequent use of prompts to seek relevant information[394].

This study benefits from broad participation demographics, including male and female participants of varying age, with a mix of active and inactive fistula, and a broad range of procedural experience, including stoma formation. This means that the expressed desires of information delivery and content might be extrapolated more broadly. This study has also been conducted with appropriate methodological oversight, dual review of interviews, and reported to meet existing guidelines[387].

15.8.6 Implications for practice

These interviews raise questions with direct relevance to clinical practice. One of these is: 'How do we discuss surgical treatments with patients?' The recent Montgomery ruling has implications around consent, specifically on discussion of options and recommendation of treatments taking into account patient values and preferences[117]. Study participants have indicated a range of factors of relevance to their decisions, the need for time to discuss with their surgeon, and the need for supporting literature or sources to use away from the clinical setting, prior to a major treatment decision being made. Current barriers to this approach include time, and the availability of relevant tools[122]. There is also a need to standardise the content of information, and this might be achieved through a core information set[395].

15.6 Conclusion

This study shows that information and counselling about surgical treatment options for Crohn's anal fistula does not meet patient needs.

16 Mixed Method II: Survey of patient experiences and preferences in receiving information on surgical interventions.

16.1 Background

Findings from a limited number of semi-structured interviews cannot be generalised to the wider population, although they might provide a framework to guide quantitative research. To test the findings of the interviews in a wider population, a survey of patients is an appropriate next study. This permits the quantification of reported findings and measurement of variables using validated tool. It is also possible to undertake statistical assessment of data to investigate underlying factors using methods such as principal component analysis.

16.2 Principal component analysis.

Principal component analysis (PCA) is a form of factor analysis and is often used in complex datasets with multiple variables[396]. The objective of PCA is to reduce the number of factors accounting for variation within a sample: a process of dimension reduction[397]. This means that a small number of factors associated with the highest amount of variability in a model can be used to predict behaviour. Principal component analysis does not mean that factors are discarded to reduce variables. Instead, new variables (components) are calculated as combinations of the measured factors. These new factors may represent unobserved or indirectly measured (latent) variables or constructs[396 398]. Each of these new components are independent of each other. Each of the components should have significant contribution from a handful of factors, and each factor should only account for significant variation in one component.

This is achieved by assessing the correlation of factors within a dataset. Correlation can be easily considered with a pair of data points, X and Y. It is possible that several factors will move in in the same direction with similar magnitude as they measure items that are similar or related. Each of these clusters of correlating factors could form a principal component. By including the Z axis, correlation can be undertaken along many different axes (multi-dimensional).

The variation between clusters can be further explored by changing the position of the axes in order to change the relationship of clusters in 3D space. This analysis may allow the same component to account significantly for variability across several factors. It is possible to adjust for this by undertaking rotation of the axis. Varimax is a rotational approach in which the axes are rotated in many dimensions to identify maximum differences in the weighting of components. This means that components have either large or small weighted values for each factor, and each component identifies with one variable only[397 398]. Several methods can be used to determine the number of factors to be extracted and which components are considered to contribute to each factor[397-399].

The underlying relationship is identified by the research team by identifying factors with higher weighting in each component. If these can be combined into a plausible single idea, this might explain the underlying concept. This degree of interpretation is a strength and a weakness of PCA[398].

Principal component analysis is an appropriate analysis to use in this study as it can be used to assess information which is considered important for patients to make a decision about surgical treatment. A reduction in items would be helpful for the development of a decision aid where space is limited, and excessive information is not helpful.

16.3 Aim

To survey of patients who have undergone recent surgery for Crohn's anal fistula to assess informational and decisional preferences.

16.4 Method

16.4.1 Item generation

Item generation was undertaken with reference to three sources: 1) semi-structured interviews, 2) expert patient panel, 3) Clinician panel and 4) summary review of relevant literature. A summary of included domains and themes is presented in table 34.

16.4.2 Semi-structured interviews

Themes identified from semi-structured interviews were reviewed by the research team and considered for relevance to the research question.

16.4.3 Expert patient panel

Patient input on the questionnaire design was solicited from members of the standing 'patient engagement' panel for the ENiGMA collaboration. This is panel involves patients who have been treated for Crohn's anal fistula. A representative from this group was asked to provide feedback on proposed areas of questioning, as well as phrasing of questions.

16.4.3 Clinician panel

The clinician panel included a colorectal surgeon and gastroenterologist with an interest in inflammatory bowel disease.

Domains identified for inclusion are summarised in table 33.

Domain	Theme	Source
Demographics	Age/Sex Ethnicity Duration of Crohn's disease Education level	Interviews Patient panel Clinician panel
Information source	Clinician Supportive information/other source How useful source was	Interviews Literature[400]
Information requirements	Items relevant to decision making Enough information received	Interviews Patient panel[401]
Decision making	Experienced decision-making style Preferred decision-making style	Interviews Literature[390]
Decision satisfaction	How patient feels about operation	Interviews Patient panel Clinician panel Literature[401]
Preferred information format	Mode of delivery Information content/presentation	Interviews Patient panel

Table 33 Domains and themes identified for inclusion in the questionnaire.

The research team collated these themes and proposed a set of fields to include in the study:

Demographics

- Age
- Sex
- Ethnicity
- Time since Crohn's disease was diagnosed
- Last operation for fistula

Information used before surgical treatment

- Sources used (aside from hospital team)
- Important items when discussing surgery

Decision making about surgery

- Was a choice offered
- How was the decision made
- Preferred decision-making style

Context about decision

- Was sufficient information provided
- Preferred people to discuss treatment with
- Regret about treatment decision

Preferred information format

- How should information be delivered?
- Do you have internet access?
- How should data be presented?

16.4.4 Identification of validated measures

Review of the literature identified two relevant measures; Control Preferences Scale (CPS) and Decisional Regret Score (DRS).

16.4.4.1 Control Preferences Scale

The control preference scale was developed in 1997 as a way of assessing the locus of control in treatment decision making[402]. This is a five-point scale which moves from decisions undertaken entirely by the patient to decisions taken entirely by the doctor, with varying degrees of input from each party along the scale (figure 46). It has been used and validated across several healthcare settings[403-405]. Whilst CPS is a broadly accepted tool, it is important to consider that it is based upon qualitative data from the 1970s. The surrounding context has changed significantly since that time[406]. There is now a cultural shift away from decisions being taken by the treating physician[122]. Patients have access to information through the internet, changing the balance of knowledge/insight around decision-making[400]. There are also many more treatment options available for fistula compared to the 1970s, and this may also affect decision making. The key advantages of the CPS are that it is short, reliable, and is widely used and understood by researchers.

I made the final selection about which treatment I had
I made the final selection of my treatment after I had seriously considered my doctor/nurse's opinion
My doctor/nurse and I shared the responsibility for deciding which treatment was best for me.
My doctor/nurse made the final decision about which treatment was used, but seriously considered my opinion.
My doctor/nurse made all the decisions regarding my treatment.

Figure 46 Control preference scale components

16.4.4.2 Decisional Regret Score

Decisional regret score was first presented in 2003[407]. This is a five-item score has statements addressing regret about a decision. Each item is rated using a five-point Likert scale ranging from strongly disagree to strongly agree (figure 47). Each point on the is attached to a score ranging from 1-5. Items 1,3 & 5 frame the decision in a positive light, and items 2&4 address potential harm from the decision. Scoring of items 2&4 are reversed. The score for each component is calculated by subtracting one from the score attached to the Likert scale, and multiplying the result by 25. The score is averaged across the five items. A score of 0 means no decision regret, and 100 means high decision regret. For a valid score to be calculated, each item must have a response[408]. Decision regret has been measured in many healthcare settings[409], and the tool has been shown to be reliable[408].

It was the right decision
I regret the choice that I made
I would go for the same choice if I had to do it over again
The choice did me a lot of harm
The choice was a wise one

Figure 47 Decision regret scale components

16.4.4.3 Selection of other measures

As no other validated measures could be found, measures were developed for this questionnaire. Respondent sex was presented using a tick box of male/female/other/prefer not to answer. Age and time since diagnosis of Crohn's disease were left as free text responses to allow continuous data to be entered. Ethnicity was defined using headline descriptors recommended by the Office for National Statistics[410]. Highest level of education was presented as a select one tick-box response.

Information sources used was populated using data from interviews, and respondents asked to tick each item used. Desired information was populated from interviews, and respondents asked to rate the importance of each item using a nine-point Likert scale. A nine point scale was selected as this offers a balance of reliability, ability to discriminate, and ease of use for respondents[411].

A three-item tick box (yes, no, not sure) was used to assess whether the respondent was offered a choice of operations. A similar three item tick box was used to assess whether the respondent felt they had enough information.

A list of potential sources for verbal sharing of information was populated from interview items, and a tick all that apply option presented. A similar list was presented for the list of potential sources for information, and presentation of information. Five-point scales were used for access to internet and whether an internet based resource would be used.

16.4.5 Questionnaire pre-pilot

The questionnaire was subjected to iterative review by the research team and supporting panels. The group ensured revision of questions to be neutral in form, and that all pertinent response items were presented.

16.4.6 Considerations within Total Survey Error framework

A summary of design considerations within the total study error framework are presented in Table 34.

Domain	Subdomain	How addressed in this study
Respondent selection	Sample size	Appropriate sample size estimated with reference to Surgical Workload and Outcomes Reporting Database. Trade-off in power for attainable sample size made.
	Sample coverage	Geographic spread of participating centres identified, including teaching hospital and district general hospitals, and those in the north and south of England.
	Non-response at unit level	Questionnaires could be distributed by post, or when a potential participant was identified in clinic.
Response accuracy	Non-response at item level	Clear rubric developed through pilot phase and anonymity in response to encourage responses which may not match practice norms. Limited length of questionnaire to avoid fatigue.
	Measurement error due to respondents	Anonymity in response to encourage responses which may not match practice norms. Limited length of questionnaire to avoid fatigue.
	Measurement error due to interviewers	N/A
Survey administration	Post-survey error	Administrative plans for handling data made. Included recording of first response only if multiple responses given to single response question.
	Mode error	Anonymous paper-based survey selected as considered more likely to be completed than web survey.
	Comparison error	No comparisons planned.

Table 34 Study considerations with reference to Total Study Error framework.

16.4.7 Ethical approval

Ethical approval was secured from the London-Westminster REC (reference 17/LO/1446) (appendix S). Health Research Authority approval was secured prior to commencement of the study.

16.4.8 Eligibility criteria

Eligibility criteria for participation in the study was set as a patient who had undergone any surgery for Crohn's anal fistula at the participating institution within the preceding 12 months.

16.4.9 Setting

Participating hospitals were identified through the ENiGMA network, and through regional research networks. The sites identified through the ENiGMA network were primarily teaching hospitals, and those through research networks were all

16.4.10 Questionnaire validation

Face validity was assessed by in a focus group. Potential participants were those who had undergone surgery for Crohn's anal fistula at Sheffield Teaching Hospitals within the preceding six months. Participants were approached through clinic appointments and further information provided if requested. The focus group was held in a non-clinical area of the Royal Hallamshire Hospital at a mutually convenient time for participants and was planned to last for 1 hour.

Five people agreed to participate in the focus group at clinic and at follow-up telephone call. Shortly before the focus group, two participants withdrew for work-related reasons. This left three participants in the focus group. The characteristics of this group are presented in table 35.

ID	Sex	Age	Last operation
FG01	F	58	Loop colostomy
FG02	M	27	Seton
FG03	M	25	Seton

Table 35 Focus group characteristics

The focus group was presented with the questionnaire and asked to complete it in silence, annotating questions as they went. All participants completed the questionnaire within 10 minutes. Each question was discussed in order, with participants invited to offer comment and feedback on wording of question or response items, as well as presentation of items. The focus group indicated that they felt the questions asked had face validity. Participants did not identify any questions as irrelevant to the scenarios under discussion, providing a form of content validity. Minor amendments were suggested and agreed by the focus group and incorporated as shown in figure 48. The revised questionnaire was reviewed by the research team. The final version of the participant invitation letter and questionnaire is presented in appendix T and U respectively.

Participants were also asked to comment on any questions which were not relevant to the scenarios under discussion, providing a form of content validity. Written and verbal feedback was collated and presented to the research team. Criterion validity was not assessed as there were no related validated questionnaires. Construct validity was not assessed as the questionnaire did not assess abstract concepts (table 36).

Section 1:

- No change

Section 2:

- Add column to table of sources used to allow patients to rate how useful a source was. Use nine-point Likert scale used elsewhere.
- Include Wikipedia as an information source
- Change wording of question on information items to be hypothetical.
- Add items on 'impact on sitting' and 'impact on sexual activity' (both identified from interviews)

Section 3:

- Change the word 'about' to 'of' in the first question in this section
- Change the order of the control preference questions to record 'what happened' first, followed by 'desired outcome'.
- Addition of support group as option for information source.

Section 4:

- Add 'not applicable' to question one.
- Include rubric of 'tick all that are relevant' in second question.

Section 5:

- Add support group as an information source
- Change smiley face image to stick people
- Labels on bar chart should be exchanged for accuracy.

Figure 48 Changes recommended by focus group

Type of validity	How assessed in this study	Reason
Face validity	Verbal feedback from steering group and feedback from focus group.	
Content validity	Informally assessed by steering group which included experts in the field.	
Construct validity	Not assessed.	No relevant validated questionnaires identified.
Criterion validity	Not assessed.	No abstract concepts assessed.

Table 36 Summary of validity assessment in questionnaire

16.4.11 Questionnaire reliability

Test- retest reliability was considered as an option for this study. The research team were concerned that there was a limited pool of potential participants with the condition and achieving a sufficient number for retesting might be a significant challenge. The reliability of measures such as CPS and DRS are already known. Intra-class correlation was assessed for the 9-point scales related to importance of information to decision making (table 37).

Type of reliability	How assessed in this study	Reason
Test-retest (stability)	Not assessed	Access to participant pool limited, and patients may undergo multiple procedures in a short period of time.
Alternate form (equivalence)	Not assessed	Rewording of questions and scales would require generation of a significant question bank, outwith resource of the study.
Internal consistency	Assessed for 9-point scales of preferred information only.	Validated tools used have well documented consistency and reliability.

Table 37 Summary of reliability assessment in questionnaire

16.4.12 Data capture

Potential participants were identified by the participating hospital and according to the eligibility criteria. Participants were sent a copy of the questionnaire, along with a cover letter explaining the study, and a prepaid envelope for return of questionnaire. Questionnaires were returned to the research team and entered into a REDCap database[286]. Decision regret was only entered where responses to all five items were available. If a respondent ticked multiple boxes where only one was required, the first item encountered on the scale (either vertically or horizontally as appropriate) was entered.

16.4.13 Sample size calculation

The surgical workload and outcomes database estimates that approximately 1000 operations are performed each year for Crohn's anal fistula. The research team estimated that approximately 200 of these were likely to be repeat procedures. This means that 86 responses are required to achieve a 10% margin of error with a 95% confidence interval. To facilitate PCA, a minimum of 5 responses per information item was required, meaning a minimum of 75 responses was need. The response rate was potentially as low as 39%[412] therefore a minimum of 225 questionnaires had to be distributed to potential participants.

16.4.14 Statistical analysis

Descriptive statistics were reported for frequencies with median or mean and either standard deviation or interquartile range presented as appropriate. Correlation between continuous variables was assessed using Spearman's correlation. Comparisons across groups were performed using analysis of variation (ANOVA) or Kruskal-Wallis tests as appropriate.

Principal component analysis of importance of factors to decision making was conducted using SPSS version 24 (IBM, Armonk, NY). The dataset was first checked for adequacy of sampling using the Kaiser-Meyer-Olkin test. The dataset was checked for sphericity (i.e. whether it contains sufficient variation to permit PCA) using Bartlett's test. Following initial tests, a correlation matrix was constructed. Communalities of factors were assessed to identify and remove any factors with values of <0.6. PCA was conducted using a varimax orthogonal rotation matrix. Factor reduction was undertaken using the Eigenvalue method, where factors with Eigenvalue <1 were removed. The loading of remaining factors was assessed. A loading value cut-off of 0.45 was selected as it is associated with 'good' discrimination between trivial and non-trivial factors[399]. The resulting factors and components were assessed by the research team for face validity of the construct. Where there was cross loading of a

factor across two components, each component was reviewed to identify the best fit for the factor. Internal consistency of each factor was assessed using Cronbach's alpha.

16.5 Results

16.5.1 Centre level responses

Ten sites participated in the study and distributed 220 questionnaires. A total of 92 responses were received giving a response rate of 41.8%. A summary of number of responses by participating site are presented in table 38.

	Sent	Returned	Response rate
Nottingham	26	7	26.9%
Cambridge	31	12	38.7%
Sheffield	19	12	63.2%
Doncaster	17	5	29.4%
Guys & St Thomas'	45	18	40%
Manchester	22	7	31.2%
Blackpool	7	4	57.1%
Oxford	20	7	35.0%
Birmingham	24	18	75.0%
Royal Devon & Exeter	9	2	22.2%
Overall	**220**	**92**	**41.8%**

Table 38 Questionnaire response by site.

16.5.2 Respondent demographics

The characteristics of respondents are shown in table 39. A broad demographic was captured with an approximately even split by sex, a wide age range and duration of Crohn's disease. There was also a

range of respondents according to educational level, ethnicity, and most recent operation on their fistula.

16.5.3 Reliability

Intra-class correlation of Likert responses showed high consistency (mean ICC 0.887, 95% C.I. 0.848-0.920).

	Frequency	Percentage
Sex		
Male	44	47.8
Female	48	52.2
Ethnicity		
Asian (British, Indian or Pakistani)	8	8.7
Black (British, African or Caribbean)	5	5.4
White British	68	73.9
Mixed or multiple heritage	5	5.4
Other	4	4.3
Prefer not to say	1	1.1
Level of highest qualification		
None	7	7.6
GCSE	23	25.0
A-level	22	23.9
Bachelor's degree	23	25.0
Higher degree e.g. MSc/PhD	12	13.0
Other	3	3.3
Last operation for fistula		
Examination under anaesthesia only	13	14.1
Seton insertion	54	58.7
Advancement flap	2	2.2
Fistula plug	6	6.5
Proctectomy	3	3.3
Diverting stoma	5	5.4
Not sure	4	4.3
Other	5	5.4
	Median	**Range**
Age (years)	42	19-87
Duration of disease (years)	8	0.08-37

Table 39 Characteristics of respondents

16.5.4 Sources of information used

Respondents were asked to report whether they were helped to make decisions by talking to surgeons, gastroenterologists or nurse specialists in clinic settings. Surgeons were helpful to 74 (80.4%) respondents, gastroenterologists to 58 (63.0%) respondents, and Nurse specialists to 46 (50.0%) respondents. The most frequent sources used to gather information aside from clinicians were leaflets from the treating hospital (43.5%) and the patient's GP (41.3%) (table 40). Friends and family had the highest median reported helpfulness score of 8, although GP, online video, NHS choices and hospital leaflets all achieved a score of 7. The range of these ratings was wide (figure 49).

	Number who used source	Percentage who used source
GP	38	41.3
Internet forum/chatroom	36	39.1
Social media	17	18.5
Wikipedia	18	19.6
Online videos	19	20.7
Charity Websites	17	18.5
NHS Choices	29	31.5
Leaflets from hospital	40	43.5
Friends or family	16	17.4

Table 40 Proportion of patients accessing different information sources.

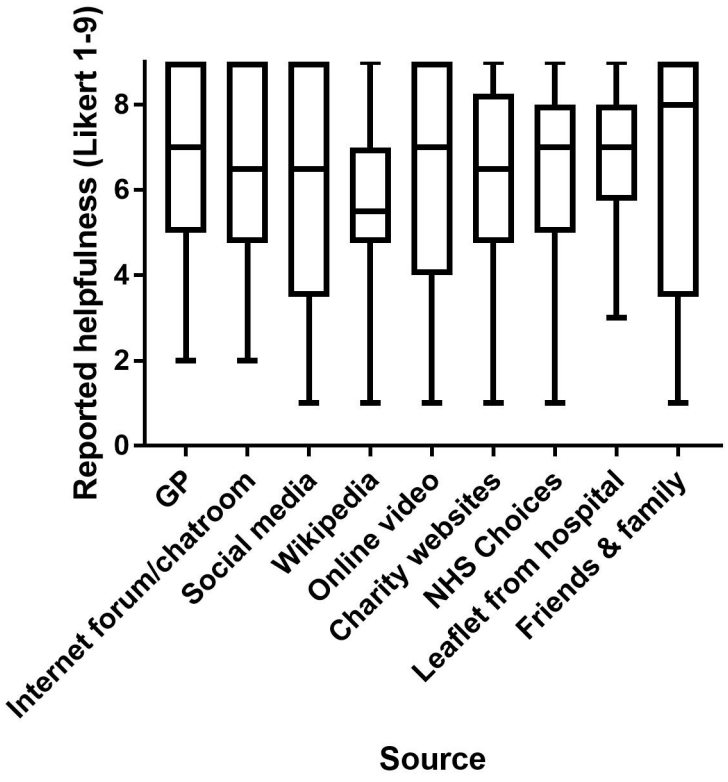

Figure 49 Respondent rating of helpfulness of different information sources.

Box and whisker plot showing median and range of values

16.5.5 Desired information

Respondents indicated the importance of items using a 9-point Likert scale. All items were felt to be important with all median ratings at 7 or above (Table 41).

	Number of responses	Median rating	Interquartile range
How long will I stay in hospital?	86	8	6-9
Will the treatment close the fistula?	85	9	8-9
The risks of the operation	88	9	8-9
How painful is the operation?	86	8	5-9
How invasive is the operation?	87	8	6-9
Will I need wound care when I go home?	88	8	6-9
Will I need to attend my GP after my operation?	85	7	5-9
Will I need to attend hospital frequently after my operation?	86	8	6-9
Will I need further surgery?	89	9	7-9
Will the treatment stop discharge?	87	9	8-9
Will the treatment affect my continence?	88	9	9-9
Will the treatment affect my ability to work?	88	9	7-9
Will the treatment affect my ability to sit down?	87	9	8-9
Will the treatment affect sexual activity?	88	8.5	7-9
Will I still need to take medications for the fistula?	86	8	6-9

Table 41 Summary of importance of information items when discussion treatments.

These values underwent factor analysis using Principal Component Analysis. Data was tested for appropriateness for this form of analysis. Kaiser-Meyer-Olkin (KMO) test for sampling of adequacy was 0.811, showing good sampling. Kaiser-Meyer-Olkin (KMO) assesses the proportion of variance within the dataset that might be due to underlying factors or co-variance; the higher the number, the more likely it is that the data is appropriate for a factor analysis methodology. Bartlett's test confirmed

sphericity of data i.e. that data and variables were summarised in such a way that variables can be summarised into fewer factors($p<0.001$). On first assessment of communalities, 10 items had communality values <0.6. These were excluded from the analysis, and communalities were recalculated. In this second round of extractions, Kaiser-Meyer-Olkin value was 0.781 showing adequate sampling and Bartlett's test for sphericity remained significant ($p<0.001$) (Table 42)

	Initial	Communality 1	Communality 2
Length of stay	1.000	.490	-
Will treatment close fistula	1.000	.442	-
Risks of procedure	1.000	.663	0.750
How painful procedure is	1.000	.782	0.787
How invasive procedure is	1.000	.753	0.779
Need help with wound at home	1.000	.638	0.734
Need to attend GP after surgery	1.000	.781	0.840
Need to attend hospital after surgery	1.000	.741	0.768
Need for further surgery	1.000	.542	-
Will treatment stop discharge	1.000	.710	0.750
Effect on continence	1.000	.772	0.817
Effect on work	1.000	.575	-
Effect on sitting	1.000	.697	0.705
Effect on sexual activity	1.000	.451	-
Need for future medications	1.000	.524	-

Table 42 Communalities of factors included in principal component analysis.

Assessment of Eigenvalues identified three components with values >1 (figure 50), accounting for 76.9% of variability (Table 44. Eigenvalues denote the spread of data across an imaginary line of correlation for data pairs. The more spread out the datapoints are along this line, the better the discriminatory function. Therefore Eigenvalues >1 are retained for their ability to discriminate.

Total Variance Explained

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings	
	Total	% of Variance	Cumulative %	Total	% of Variance
1	4.158	46.198	46.198	4.158	46.198
2	1.673	18.591	64.789	1.673	18.591
3	1.099	12.207	76.996	1.099	12.207
4	.537	5.965	82.961		
5	.430	4.776	87.737		
6	.356	3.956	91.693		
7	.304	3.383	95.076		
8	.277	3.079	98.155		
9	.166	1.845	100.000		

Table 43 Table describing total variance of values in principal component analysis

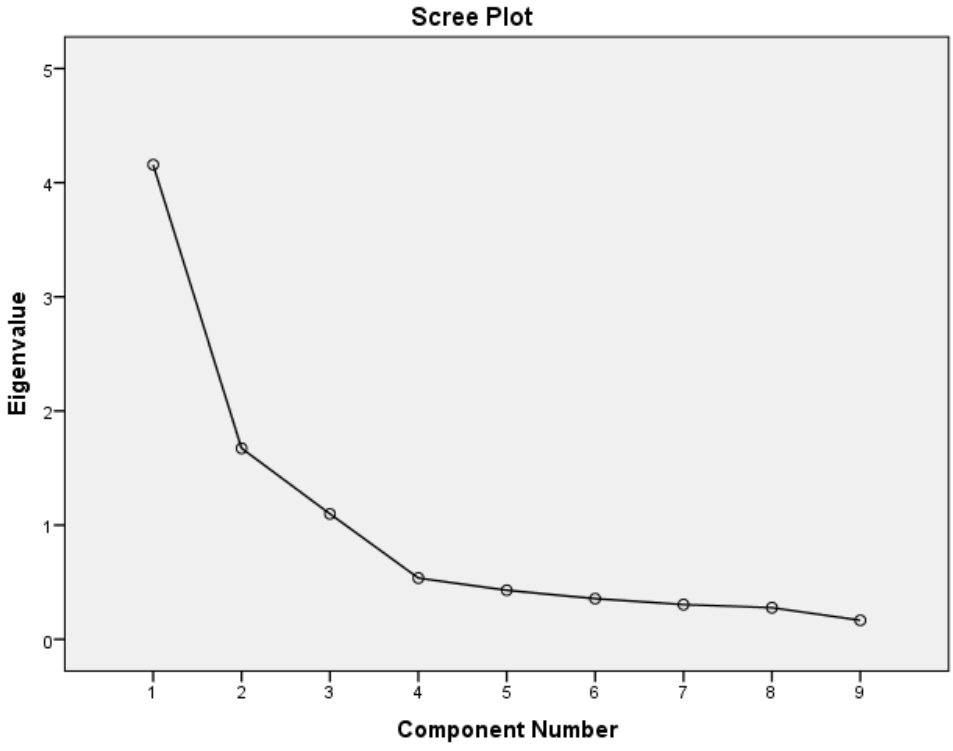

Figure 50 Scree plot of Eigenvalues.

Demonstrates that components 1-3 have Eigenvalues>1

In component 1, wound care, including attendance at general practice and hospital following surgery were heavily weighted (Table 44). This fits with a theme of 'Wound and aftercare'. Procedure related pain was weighted >0.450, but also cross-loaded with component three, where it was conceptually a better fit.

For component 2, effect of treatment on discharge, continence and sitting were weighted >0.450. This may reflect the effect of treatment on perianal symptoms.

For component 3, risks of procedure, procedure related pain, and invasiveness of procedure were weighted >0.450. This may reflect the severity of the procedure.

	Component		
	1: Wound and immediate aftercare	2: Effect on perianal region	3: Severity of procedure
Risks of procedure	.078	.156	.848
How painful procedure is	.656	.033	.596
How invasive procedure is	.254	.050	.844
Need help with wound at home	.744	.370	.208
Need to attend GP after surgery	.905	.094	.106
Need to attend hospital after surgery	.839	.195	.160
Will treatment stop discharge	.125	.836	.190
Effect on continence	.083	.899	-.044
Effect on sitting	.301	.773	.128

Table 44 Weighted factors associated with components in PCA.

Highlighted components are those exceeding cut off of 0.450.

Reliability was calculated for each of these components. Corrected item correlation was >0.5 for all scale items. Cronbach's alpha showed good correlation of items in all components (Table 45).

Component	Scale item	Corrected item total correlation	Cronbach's alpha
Wound and immediate aftercare	Need help with wound at home	.707	0.859
	Need to attend GP after surgery	.801	
	Need to attend hospital after surgery	.704	
Effect on perianal region	Will treatment stop discharge	.575	0.793
	Effect on continence	.729	
	Effect on sitting	.649	
Severity of procedure	Risks of procedure	.569	0.788
	How painful procedure is	.640	
	How invasive procedure is	.701	

Table 45 Summary of scale reliability for principal component analysis.

16.5.6 Choice and CPS profile

Respondents stated that 34 (40.2%) had been offered a choice of operation, 46 (50.0%) were not offered a choice of operation, and 9 (9.8%) were not sure if they were offered a choice. Sixty-four (69.6%) respondents felt they had enough information to support decision making; 22 (23.9%) did not feel they had enough information and 6 (6.5%) respondents responded 'not applicable' as they did not feel they made a decision.

Respondents reported that decisions were made by doctors entirely in 22.8% cases, or with patient input in 13.0% cases. The decision was shared in 32.6% cases. In contrast, the preferred locus of control for respondents was closer to the patient with 45.7% desiring shared responsibility for decisions, 17.4% wanting the doctor to make the decision with their wishes in mind, and 29.3% wanting to make the decision with the doctor's input. The difference between actual and preferred decision making was statistically significant (χ^2 $p<0.001$). This is shown in figure 51.

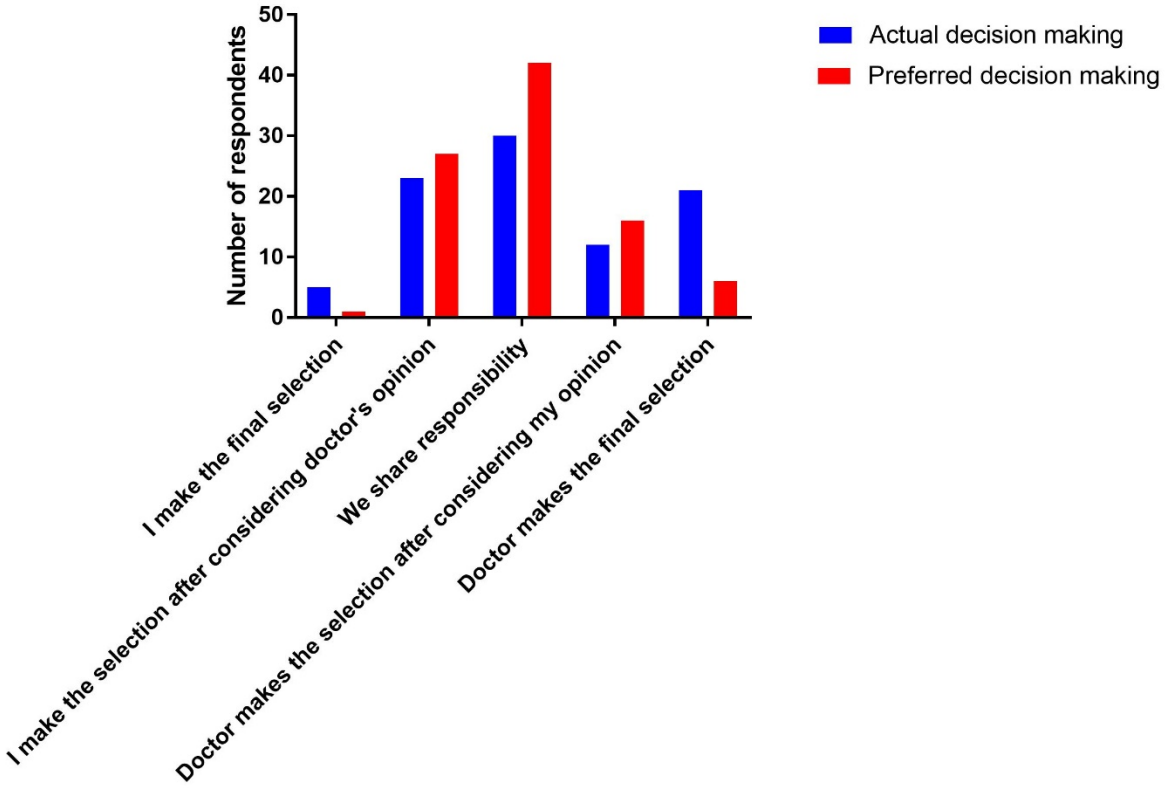

Figure 51 Differences between experienced and preferred decision making about last operation reported using control preference scale categories.

Demonstrates trend towards difference in experienced vs preferred decision making styles (p=0.054, two-way ANOVA).

16.5.7 Decisional regret

Decisional regret was assessed across the group 74 complete responses were received. The median decision regret score was 17.2 (range 5.6-33.3). There was no significant difference in the reported decision regret by operation (ANOVA, p=0.54) (table 46 & figure 52), or who made the decision for surgery (Kruskall-Wallis, p=0.14). Both increasing age and increasing duration of disease were associated with increased levels of decisional regret (Spearman r 0.935, p<0.001 and 0.790, p<0.001 respectively). Spearman correlation between last treatment decision according to control preference scale showed that decision regret decreased as the decision moved closer to the clinician (Spearman r = -0.241, p=0.025) (figure 53). This association was the same as that with decision maker and age, with younger patients reporting a more clinician centred decision making process (Spearman r = -0.241, p=0.025).

Last operation	Number of respondents	Median decisional regret score	Range
Examination under anaesthesia only	12	16.5	5.6-31.3
Seton insertion	43	13.7	7.0-31.3
Advancement flap	2	20.4	19.3-21.5
Fistula plug	5	19.4	9.6-29.0
Proctectomy	1	20.7	-
Diverting stoma	3	24	21.3-24
Not sure	3	16.3	10.6-27.5
Other	5	11	8.3-17

Table 46 Decisional regret according to last operation.

The lowest possible score is 0 (no regret) and the maximum score is 100 (maximum regret)

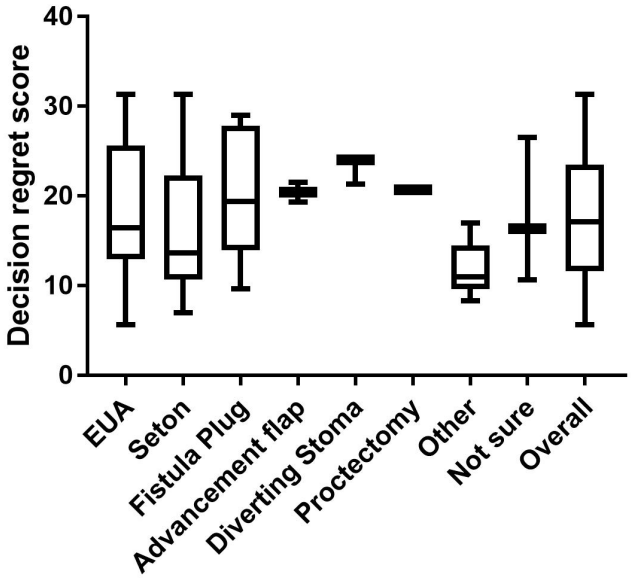

Figure 52 Decisional regret according to last operation

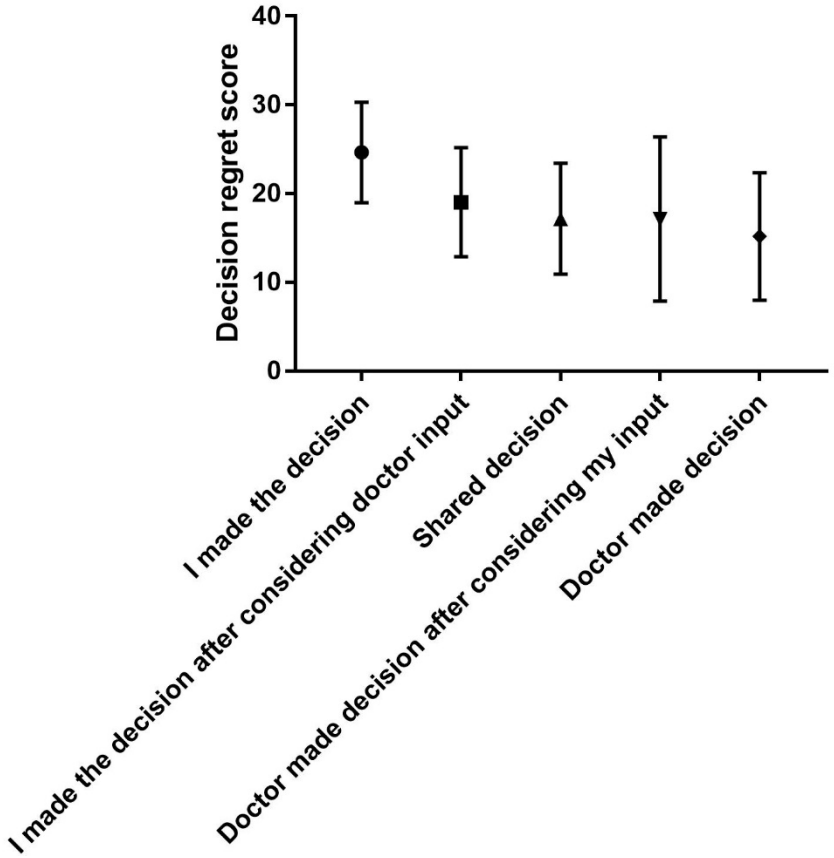

Figure 53 Decision regret according to decision making process.

Shows association between decreasing regret and increasing clinician input

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16.5.8 Preferred information format

The preferred format for sharing of information to support decision making was from the surgeon 80/92 (87.0%), and booklet 58/92 (63.0%). Nurse specialists may also have a role to play for 43/92 (46.7%). Other resources scored much lower in terms of preference (table 47).

	Number who would like resource	Percentage of respondents
Booklet	58	63.0%
DVD	21	22.8%
Patients	32	34.8%
Interactive website	29	31.5%
Webpage	34	37.0%
Surgeon	80	87.0%
Nurse	43	46.7%
Don't want	0	-
Support group	8	8.7%
Not sure	4	4.3%

Table 47 Desired information format

16.6 Discussion

This study has two main findings. Firstly, patients use a range of information sources when considering surgery for Crohn's anal fistula. Secondly, there are specific items of information that will help patients to make treatment decisions. The study suggests that patients would prefer to make decisions in a more shared manner than occurs at present, although this was not statistically significant.

16.6.1 Findings in context of literature

The finding that a range of information sources are used is not novel[253 400]. This study does provide an estimate of how useful patients consider the different sources, although this is limited by the sample size. In context, this study tells us that patients are likely to prefer information being shared directly by the surgeon and supported by a written information leaflet.

In keeping with the wider cultural shift, respondents tended to favour control preferences that involved a sharing of decision responsibility between patient and clinician[123]. This was in contrast to the experienced decision-making style, which tended towards clinician centred in many cases.

Decision regret has been recorded in one previous study in Crohn's disease in a small cohort undergoing a single procedure: Video Assisted Anal Fistula Treatment, (VAAFT)[413]. Unfortunately this has not been calculated as described by the user manual[408], and instead proportion of patients indicating each response item have been reported. Decisional regret has been used across other surgical conditions[414 415] and should be investigated further in Crohn's disease. In a condition where healing is rare, more patient focussed measures may be of greater help to distinguish 'good' treatments.

16.6.2 Strengths and limitations

The main strength of this study arises from its wide geographical sampling of respondents. This has ensured a mix of age, sex and ethnicity that would have been challenging to achieve in a single centre.

Findings of the PCA can be considered robust as tests have confirmed adequacy of data sampling. There are also recognisable limitations. Survey based research is affected by responder bias[251 252]. Whilst efforts were made to facilitate easy return of the questionnaire, respondents may have been drawn from the extremes of positive and negative experience. There was limited response from some hospitals, and this may reflect the local demographic or patient experience at the unit. Visual inspection of data and statistical analysis shows that the sample is balanced and suggests a range of experiences are represented here. Recall bias may also be an issue, as the survey was administered at various times following surgery[251 252]. These strengths and limitations are considered within the total survey error framework in table 48.

Domain	Subdomain	Considerations from this study
Respondent selection	Sample size	Sample size reached.
	Sample coverage	Broad spread across England. Mix of age, sex and ethnicity achieved.
	Non-response at unit level	Moderate non-response, with rates lower at some hospitals. May reflect care experiences or local demographics.
Response accuracy	Non-response at item level	Missing responses in decision regret scoring. Standard rubric used.
	Measurement error due to respondents	Some responses missing, may reflect fatigue. Risk of recall bias.
	Measurement error due to interviewers	N/A
Survey administration	Post-survey error	Plans for handling of data adhered to.
	Mode error	Paper survey likely most effective mode. Some attrition at end of questionnaire.
	Comparison error	N/A

Table 48 Study considerations with reference to Total Study Error framework.

16.6.3 Policy impact

The findings of this study should affect clinical practice. The consensus guidance described in chapter 13 advocates a shared decision-making approach to treatment options. This statement should be strengthened in future iterations to make it a key principal of management. Guidelines and quality markers have been developed by several stakeholder groups. These largely focus upon clinical outcome measures such as clinical recurrence, mortality and use of diverting stoma[416]. Patient reported outcomes such as the 'friends and family' test are now routinely collected as part of NHS practice[417]. It should be possible to integrate an assessment of a patient reported outcome measure of decision making, such as the control preference scale, into routine clinical practice and use this as a quality metric. The use of a wide number of sources including websites and booklets also presents a challenge to policymakers. These sources have been shown to be difficult to read and have limited function in support of treatment decisions[125 418 419]. Policymakers should recognise this and develop appropriate material to fulfil this role.

16.6.4 Impact for researchers

The study suggests variation between desired and perceived experiences of decision making, and identifies key items required to support patients to make treatment decisions. These items have shown great reliability and could be used to develop a tool to assess condition-specific preparedness for decision making. This may support engagement of patients in decision making. The study has also shown that decision regret can be collected in this patient group. Decision regret is difficult to interpret in isolation of outcomes and clinical factors. A prospective study using changes in quality of life might aid estimation of clinically important differences in decision regret for different treatments. Characterisation of patients with high and low decision regret might facilitate a stratification method for treatment approaches, although this would require a large sample to complete.

16.7 Conclusion

Patients use a range of information items to retrieve information about surgery and require information on three key areas to support decision making.

17 Mixed Method III: Triangulation of qualitative and quantitative data on patient informational preferences

17.1 Background

The previous chapters explore the experience s of those treated for Crohn's anal fistula using different research methods. The interpretation of these findings can be strengthened through use of mixed methods analysis. The benefits of this approach have been discussed in chapter 14. This chapter describes triangulation and comparison of the two data sources used.

17.2 Justification of triangulation methodology

As outlined in Chapter 14, quantitative and qualitative data can be combined in several different ways, each of which is able to demonstrate convergence or dissonance of findings.

17.3 Aim

The aim of this study was to triangulate findings from the qualitative and quantitative interviews.

17.4 Method

Data was combined using a 'merged' approach, where preliminary analysis of each study is completed prior to combination of each dataset. The relationship is shown in figure 54. Integration of data was achieved through triangulation of methods following the triangulation protocol[378]. Findings from the qualitative and quantitative studies were given equal weighting.

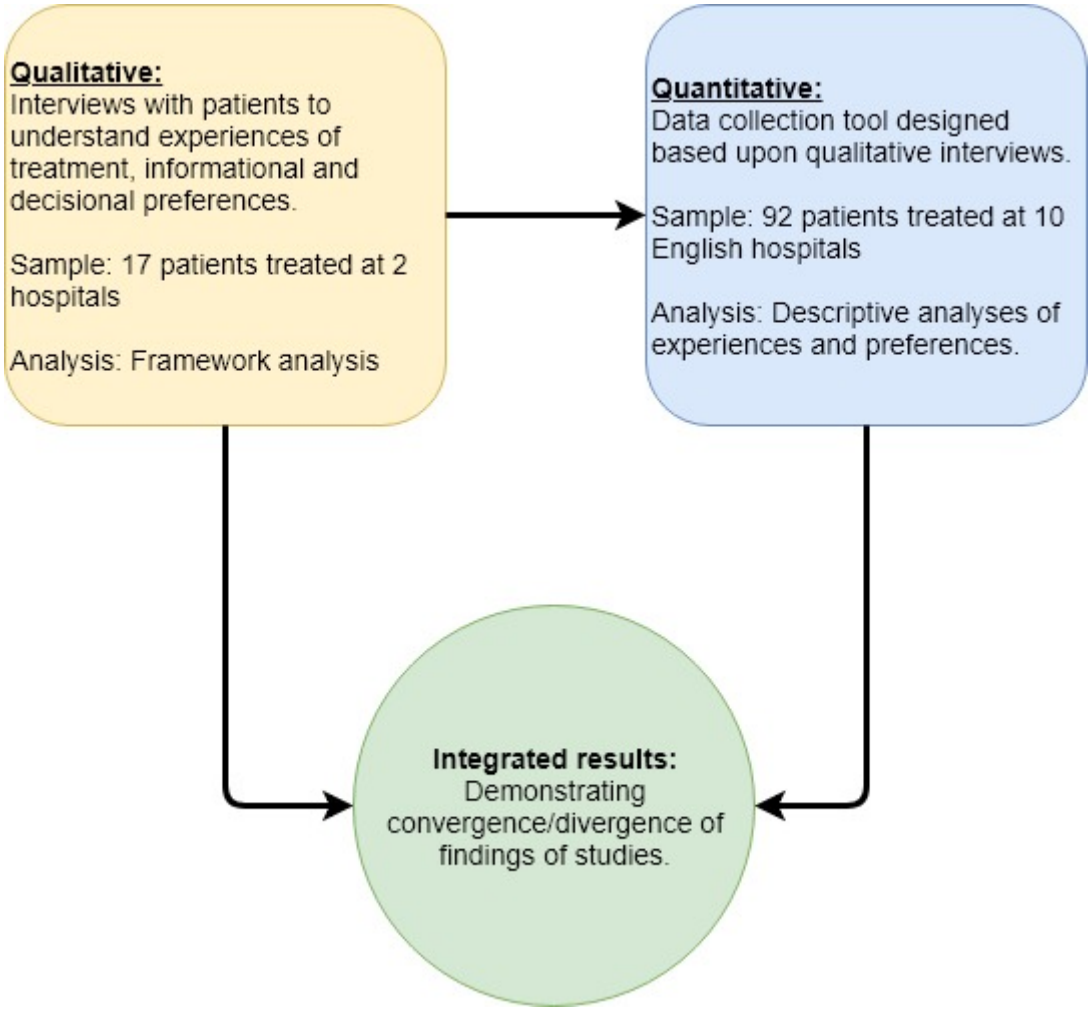

Figure 54 Flow of information in merged study.

17.4.1 Sorting of findings

The findings of the two studies were reviewed by a single researcher to identify key categories or themes in each dataset. The themes from each component study were combined into one unified list. This formed the basis of the subsequent assessments.

17.4.2 Assessments of extent of agreement

For each theme identified on the unified list, the data was compared to identify whether the two sources showed agreement. This can be described as complete agreement, partial agreement, silence, or dissonance.

17.4.3 Assessment of overall convergence

Convergence was assessed by assessing both meaning expressed in each theme. If a range of opinions were expressed in one study, and this range was reflected in the other study, the sources would be considered convergent. The datasets were also assessed for prominence of data i.e. the frequency with which a theme is mentioned or reported. Convergence could be defined as:

- Agreement: Full agreement in meaning and prominence of themes
- Partial agreement: Agreement on one but not both components
- Silence: One source does not report or discuss a theme identified in the other
- Dissonance: Disagreement between both sources on meaning and prominence of findings

17.4.4 Completeness of data

Completeness was assessed by comparing questions asked around each theme in each study, and identifying where the datasets overlap allowing complete assessment of the sources. It is also used to identify areas where the sources do not overlap and findings are incompletely assessed.

17.5 Results

17.5.1 Categorisation

The unified list of themes contained six items: clinicians as an information source, other sources of information, the information needed to make treatment decisions, decision making experiences and preferences, and satisfaction with treatment choice. Themes, prevalence in the two studies, and sample quotes are presented in table 49.

Theme	Number mentioning in interview	Number responding in survey	Sample quote
Clinicians as a source of information	15	92	'It's just sitting down and taking the time….it would be helpful to give a leaflet…maybe even some pictures of stuff.'
Available information sources aside from clinicians	15	92	'I used the Crohn's forum and there's different sections for stuff. You can literally just click on one that's about fistulas, and it will tell you loads of stuff. You can type in and message that I'd had one done, and can anyone offer some advices – loads of people come back and tell you stuff, it's great.'
Satisfaction with information received	15	92	'It just seems like everything is really rushed and they haven't got time to really talk to you. They don't actually sit down half of the time and it's like duh, duh, duh, and they go into their offices, and it's like…are we done?'
Information needed to make treatment decisions	18	89	'Recovery time. I want to know about aftercare and exactly what's going to happen…..Speed and effectiveness really.'
Decision making experience and preferences	18	92	'I like to be led by somebody who knows what they're on about. I like to make my own decision, but I like to be led in the right direction….as long as they're honest with me and lay all the information out, and not concentrating too much on worst and best. [Talk] about the middle ground where most people end up. I think I can make a pretty informed decision.'
Satisfaction with treatment	5	72	'I was reasonably happy to have it ….I was going through a 'no-life' situations, and I thought 'stoma bag can't be any worse than this is'….which as it's proving, it's not.'

Table 49 Summary of themes with prevalence in each study documented.

17.5.2 Assessment of agreement

Sources were assessed for agreement according to prevalence and meaning of themes.

17.5.3 Full agreement

Decision making experiences and preferences was the only theme with consistent spread of findings across both sources. Both sources showed equally high prevalence of this theme. The style of decision making experienced was typically felt to be clinician led with minimal input from the patient. Sources also agreed that patients wanted to be more involved in decision making; a shared decision model, or one skewed slightly towards either participant was consistently preferred.

17.5.4 Partial agreement

17.5.4.1 Clinicians as a source of information

Partial agreement of meaning was identified for the theme 'clinicians as a source of information'. This theme centred upon how useful different clinician groups were at providing treatment information. Both sources agreed that surgeons were good sources for information. Nurse specialists were accessed as sources of information about surgery in both groups, although there were differing opinions on how helpful they were, with some very negative opinions expressed in interviews. A similar pattern was seen with respect to gastroenterologists.

17.5.4.2 Information sources other than clinicians

Partial agreement was also identified in for the theme Information sources other than clinicians. Whilst highly prevalent, there were differences in findings between the two sources. The survey indicated that when used, other sources of information were very useful. Interview participants did find many different sources useful such as leaflets provided by the hospital. The interview participants expressed concern over some online information sources such as online forums. There was some

scepticism expressed over the accuracy or reliability of the information provided in these settings. The ability of online information to support decision making has been assessed , and was not of adequate quality to support decision making[125].

17.5.4.3 Information needed to make decisions

This was rated as partial agreement as the prevalence of the theme was not consistent across the sources, nor were the findings, although they showed some common trends. Items related to decision making addressed in the quantitative study (questionnaire) were identified from the patient questionnaire. All items presented in the questionnaire were rated as highly important, with a median score of 8. This matched the emphasis placed on many items in the interviews as being 'key' to making treatment decisions. Although items such as impact on sexual function were not as prevalent in the interviews, they were rated highly in the questionnaire.

17.5.4.4 Satisfaction with treatment decisions

Satisfaction with treatment decisions was mixed, including extremes of opinions about their treatment. Decisional regret scores had a relatively consistent median. Whilst there were extremes of scores, there was no statistically significant difference across groups by procedure. This may reflect under sampling of specific procedures in both the interviews and the questionnaire.

17.5.5 Convergence assessment

Overall assessment showed full agreement for 1/5 themes and partial agreement for 4/5 themes. No examples of dissonance or silence were identified. This shows a moderate level of agreement across the two studies. A convergence matrix is presented in table 50.

17.5.6 Completeness comparison

Comparison of the data sources for completeness. The questionnaire was based upon the interviews therefore it did not identify any new areas for assessment. The interviews provide additional content describing reasons why specific opinions may be given (e.g. bad previous experience with a clinician).

The datasets support the identification of these themes and provide potential reasons for variation in responses. It is possible that some data is lacking on the satisfaction/regret associated with specific procedures.

	Prevalence & Meaning			
Theme	**Agreement**	**Partial agreement**	**Dissonance**	**Silence**
Clinicians as a source of information		**X**		
Available information sources aside from clinicians		**X**		
Information needed to make treatment decisions		**X**		
Decision making experience and preferences	**X**			
Satisfaction with treatment decisions		**X**		

Table 50 Convergence matrix demonstrating agreement of themes according to prevalence and meaning.

17.6 Discussion

Mixed methods assessment of the two sources has demonstrated complementarity of sources discussing informational and decisional preferences in Crohn's anal fistula. Findings show convergence with no evidence of dissonance.

17.6.1 Findings in context

Complete agreement was achieved for the theme on decision making experiences and preferences. This was consistent across the two sources and showed the imbalance between experienced and preferred models. This is in keeping with the literature where a shared approach is preferred by both patients and clinicians[122 390].

There were varying levels of satisfaction with treatment outcomes. Moderate levels of decisional regret related to surgery have been identified in other complex settings related to biologic use[401] and following surgery[420]. A single centre study assessing patients undergoing planned major procedures, the majority of which were for cancer, found low levels of regret[421]. This may reflect that operations associated with cure or treatment of cancer are easily considered a good idea as outcomes may be framed in terms of survival from cancer, whereas surgery for Crohn's anal fistula is typically considered in terms of quality of life.

The role of clinicians in giving information and the role of alternative information sources has been discussed in the previous two chapters.

17.6.2 Strengths and limitations

This study has been conducted in line with the published triangulation protocol[378], ensuring a robust approach has been employed. For pragmatic reasons the assessment has been carried out by a single researcher. This means that while triangulation was completed across themes and sources, it was not completed across researchers.

17.6.3 Impact for policy makers & researchers

These sources show partial to full agreement across all themes, and findings should be considered reliable. Stakeholders such as inflammatory bowel disease charities, clinical professional associations, and patient advocacy groups should consider how this study can impact patient care. Addressing the standards of information provided in a clinical setting, both in terms of content and format, could address some of the issues raised by patients. Implementation of an assessment of shared decision-making following clinic appointments might help to shift the decisional model.

Researchers should investigate the characteristics of patients associated with their preferred decision-making model, to ensure resources for shared decision making can be deployed appropriately. Studies eliciting patient treatment goals and matching these with different procedure types and outcomes would assist in tailoring treatments appropriately. This could be achieved using a discrete choice experiment or similar methodology.

17.7 Conclusion

Mixed method assessment of informational and decisional preferences shows the importance of information from multiple sources, the imbalance between preferred and experienced decision-making processes, and the varying degrees of satisfaction in treatment outcomes.

18 Summary of findings in thesis

Systematic reviews:

- There is no clear front running surgical intervention. The available literature is severely limited by study design bias and outcome definitions.
- Pooling of all patients with fistulating Crohn's disease demonstrated a benefit from anti-TNF-α agents in the induction and maintenance of fistula response. Stem cells show benefit and may be used as a second or third line treatment.

Variation of clinical practice:

- There is variation in medical practice, including the initial medical management of fistula. The timing of reassessment, and the strategies for escalation or de-escalation of medical therapy also show wide divergence in practice.
- There is wide variation in surgical practice, and the range of definitive procedures offered.
- Clinical pathways show wide variation in the time taken to access definitive therapy. There are potential barriers in the form of diagnosis and interface between specialties.
- A consensus exercise on the surgical management of Crohn's anal fistula among UK surgeons has identified a strategy preferring sphincter-sparing procedures. It also proposes criteria for consideration of faecal diversion.

Mixed method research:

- Patients are not satisfied with the content or delivery of information from clinicians. They seek information from other sources including peers.
- Patients would like to be involved in making treatment decisions.
- Wound care, effect on perianal region, and severity of operation are key information domains for patients to make decisions about their treatment. These items could form a preparedness for decision making tool.

18.1 Impact for policy makers

This thesis has identified variation in the treatment of Crohn's anal fistula. This variation could be linked to worse care experiences for some patients. There is a major policy drive to reduce variation across general surgery in emergency and elective settings[422 423]. It is important to extend this to the care of patients with inflammatory bowel disease who are cared for by both surgeons and physicians, increasing the opportunity for variation. As previously highlighted, variation can be due to limited information and limited resources[284]. Policy makers should consider factors outlined below (Figure 55).

18.1.1 Addressing the information gap

Whilst this thesis highlights many of the unknowns in the management of Crohn's anal fistula, it does identify aspects of evidence-based practice, such as the use of anti-TNF-α drugs for induction and remission of fistula. There are many unknowns, and specific areas of need include the optimum timing, delivery, dosage of drugs, and role of surgery. Policy makers should work with funding bodies to commission work to address these knowledge gaps.

Policy makers should use available information to synthesise evidence-based treatment guidelines. Given the level of variability in patient disease patterns, it is unlikely that a one-size fits all pathway will be appropriate. Current key performance indicators for Crohn's anal fistula are based around outcomes such as abscess recurrence, stoma, and proctectomy rate[416] These indicators are clinical outcomes based, and consideration should be given to patient-centred performance indicators. The evaluation of any evidence-based pathway should focus on the implementation of processes as outcomes may be influenced by factors beyond the care pathway.

18.1.2 Addressing the resource gap

Pathway work highlighted the challenge of moving a patient through a treatment pathway, even in centres with a large IBD practice. This may partly reflect capacity within the service to deliver the treatment pathway, including radiology and surgical services. Arguments have been made for the centralisation of pouch surgery[424], and patients are willing to accept longer travel times to reduce the risks of complications of treatment[425]. Policy makers should consider whether this is a strategy that should be pursued in the context of Crohn's anal fistula.

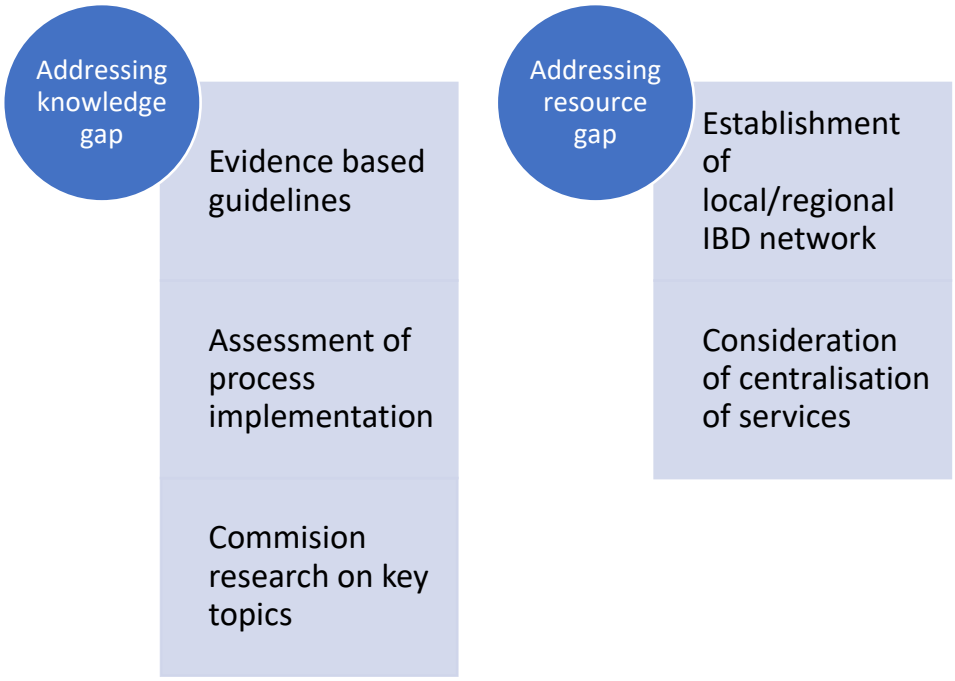

Figure 55 Impact for policy makers

18.2 Impact for researchers

This thesis suggests aspects of Crohn's anal fistula treatment that require further investigation; decision making and regret, timing of treatment, and stratification & classification.

18.2.1 Decision making & regret

This thesis has explored practices around decision making. Patients have demonstrated a desire to be involved in decision making. Given the important of patient preferences in this condition, methods to improve patient participation in decisions should be investigated. The development of a patient decision aid would be a useful next step to address this. This thesis addresses the requisite early steps for the development of a patient decision aid[128], and could be used to support the pilot and validation of such a tool. Mixed method work has supported the generation of a tool that might be used for procedure specific preparedness for decision making. Provision of information about surgical interventions might provide sufficient information to avoid decisional conflict and regret. This tool should undergo iterative development and assessment of validity using a generic preparedness for decision-making questionnaire as a reference anchor, and testing of reliability. The effect of this on decisional regret and other decision measurement indices could be tested in a randomised controlled trial.

Decision regret has also been recorded following different procedures at various time points. This could be a useful outcome measure when counselling patients. This tool could be embedded in a cohort study of patients undergoing surgical treatment of Crohn's anal fistula. This might give helpful information on its own, or coupled with an appropriate clinical outcome measure.

18.2.2 Timing of interventions and effect on outcomes

There is variation in the time to complete the initial treatment pathway. It is not clear whether this affects outcomes. Whilst it would be logistically easier to conduct a cohort study to assess this relationship, this would be subject to significant confounding. Therefore, a randomised trial of a rapid initial treatment pathway should be considered. The proposed PICO is shown in figure 56.

Population: Presentation of new symptomatic Crohn's fistula in TNF naïve patient Intervention: Rapid treatment pathway starting anti-TNF in 30 days. Includes preparation of fistula for healing by EUA with curettage of track as per Panes[246]. Control: Pragmatic control (standard care). Outcome: Fistula drainage index 6 months after starting treatment. Secondary outcomes as per core outcome set[173].

Figure 56 PICO for a time-based trial

18.2.3 Stratification/Classification

There are several different classification systems in use for Crohn's anal fistula[53 54 247], none of which are truly satisfactory in terms of describing and predicting disease behaviour. Prognostic factors identified are typically those which are clinically apparent[315]. To ensure appropriate comparisons and to stratify patients by likely clinical outcomes, a new classification system is needed. This could be achieved through a prospective cohort study, with profiling of demographics and baseline physiology (including tissue sampling for potential biomarkers), and collection of treatment parameters. Outcome measures should include fistula drainage at 6 months, fistula recurrence, complications of fistulating disease, and a quality of life measure[173]. Decision regret could be included in this study to ensure efficient conduct and not to exhaust the potential participant population.

19 Conclusion

In Crohn's anal fistula, anti-TNF-α drugs and azathioprine can be used for induction treatment, and the former for maintenance of treatment response. There is no front running surgical treatment for this condition. The limited evidence base is reflected in the variation reported in clinical practice by surgeons and gastroenterologists, and in the initial treatment pathway. Patients would like to be involved in decisions about their treatment, and have identified key information items that are needed to support decision making.

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Appendix A: Search Strategy Medical Systematic Review

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS (CENTRAL)

#1 MeSH descriptor: [Crohn Disease] explode all trees
#2 Crohn
#3 #1 or #2
#4 MeSH descriptor: [Rectal Fistula] explode all trees
#5 fistula
#6 fistul*
#7#4 or #5 or #6
#8 #3 and #7

EMBASE

1 random$.tw.
2 factorial$.tw.
3 (crossover$ or cross over$ or cross-over$).tw.
4 placebo$.tw.
5 single blind.mp.
6 double blind.mp.
7 triple blind.mp.
8 (singl$ adj blind$).tw.
9 (double$ adj blind$).tw.
10 (tripl$ adj blind$).tw.
11 assign$.tw.
12 allocat$.tw.
13 crossover procedure/
14 double blind procedure/
15 single blind procedure/
16 triple blind procedure/
17 randomized controlled trial/
18 or/1-17
19 Limit 18 to human
20 Exp Crohn disease/
21 Crohn*.mp.
22 20 or 21
23 Exp Rectal fistula/
24 Fistula.mp.
25 Fistul*.mp.
26 or/23-25
27 19 and 22 and 26

MEDLINE

1 random$.tw.

2 factorial$.tw.
3 (crossover$ or cross over$ or cross-over$).tw.
4 placebo$.tw.
5 single blind.mp.
6 double blind.mp.
7 triple blind.mp.
8 (singl$ adj blind$).tw.
9 (double$ adj blind$).tw.
10 (tripl$ adj blind$).tw.
11 assign$.tw.
12 allocat$.tw.
13 crossover procedure/
14 double blind procedure/
15 single blind procedure/
16 triple blind procedure/
17 randomized controlled trial/
18 or/1-17
19 Limit 18 to human
20 Exp Crohn disease/
21 Crohn*.mp.
22 20 or 21
23 Exp Rectal fistula/
24 Fistula.mp.
25 Fistul*.mp.
26 or/23-25
27 19 and 22 and 26

Appendix B: GRADE PRO Medical Systematic Review

Comparison 1: Drug therapy versus placebo

Drug class	Outcome	Pooled RR (95% CI, p)	Number of participants	Quality*
Antibiotics	Induction of fistula response	1.68 (0.34 to 8.22, p = 0.52)	25 (1 study)	⊕⊕⊖⊖[1] Low
	Induction of fistula remission	1.20 (0.17 to 8.38, p = 0.85)	25 (1 study)	⊕⊕⊖⊖[2] Low
Immunosuppressives	Induction of fistula response	2.53 (1.22 to 5.23, p = 0.01)	123 (6 studies)	⊕⊕⊖⊖[3] Low
	Induction of fistula remission	2.47 (0.85 to 7.21, p = 0.10)	114 (4 studies)	⊕⊕⊖⊖[4] Low
	Maintenance of fistula response	0.33 (0.03 to 4.19, p = 0.0006)	2 (1 study)	⊕⊕⊖⊖[5] Very low
TNF-alpha antagonists	Induction of fistula response	1.44 (1.09 to 1.90, p = 0.01)	509 (7 studies)	⊕⊕⊕⊖[6] Moderate
	Induction of fistula remission	2.06 (1.40 to 3.04, p = 0.0003)	432 (6 studies)	⊕⊕⊕⊖[7] Moderate
	Maintenance of fistula response	1.97 (1.34 to 2.89, p = 0.0006)	253 (2 studies)	⊕⊕⊕⊖[8] Moderate
	Maintenance of fistula remission	1.94 (1.25 to 3.02, p = 0.003)	253 (2 studies)	⊕⊕⊕⊖[9] Moderate
Vedolizumab	Induction of fistula remission	2.54	57	⊕⊕⊖⊖[10]

		(0.63 to 10.29, p = 0.19)	(1 study)	Low
Ustekinumab	Induction of fistula response	1.66 (1.10 to 2.51, p = 0.02)	318 (3 studies)	⊕⊕⊕⊖[11] Moderate
	Induction of fistula remission	1.77 (0.93 to 3.37, p = 0.08)	238 (1 study)	⊕⊕⊕⊖[12] Moderate
AST-120	Induction of fistula response	1.19 (0.72 to 1.97, p = 0.50)	306 (2 studies)	⊕⊕⊕⊖[13] Moderate
	Induction of fistula remission	1.45 (0.79 to 2.66, p = 0.22)	306 (2 studies)	⊕⊕⊕⊖[14] Moderate
Mysenchymal stem cell therapy	Induction of fistula response	1.27 (1.02 to 1.59, p = 0.03)	133 (2 studies)	⊕⊕⊕⊖[15] Moderate
	Induction of fistula remission	1.31 (0.98 to 1.73, p = 0.06)	133 (2 studies)	⊕⊕⊕⊖[16] Moderate

Comparison 2: Biologic versus biologic combined with antibiotic

	Outcome	**Pooled RR (95% CI, p)**	**Number of participants**	**Quality**
Infliximab or certolizumab	Induction of fistula response	1.58 (1.09 to 2.28, p = 0.01)	96 (2 studies)	⊕⊕⊕⊖[17] Moderate
	Induction of fistula remission	1.94 (1.14 to 3.29)	72 (1 study)	⊕⊕⊖⊖[18] Low

Comparison 3: Methotrexate versus azathioprine

	Outcome	**Pooled RR (95% CI, p)**	**Number of participants**	**Quality**
	Induction of fistula remission	2.00	12	⊕⊖⊖⊖[18]

	(0.56 to 7.09)	(1 study)	Very low

*Studies were downgraded due to risk of bias; indirectness of evidence; unexplained heterogeneity; sparse data; and publication bias. In the case of very sparse data (< 35 events) and sparse data (< 300 events) the quality of evidence was downgraded by 2 levels and 1 level, respectively.

[1]Downgraded 2 levels due to very sparse data (6 events)
[2]Downgraded 2 levels due to very sparse data (4 events)
[3]Downgraded 2 levels due to very sparse data (29 events)
[4]Downgraded 2 levels due to very sparse data (17 events)
[5]Downgraded 3 levels due to very sparse data (1 event)
[6]Downgraded 1 level due to sparse data (172 events)
[7]Downgraded 1 level due to sparse data (118 events)
[8]Downgraded 1 level due to sparse data (81 events)
[9]Downgraded 1 level due to sparse data (66 events)
[10]Downgraded 2 levels due to very sparse data (13 events)
[11]Downgraded 1 level due to sparse data (83 events)
[12]Downgraded 1 level due to sparse data (47 events)
[13]Downgraded 1 level due to sparse data (74 events)
[14]Downgraded 1 level due to sparse data (38 events)
[15]Downgraded 1 level due to sparse data (138 events)
[16]Downgraded 1 level due to sparse data (109 events)
[17]Downgraded 1 level due to sparse data (54 events)
[18]Downgraded 2 levels due to very sparse data (34 events)
[19]Downgraded 3 levels due to very sparse data (6 events) and high risk of bias for blinding of participants and selective reporting

Appendix C: Sensitivity analysis results – including only studies that used fistula disease activity as the primary outcome

Comparison 1: Drug therapy versus placebo			
Outcome	**Subgroup**	**Pooled RR (95% CI, p)**	**Adjusted Pooled RR (95% CI, p)**
Induction of fistula response	Antibiotics	1.68 (0.34 to 8.22, p = 0.52)	Not estimable
	Thiopurines	1.86 (0.73 to 4.75, p = 0.20)	Not estimable
	Tacrolimus	3.82 (1.17 to 12.40, p = 0.03)	5.36 (1.30 to 22.12)
	TNF-alpha antagonists	1.44 (1.09 to 1.90, p = 0.01)	1.97 (1.19 to 3.28, p = 0.009)
	Ustekinumab	1.55 (0.86 to 2.80, p = 0.14)	Not estimable
	AST-120	1.19 (0.72 to 1.97, p = 0.50)	1.19 (0.72 to 1.97, p = 0.50)
	MSC	1.27 (1.02 to 1.59, p = 0.03)	1.27 (1.02 to 1.59, p = 0.03)
Induction of fistula remission	Antibiotics	1.20 (0.17 to 8.38, p = 0.85)	Not estimable

	Thiopurines	3.38 (0.76 to 15.71, p = 0.11)	Not estimable
	Tacrolimus	1.58 (0.33 to 7.51, p = 0.57)	1.19 (0.18 to 7.74)
	TNF-alpha antagonists	2.06 (1.40 to 3.04, p = 0.0003)	3.57 (1.38 to 9.25, p = 0.009)
	Vedolizumab	2.54 (0.63 to 10.29, p = 0.19)	Not estimable
	Ustekinumab	1.77 (0.93 to 3.37, p = 0.08)	Not estimable
	AST-120	1.45 (0.79 to 2.66, p = 0.22)	1.45 (0.79 to 2.66, p = 0.22)
	MSC	1.31 (0.98 to 1.73, p = 0.06)	1.31 (0.98 to 1.73, p = 0.06)
Maintenance of fistula response	Immunosuppressives	0.33 (0.03 to 4.19, p = 0.0006)	Not estimable
	TNF-alpha antagonists	1.97 (1.34 to 2.89, p = 0.0006)	1.88 (1.23 to 2.88, p = 0.003)
	Ustekinumab	1.82 (1.04 to 3.17, p = 0.04)	Not estimable
Maintenance of fistula remission	TNF-alpha antagonists	1.94 (1.25 to 3.02, p = 0.003)	1.79 (1.10 to 2.92, p = 0.02)

Comparison 2: Biologic versus biologic combined with antibiotic for induction of remission			
Induction of fistula response		1.58 (1.09 to 2.28, p = 0.01)	1.58 (1.09 to 2.28, p = 0.01)
Induction of fistula remission		1.94 (1.14 to 3.29, p = 0.01)	1.94 (1.14 to 3.29, p = 0.01)

Appendix D: Sensitivity analysis results – including only studies that exclusively enrolled patients with peri-anal fistula

Comparison 1: Drug therapy versus placebo			
Outcome	**Subgroup**	**Pooled RR (95% CI, p)**	**Adjusted Pooled RR (95% CI, p)**
Induction of fistula response	Antibiotics	1.68 (0.34 to 8.22, p = 0.52)	1.68 (0.34 to 8.22, p = 0.52)
	Thiopurines	1.86 (0.73 to 4.75, p = 0.20)	Not estimable
	Tacrolimus	3.82 (1.17 to 12.40, p = 0.03)	1.00 (0.08 to 12.56)
	TNF-alpha antagonists	1.44 (1.09 to 1.90, p = 0.01)	Not estimable
	Ustekinumab	1.55 (0.86 to 2.80, p = 0.14)	1.55 (0.86 to 2.80, p = 0.14)
	AST-120	1.19 (0.72 to 1.97, p = 0.50)	1.19 (0.72 to 1.97, p = 0.50)
	MSC	1.27 (1.02 to 1.59, p = 0.03)	1.27 (1.02 to 1.59, p = 0.03)
Induction of fistula remission	Antibiotics	1.20 (0.17 to 8.38, p = 0.85)	1.20 (0.17 to 8.38, p = 0.85)
	Thiopurines	3.38 (0.76 to 15.71, p = 0.11)	Not estimable

	Tacrolimus	1.58 (0.33 to 7.51, p = 0.57)	3.00 (0.15 to 61.74)
	TNF-alpha antagonists	2.06 (1.40 to 3.04, p = 0.0003)	Not estimable
	Vedolizumab	2.54 (0.63 to 10.29, p = 0.19)	Not estimable
	Ustekinumab	1.77 (0.93 to 3.37, p = 0.08)	1.77 (0.93 to 3.37, p = 0.08)
	AST-120	1.45 (0.79 to 2.66, p = 0.22)	1.45 (0.79 to 2.66, p = 0.22)
	MSC	1.31 (0.98 to 1.73, p = 0.06)	1.31 (0.98 to 1.73, p = 0.06)
Maintenance of fistula response	Immunosuppressives	0.33 (0.03 to 4.19, p = 0.0006)	Not estimable
	TNF-alpha antagonists	1.97 (1.34 to 2.89, p = 0.0006)	Not estimable
	Ustekinumab	1.82 (1.04 to 3.17, p = 0.04)	1.82 (1.04 to 3.17, p = 0.04)
Maintenance of fistula remission	TNF-alpha antagonists	1.94 (1.25 to 3.02, p = 0.003)	Not estimable
Comparison 2: Biologic versus biologic combined with antibiotic for induction of remission			

Induction of fistula response		1.58 (1.09 to 2.28, p = 0.01)	1.58 (1.09 to 2.28, p = 0.01)
Induction of fistula remission		1.94 (1.14 to 3.29, p = 0.01)	1.94 (1.14 to 3.29, p = 0.01)

Appendix E: Search strategy surgical systematic review

1. *Crohn disease AND *rectal fistula AND *surgery
2. *Crohn disease AND *rectal fistula AND seton.mp
3. *Crohn disease AND *rectal fistula AND LIFT.mp
4. *Crohn disease AND *rectal fistula AND fistula plug.mp
5. *Crohn disease AND *rectal fistula AND advancement flap.mp
6. *Crohn disease AND *rectal fistula AND VAAFT.mp
7. *Crohn disease AND *rectal fistula AND OTSC.mp
8. *Crohn disease AND *rectal fistula AND stoma.mp
9. *Crohn disease AND *rectal fistula AND proctectomy.mp
10. OR/1-9

Appendix F: ROBINS-2 risk of bias assessment surgical systematic review

Risk of bias table for non-randomised studies. L=Low, M=Moderate, S=Severe, C=Critical, NI = Not indicated

Year and Author	Confounding	Selection	Classification	Deviations from intervention	Missing Data	Measurement of outcomes	Selection of outcomes	Overall
1995 Makowiec	S	C	M	NI	NI	M	M	M
1995 Halme	S	S	S	NI	L	S	S	S
1995 Sugita	S	M	M	NI	NI	S	S	S
1996 Faucheron	C	C	S	NI	NI	C	C	C
1996 Ozuner	S	S	S	NI	NI	C	M	S
1996 Scott	S	S	S	NI	NI	C	C	S
1998 Bodzin	S	C	M	NI	NI	S	S	S
1998 Joo	S	S	M	NI	NI	C	S	S
1998 Marchesa	S	M	L	NI	NI	S	S	S
1999 Hyman	S	M	S	NI	NI	S	S	S
1999 Rieger	S	S	L	NI	M	C	C	S
2000 Park	S	S	L	NI	L	C	C	S
2000 Yamamoto	M	S	M	NI	L	M	M	M
2000 Nelson	C	C	S	M	NI	S	S	S
2001 Sentovich	S	S	M	NI	NI	S	S	S
2002 Sonoda	S	S	M	NI	L	M	M	M
2002 Mizrahi	S	S	M	NI	L	C	C	S
2003 Buchanan	S	S	S	NI	NI	S	S	S
2003 Sentovich	S	S	M	NI	L	S	S	S
2003 Zmora	S	S	L	NI	M	S	M	S
2003 Reguiero	M	M	S	NI	NI	M	M	M

Year and Author	Confounding	Selection	Classification	Deviations from intervention	Missing Data	Measurement of outcomes	Selection of outcomes	Overall
2004 Loungranath	S	S	M	NI	L	S	S	S
2005 Thornton	M	S	M	NI	NI	S	M	M
2006 Moy	S	S	M	NI	NI	M	M	M
2006 O'Connor	M	M	M	NI	NI	M	M	M
2006 Asteria	L	L	L	NI	NI	M	M	L
2006 Van der Hagen	S	M	S	NI	S	S	M	S
2007 Gaertner	M	S	M	NI	NI	S	M	M
2007 Schaden	S	S	M	NI	NI	S	S	S
2008 Ky	S	S	M	NI	L	S	M	S
2008 Schwander	M	M	L	NI	L	M	M	M
2009 Schwander	M	M	L	NI	L	S	M	M
2009 Zubaidi	S	M	L	NI	NI	M	M	M
2009 van Koperen	M	S	S	NI	L	M	S	S
2010 Chung	C	M	M	NI	NI	M	M	M
2010 El-Gazzaz	M	M	L	NI	NI	S	M	M
2010 Owen	S	S	M	NI	NI	C	M	S
2010 de Paredes	S	M	L	Ni	Ni	M	M	M
2010 Gligorijevic	M	S	S	NI	NI	M	M	M
2010 Sciaduone	M	M	S	NI	NI	M	M	M
2010 Tanaka	M	S	M	NI	NI	S	M	M
2011 Jarrar	S	M	S	NI	M	C	C	S

Year and Author	Confounding	Selection	Classification	Deviations from intervention	Missing Data	Measurement of outcomes	Selection of outcomes	Overall
2011 Alessandroni	L	M	L	NI	NI	M	L	L
2011 Ciccocioppo	L	M	L	L	L	L	L	L
2011 Uchino	S	M	M	NI	NI	S	M	M
2012 Ommer	C	S	S	NI	M	C	S	S
2013 Cintron	C	S	M	NI	NI	S	S	S
2013 Schwander	L	M	L	NI	NI	S	M	M
2013 Cho	M	M	L	L	L	L	M	L
2013 de la Portilla	L	L	L	L	L	L	L	L
2013 Lee	L	M	L	L	NI	M	M	M
2014 Gingold	M	M	M	NI	NI	S	M	M
2014 Ozturk	S	M	M	NI	NI	S	M	M
2014 Dursun	M	S	S	NI	NI	S	M	S
2014 Kotze	M	S	M	NI	NI	S	M	M
2015 Mennigen	M	S	M	NI	NI	M	S	M
2015 Cho	M	M	L	L	M	M	M	M
2015 Garcia-Olmo	C	S	M	L	NI	S	S	S
2015 Gottgens	M	M	M	NI	NI	M	S	M
2015 Graf	M	S	S	NI	NI	S	S	S
2015 Schlegel	S	C	M	S	NI	S	S	S

Appendix G: Cochrane ROB for randomised studies surgical systematic review

Risk of bias table for randomised studies. L=Low, M=Moderate, H= High, S=Some concern

Year and Author	Random sequence	Allocation Concealment	Blinding of participants	Blinding of assessors	Incomplete outcome data	Selective reporting	Other bias
2009 Garcia-Olmo	L	H	H	L	L	L	S
2015 Molendijk	S	L	L	L	L	L	S
2016 Senejoux	L	H	H	S	L	L	S

Appendix H: Gastroenterologist questionnaire

Current management of fistulating perianal Crohn's disease: Pilot Questionnaire

The optimum management of fistulating perianal disease has been identified as a key topic for colorectal surgeons in the recent ACPGBI Delphi exercise. As fistulating perianal Crohn's is a condition which requires multidisciplinary involvement, we are keen to understand current practice amongst gastroenterologists in this condition. Findings from this questionnaire will be used to inform the design of a future trial and/or consensus exercise.

All these questions relate ONLY to FISTULATING PERIANAL CROHN'S DISEASE. Please answer with what you would *most commonly* do. It is accepted that clinicians may exercise judgement and tailor decision-making depending on clinical presentation.

Thank you for taking the time to complete this questionnaire. Your support is appreciated!

Questions or comments to m.j.lee@sheffield.ac.uk

Section 1: Questions in this section relate to emergency presentations of perianal sepsis in established or clinically suspected Crohn's disease. Please answer with what you would *most commonly* do.

If you review a patient and you believe they have a perianal abscess related to Crohn's, would you start antibiotics:

Always Usually Occasionally Never

If yes, which antibiotic(s)?

Ciprofloxacin
Metronidazole
Augmentin
Gentamicin
Other (please specify)_____

Section 2: Questions in this section relate to presentations of perianal fistulae in established or clinically suspected Crohn's disease. Please answer with what you would *most commonly* do. This assumes no fulminant sepsis requiring immediate drainage.

In your experience, how does a patient with perianal fistula related to Crohn's usually access treatment?

Via surgical clinic Via acute surgical take Via IBD nurse

Via medical clinic Via acute medical take Via gastroenterology Via GP

If you saw a patient with a symptomatic fistula, would you refer directly to a surgeon or would you obtain imaging first?

Usually obtain imaging first Usually refer direct to surgeon

If referring to a surgeon, do you refer to a named surgeon or the acute surgical take?

Usually a named surgeon Usually to acute take

If you undertake imaging, which modality do you prefer?

MRI perineum CT Endoanal Ultrasound

Other (please specify)_____

What is the minimum set of investigations you would perform for a known Crohn's patient with a new perianal fistula?

Rigid sigmoidoscopy

Flexible sigmoidoscopy

Colonoscopy

Faecal Calprotectin

MRI pelvis

Other:_____

If the diagnosis of Crohn's is not yet established, but is suspected, which of the following investigations would you undertake?

Faecal Calprotectin:

Almost always Frequently Occasionally Never

Colonoscopy:

Almost always Frequently Occasionally Never

Flexible sigmoidoscopy:

Almost always Frequently Occasionally Never

Video capsule endoscopy:

Almost always Frequently Occasionally Never

MRI small bowel:

Almost always Frequently Occasionally Never

Other (please specify): _____

Section 2: Questions in this section are related to the postoperative management after sepsis control or first EUA. Please answer with what you would most *commonly* do.

Does your unit have an IBD Multi-disciplinary meeting?

YES NO

Are patients with fistulating Crohn's disease discussed in your IBD MDT?

Always Usually Sometimes Never N/A

In your practice, are immunosuppressant drugs used to treat fistula in ano associated with Crohn's?

Almost always Frequently Occasionally Never

In your practice, would you start with a single therapy or with multiple therapies?

Single therapy
Antibiotics and thiopurine
Antibiotics and anti-TNF Antibiotics,
thiopurine and anti-TNF
Other combination:_____

If you use antibiotics in this setting, which do you tend to use?

Ciprofloxacin
Metronidazole
Augmentin
Gentamicin
Other (please specify)_____

How long do you use antibiotics for?

1 week
2 weeks
1 month
2 months
>2 months

Generally speaking, what drug is your first-line immunosuppressant in the management of fistulating perianal Crohn's

Steroid therapy
Aminosalicylates (sulfasalazine, mesalamine)
Azathioprine
Mercaptopurine
Methotrexate
Anti-TNF agent
Other (which?) _____

If you selected anti-TNF, which agent is your first choice for perianal Crohn's disease?

Infliximab
Adalimumab

Does the type of fistula (simple/complex) affect your treatment decision?

Yes
No

What interval between sepsis drainage and commencement of immunosuppressant/add-in anti-TNF therapy do you usually leave?

1-2 weeks 3-4 weeks 5-6 weeks 7-8 weeks 9 weeks +

Do you ask for evidence of sepsis resolution prior to immunosuppression?

Almost always Frequently Occasionally Never

If so, what evidence do you take into account (tick all that apply)?

Surgeon's report from EUA

Patient Symptoms

Repeat imaging

Overall disease activity

When would you normally reassess symptoms after commencement of medical therapy?

1 month

3 months

6 months

Other:_____

In the context of fistula that is not responding to therapy based on clinical assessment, for how long do you typically continue first-line immunosuppression before escalating therapy?

up to 3 months up to 6 months up to 12 months up to 24 months

as per clinical symptoms other_____

After a period of first-line immunosuppression with improvement in symptoms, do you typically stop therapy, continue therapy or 'step-down'?

Stop therapy Continue therapy Step down therapy

If you answered 'step down' therapy, please indicate what drug(s) you would typically move to.

Steroid therapy
Aminosalicylates (sulfasalazine, mesalamine)
Azathioprine
Mercaptopurine
Methotrexate
Infliximab
Adalimumab
Other (which?) _____

After a period of first-line immunosuppression without improvement in symptoms, what would you typically do next?

Change medical therapy

Re-image

Obtain further surgical opinion

If you would change medical therapy, what would you change it to?

Steroid therapy
Aminosalicylates (sulfasalazine, mesalamine)
Azathioprine

Mercaptopurine
Methotrexate
Infliximab
Adalimumab
Other (which?) _____

In a stable or improving patient, how would you monitor response?

Repeat imaging Clinical response

Do you use any strategies to optimise medical therapy (tick those which apply):

Assessment of thiopurine levels and optimisation of dose

Assessment of anti-TNF levels and optimisation of dose

Assessment of anti-TNF antibodies

What factors would make you consider referral to a surgeon for repeat EUA?

Length of time on anti-TNF or immunomodulators Loss of response to drugs

Quality of life Other:_____

If proctitis is present, does this typically alter your management?

Yes No

What aspects of your care does it affect (tick all that apply)?

Surveillance – radiological/endoscopic Duration of immunosuppressant therapy

Use of PR medications Choice of immunosuppressant therapy

Other_____

Section 3: Definitive management aimed at fistula healing/control

If your first line choice of immunosuppressant fails to resolve symptoms, what are your second and third line choices?

Second line: _____

Third line: _____

In what situations would you seek an opinion on formation of a defunctioning stoma?

_____
_____
_____

In what situations would you seek an opinion on proctectomy?

_____
_____
_____

Optional: If you would like to sketch your management algorithm for perianal Crohn's disease, please feel free to do so below. This has been undertaken on the corresponding colorectal surgeon questionnaire and has identified common decision points and approaches to the disease.

Thank you for taking the time to complete this questionnaire.

If you would like to be involved in a consensus exercise, please write your email address below. It is anticipated that this will take place in September 2016

_____

Appendix I: Ethical approval for gastroenterologist survey

Downloaded: 21/06/2016
Approved: 15/02/2016

Matthew Lee
Registration number: 150245409
Oncology
Programme: DDP

Dear Matthew

PROJECT TITLE: Assessment of medical audit/service evaluation data on management of fistulating perianal Crohn's disease
APPLICATION: Reference Number 007595

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 15/02/2016 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 007595 (dated 02/02/2016).

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Yours sincerely

Paula Blackwell
Ethics Administrator
Medical School

Appendix J: Surgeon questionnaire

Current management of fistulating perianal Crohn's disease: Questionnaire

The optimum management of fistulating perianal disease has been identified as a key topic for colorectal surgeons in the recent ACPGBI Delphi exercise. This questionnaire is intended to provide a survey of current national practice and will help determine the intervention arm for a prospective randomised trial.

All these questions relate ONLY to FISTULATING PERIANAL CROHN'S DISEASE. Please answer with what you would *most commonly* do. It is accepted that clinicians may exercise judgement and tailor decision-making depending on clinical presentation.

Thank you for taking the time to complete this questionnaire. Your support is appreciated!

Matthew Lee, Registrar in General Surgery
Nick Heywood, Pelvic Floor Research Fellow
Steven Brown, Consultant Colorectal Surgeon
Peter Sagar, Consultant Colorectal Surgeon
Nicola Fearnhead, Consultant Colorectal Surgeon

Email: lee.mattjames@gmail.com

The Association of Coloproctology of Great Britain and Ireland

Delphi Exercise: Optimum management of perianal Crohn's disease

<u>Section 1: Questions in this section relate to emergency presentations of perianal sepsis in established or clinically suspected Crohn's disease</u>

Do you use antibiotics peri-operatively if a patient with fistulating perianal disease presents as an emergency and needs an EUA?

Always Frequently Occasionally Never

If yes, when do you start these?

In clinic/on ward
At induction of anaesthesia
Post-operatively
Other (please specify)_____

If yes, which antibiotic(s)?

Ciprofloxacin
Metronidazole
Augmentin
Gentamicin
Other (please specify)_____

Do you obtain imaging pre-operatively?

Always Frequently Occasionally Never

Which modality do you prefer?

MRI perineum CT EAUS

Other(please specify)_____

If the diagnosis of Crohn's is not yet established, but is suspected, which of the following investigations would you undertake?

Faecal Calprotectin:

Almost always Frequently Occasionally Never

Colonoscopy:

Almost always Frequently Occasionally Never

Flexible sigmoidoscopy:

Almost always Frequently Occasionally Never

Video capsule endoscopy:

Almost always Frequently Occasionally Never

MRI enteroclysis:

Almost always Frequently Occasionally Never

Other (please specify):_____

<u>Section 2: Questions in this section are related to the initial surgical management of established or clinically suspected Crohn's fistulae from clinic leading up to and then including first EUA</u>

How do <u>you</u> typically manage perianal sepsis associated with Crohn's perianal fistula in the emergency setting?

Incision and drainage (I&D) alone:

Almost always Frequently Occasionally Never

***Placement of draining seton**:*

Almost always Frequently Occasionally Never

Placement of a cutting seton:

Almost always Frequently Occasionally Never

Excision of tract:

Almost always Frequently Occasionally Never

Other (please specify):

If called for advice by a colleague or registrar who is doing an EUA for perianal sepsis associated with Crohn's perianal fistula in the emergency setting, what would you advise?

Incision and drainage (I&D) alone:

Almost always Frequently Occasionally Never

***Placement of draining seton**:*

Almost always Frequently Occasionally Never

Placement of a cutting seton:

Almost always Frequently Occasionally Never

Excision of tract:

Almost always Frequently Occasionally Never

Other (please specify):

At first scheduled EUA, how do you typically manage symptomatic Crohn's fistulae <u>without</u> focal sepsis?

***Placement of draining seton**:*

Almost always Frequently Occasionally Never

Placement of a cutting seton:

Almost always Frequently Occasionally Never

Excision of tract:

Almost always Frequently Occasionally Never

Fistulotomy:

Almost always Frequently Occasionally Never

Faecal diversion (stoma):

Almost always Frequently Occasionally Never

Other (please specify):_____

When using a seton in Crohn's disease:

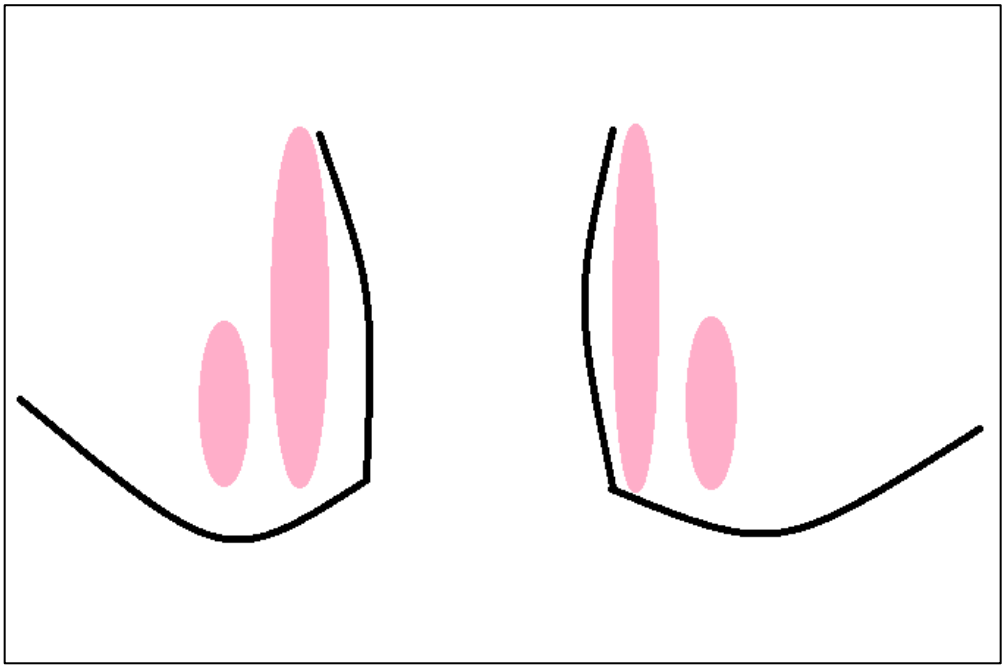
What material do you use? _____

How do you insert the seton?_____

If you secure seton with another material, what do you use to secure it?

_____

Please indicate on the diagram below how you secure a seton:



Section 3: Questions in this section are related to the postoperative management after sepsis control

Questions in this section are related to the management of patients after initial surgical assessment and management, including medical therapy.

When you have found a fistula, do you routinely perform follow-up imaging?

Almost always Frequently Occasionally Never

When you suspect but have NOT found a fistula, do you routinely perform follow-up imaging?

Almost always Frequently Occasionally Never

If so, what modality do you use?

MRI EUS CT Other

Do you routinely perform follow-up examination under anaesthetic?

Almost always Frequently Occasionally Never

If so, when/which cases?

_____

Do you routinely give post-operative antibiotics?

Almost always Frequently Occasionally Never

If so, which cases? _____

If so, which antibiotic(s)?

Ciprofloaxacin
Metronidazole
Augmentin
Gentamicin
Other (which)_____

And for what duration?_____

Does your unit have an IBD Multi-disciplinary meeting?

YES NO

Are patients with fistulating Crohn's disease discussed in your IBD MDT?

Always Usually Sometimes Never N/A

Is there a pathway for access to a gastroenterologist after surgical treatment?

YES NO

Do you arrange follow-up with a gastroenterologist after new diagnosis of fistulating Crohn's disease?

Almost always Frequently Occasionally Never

In your practice, are immunosuprresant drugs used to treat fistula in ano associated with Crohn's?

Almost always Frequently Occasionally Never

Which immunosuppressants would you commonly use (circle as many as apply)?

Steroid therapy
Aminosalicylates (sulfasalazine, mesalamine)
Azathioprine
Mercaptopurine
Methotrexate
Anti-TNF eg Infliximab, Adalimumab (Humira)
Immunosuppression choices managed by gastroenterologist
Other (which?) _____

For how long do you leave a seton in situ? _____

Who makes the decision to remove the seton?

Surgeon Gastroenterologist Joint decision/MDT Patient N/A

Do you use multimodal (combined immunosuppression with surgical intervention) therapy?

Usually Sometimes Rarely Never

Section 4: Definitive management aimed at fistula healing/control

***If you were considering surgical options to try and heal perianal Crohn's fistulae, what options would you most commonly use*? Tick all that apply.**

Removal of seton only
Fistulotomy
Fistulectomy
Anal fistula plug
Mucosal advancement flap
Fibrin glue
LIFT procedure
Over the Scope Clip
Video-assisted anal fistula treatment (VAAFT)
Fistula laser closure (FiLaC)
Local perineal flap
Other (please specify)

Do you use a diverting stoma?

Always Often Sometimes Never

If you do use a diverting stoma, in which circumstances would a stoma be of benefit?

_____
_____
____

Do you treat Crohn's rectovaginal fistulae (RVF)?

Yes No

Which procedure(s) would you usually use for Crohn's RVF?

_____
__
_____
__

Would you perform a proctectomy for perianal Crohn's disease?

Always Often Sometimes Never

In what circumstances would you advise proctectomy?

_____
__
_____
__

What method(s) do you use for perineal wound closure after proctectomy for perianal Crohn's disease?

_____
_____
_____
_____

Optional: If you would like to sketch your management algorithm for perianal Crohn's disease, please feel free to do so below.

Thank you for taking the time to complete this questionnaire.
If you would like to be involved in a consensus exercise or be updated on the findings of this survey, please write your email address below.

_____

Appendix K: Ethical approval for surgeon survey

Downloaded: 21/06/2016
Approved: 29/01/2016

Matthew Lee
Registration number: 150245409
Oncology
Programme: DDP

Dear Matthew

PROJECT TITLE: Assessment of surgical audit/service evaluation data on management of fistulating perianal Crohn's disease
APPLICATION: Reference Number 007386

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 29/01/2016 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 007386 (dated 28/01/2016).

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Yours sincerely

Laura Williams
Ethics Administrator
Medical School

Appendix L: Audit approval for pathway mapping

Dear Matthew Lee

Your proposed Service Evaluation project, titled **'Pathway assessment in fistulating perianal crohn's disease.'**, has been approved following our telephone conversation yesterday and I have registered it on the database as Ref **7130**. Please use this reference number when corresponding with the unit about this project.

It has been included on the Directorate's Clinical Audit and Effectiveness Programme to ensure that the project's progress can be monitored throughout all the stages of the cycle. It is placed on the programme as a P4 Locally Managed project.

At this point I must remind you of the importance of the submission of a report for the project on completion. To help with this I will be able to provide you with a draft report template at that stage of the project. The Trust is required by the Department of Health to provide evidence of audit and evaluation in the form of written reports, not presentations, to maintain our Foundation status. We are also required to provide evidence of where and when results were reviewed so we also require you to identify in the report the group or meeting within your directorate where this happened or a timescale for when this would happen.

The Trust has a legal obligation to preserve Service Evaluation reports for five years post date of submission to the Clinical Effectiveness Unit. However, any project relating to NICE is stored indefinitely within the Trust and any national audit will be kept for ten years. The Clinical Effectiveness Unit will store and record these audit reports for this period of time.

Kind regards

Louise Wake

Appendix M: Ethical approval for surgical consensus exercise

Downloaded: 21/06/2016
Approved: 15/02/2016

Matthew Lee
Registration number: 150245409
Oncology
Programme: DDP

Dear Matthew

PROJECT TITLE: Assessment of medical audit/service evaluation data on management of fistulating perianal Crohn's disease
APPLICATION: Reference Number 007595

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 15/02/2016 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 007595 (dated 02/02/2016).

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Yours sincerely

Paula Blackwell
Ethics Administrator
Medical School

Appendix N: Ethical approval for qualitative interviews

NHS
Health Research Authority

Telephone: 0207 104 8002

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

23 August 2016

Mr Steven Brown
Department of General Surgery
First Floor, Old Nurses Home, Northern General Hospital Herries Road
S5 7AU

Dear Mr Brown

Study title:	**Patient experience of information around surgery for fistulating perianal Crohn's disease**
REC reference:	**16/NW/0640**
Protocol number:	**STH19512**
IRAS project ID:	**210158**

Thank you for your letter of 23 August 2016 responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Kieran Hall, nrescommittee.northwest- gmsouth@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [Interview guide]	1	08 June 2016
IRAS Application Form [IRAS_Form_15082016]		15 August 2016
IRAS Checklist XML [Checklist_15082016]		15 August 2016
Participant consent form	4	23 August 2016
Participant information sheet (PIS)	4	23 August 2016
Referee's report or other scientific critique report [reviewers report]	v4	
Research protocol or project proposal [Protocol]	5	21 July 2016
Response to Request for Further Information		23 August 2016
Summary CV for Chief Investigator (CI) [CV for CI]		
Summary CV for student [CV for PhD Student]		
Summary CV for student [CV student]		
Summary CV for supervisor (student research) [CV for supervisor]		
Summary CV for supervisor (student research) [CV Supervisor]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports

- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/NW/0640	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project. Yours sincerely

On behalf of
Professor Sobhan Vinjamuri Chair

Email: nrescommittee.northwest-gmsouth@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Mr Luke Barron,
Sheffield Teaching Hospitals NHS FT

Appendix O: Participant information sheet for qualitative interviews

Patient experience of information about surgery for perianal Crohn's fistula

You are being invited to take part in a research project to explore patient experience of surgical treatment of perianal Crohn's fistula. Before you decide whether you wish to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please feel free to ask us if there is anything that is not clear or if you would like more information.

What is the project's purpose?
Perianal fistula in Crohn's disease can be challenging to manage. There is sometimes more than one option for surgical treatment, which can depend on patient and surgeon preference. We would like to help people understand their options by providing better information. We first need to understand the information we are currently giving.

Why have I been chosen?
You have been identified by your clinical team as someone who has been treated for perianal Crohn's fistula.

Do I have to take part?
You do not have to take part in this research project. Your care will not be affected whether or not you choose to participate.

What will happen to me if I take part?
At the bottom of this form is an opt-in sheet which allows you to register an interest. If you choose to register an interest in the study your contact details will be passed to the research team who will telephone you to discuss the study further. They will answer any questions about what is involved in the project during that phone-call. They will arrange to meet you at either the Royal Hallamshire Hospital or the Northern General Hospital at a convenient time. When you arrive, we will ask you to complete a consent form. We will then undertake an interview that will last for about one hour. The interview will be recorded on a digital recorder. During the interview, we will ask questions about your experience of surgery in the management of your fistula, and ask you about how you made decisions about your treatment. Afterwards, the researchers will analyse a transcript of your interview, along with others, to understand important themes about information about surgery. You are free to withdraw from the study at any point. Withdrawing will not affect the care you receive.

What do I have to do?
We would like you to participate in the interview and share your experience of discussions about surgery for perianal Crohn's fistula. You will have to arrange your own transport to the meeting, but we will reimburse travel expenses.
What are the possible disadvantages and risks of taking part?
Some people may be upset at discussing previous health-care experiences. If this happens, we will offer to pause or end the interview. If you want further help or support as a result of this, we will ensure that you are put in contact with the Inflammatory Bowel Disease Nurse Specialists.

What are the possible benefits of taking part?

There are no direct benefits to you for participating, but the information we get from this interview will help us to give better information about operations to patients with this condition. This might improve experience and help

What should I do if I have concerns about the project?
If you have any concerns about the project please do not hesitate to contact the following:
Mr Matthew Lee
PhD Student, University of Sheffield/Clinical Research Fellow
m.j.lee@sheffield.ac.uk
07791 519678

Will my taking part in this project be kept confidential?
All the information that we collect about you during the course of the research will be kept strictly confidential. You will not be able to be identified in any reports or publications. Excerpts from transcripts will use pseudonyms.

What type of information will be sought from me, and why is the collection of this information relevant for achieving the research project's objectives?
The information collected is preferences in management of aspects of the condition and results of votes. These are counted at group level, not individual level.

What will happen to the results of the research project?
Following this research, the results may be published in a medical journal and/or presented at an academic meeting. All data presented in either format will be anonymised and you will not be identified in any report or publication. We will share the results with you when the project is completed.
We may use the results of this work to help us to design further research such as surveys, or to develop information resources.
It is possible that researchers in this field may wish to access data from this project. If this is the case, we would allow access to interview transcripts, but would ensure that any identifiable data (names, places, etc.) are censored.

Who is organising and funding the research?
The research is being organised by the following;
Mr Matthew Lee
PhD Student, University of Sheffield/Clinical Research Fellow
m.j.lee@sheffield.ac.uk
07791 519678

Mr Steven Brown
Consultant Colorectal Surgeon, Sheffield Teaching Hospitals
steven.brown@sth.nhs.uk
0114 243 4343

Travel expenses are being funded as part of a grant from the Bowel Disease Research Foundation.

Who has ethically reviewed the project?
This project has been ethically approved by the Research and Ethics committee (REF XXXXX)

Contact for further information
Should you require any further information please do not hesitate to contact the following
Mr Matthew Lee
PhD Student, University of Sheffield/Clinical Research Fellow
m.j.lee@sheffield.ac.uk
07791 519678

Thank you for your time.
Should you agree to take part in the research you will be supplied with a copy of this information sheet and also a copy of the consent form you and the researcher have signed.

……

CUT OFF SLIP

I WISH TO REGISTER AN INTEREST IN THIS STUDY
SIGNED……. DATED……..
FIRST NAME…….. CONTACT NUMBER……

Appendix P: Interview Schedule

Introduction:
Hello, my name is XXXXXX from the Medical School, at the University of Sheffield. Thank you very much for agreeing to talk to me today about your experiences of surgery for anal fistula in Crohn's disease.

If you are happy I would like to record the conversation. I just wanted to reassure you that anything with say to me will all be anonymised. It will not be possible to identify you on any of the publications or transcripts arising from this research as only your age and gender will be reported. The digital recording will not include your name (just your study ID and initials) and it will be erased after transcription

As this interview will be exploring issues around your experiences of living with and being treated for Crohn's disease, this may result in the discussion of sensitive, upsetting or embarrassing topics. If at any point in the interview you are concerned about confidentiality or are uncomfortable in discussing these issues, then please tell me and we can discuss stopping the recording or withdrawing from the study.

Context/Background:
Tell me about yourself.
Prompts
- How long have you had Crohn's disease?
- When did you have your first anal fistula?
- What problems did it cause you?
- How did we treat it?
- How may operations have you had for your fistula?
- What operations have you had for your fistula?

Information experience:
Can you tell me about your experiences of receiving information about your procedure?
Prompts
- Did you receive any information prior to undergoing surgery?
- Explore what the patient was told, by whom, at which time point in the pathway.
- What risks were you told about?
- What were you told about the aims of the operation?
- What were you told about things such as incontinence, need for more operations?
- Explore the time points this was received e.g. well in advance of treatment, just before surgery
- Explore what type of information this was e.g. paper format, web-based, app etc
- What did you think about this information? Explore content e.g. if too long/short/complex/clinical?
- In terms of your own experiences, did the information you receive and read cover all aspects of your operation?
- Discuss information about recovery and future care plan.
- What do you wish you had been told?

Stoma discussion

Did anyone discuss the option of a stoma (bag on the tummy wall) with you?

Prompts

- What did they say?
- How did you find this discussion?
- Why did you choose to have it/not to have it?
- Did anyone discuss the option of removing your back passage (proctectomy)?
- What did they say?
- Why did you choose to have it/not to have it?

Information sources:

Did you access any other information about your procedure outside of that given to you by your doctor?

Prompts

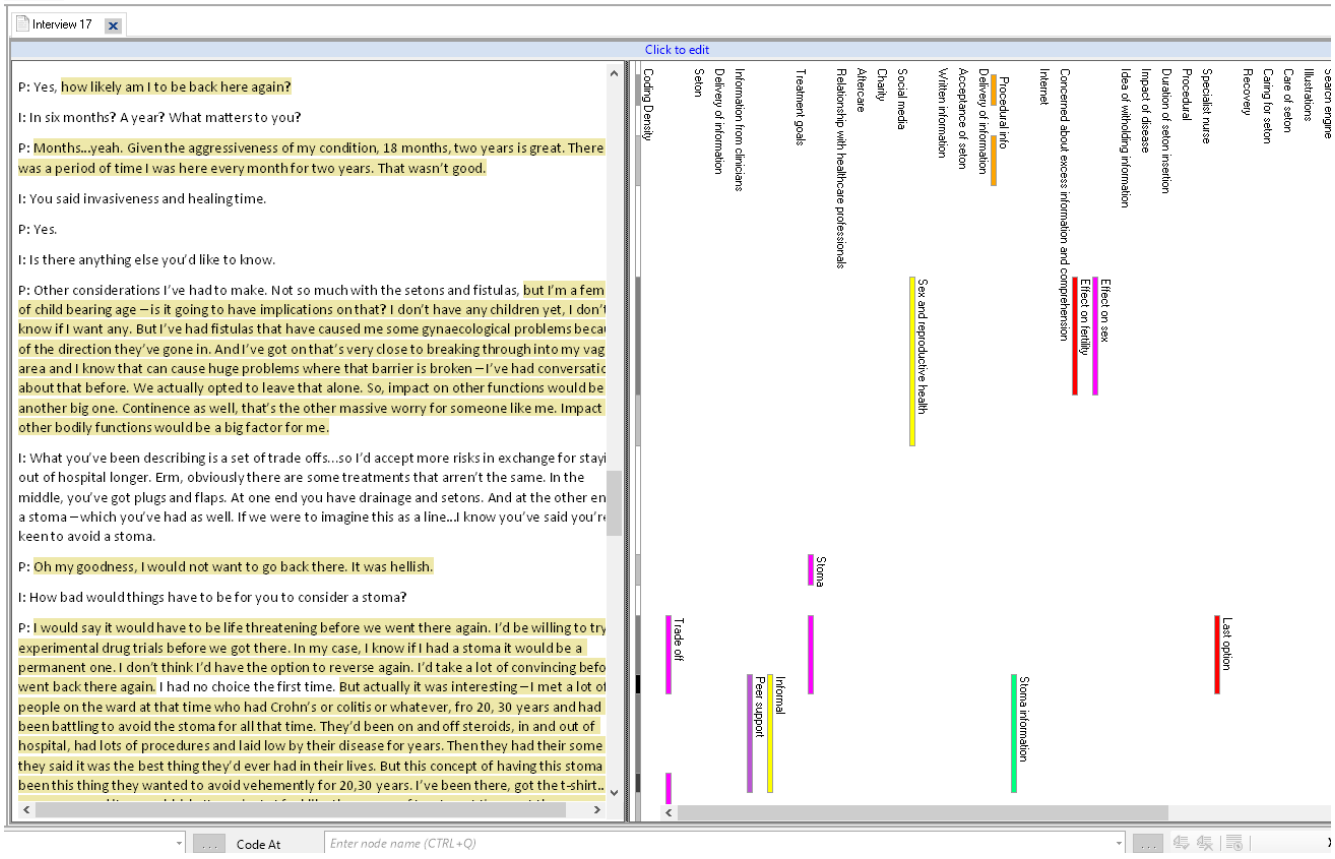
- Explore where they looked for additional information e.g. Internet, Friends and Family, Books, Library, Apps.
- Explore if the Internet what resources e.g. Youtube, Charity websites, NHS website etc?
- Explore what they felt about these resources in terms of quality of information, content, ease of understanding.

If we were to give you information about treatment options, what would be the best way?

Prompts

- Explore formats e.g web-based, app, booklets etc
- Explore what is the optimal time in the pathway from the patient's perspective to be given such information.
- Explore what type of content they would find it helpful to include in any new information resource?
- Explore if anything has been missed from existing resources they have accessed that from their own experiences they feel should be covered in a new resource.

Appendix Q: Interview Coding



Example of NVivo Coding view with nodes highlighted.

Appendix R: Sample transcript

Interview 15

I: Thank you for coming to talk to me. As I started to say, this conversation is completely confidential and anonymised. If at any time you feel uncomfortable and you want to stop or need a break, let me know and I'll stop the recording.

P: Ok.

I: First of all, as I said I don't have your notes or know anything about you. Could you tell me a bit about yourself?

P: Oh I don't know where to start…

I: It's a blind date type question.

P: Oh you don't want to know everything like that about me on a blind date! [laughs]. Do you want me to start from my first…when my problems started? It was about… I've had five operations to do with this and I've literally just had one on the 16th October. So I've always had like Crohn's symptoms, but I ignored my symptoms for way too long. I've got a little girl and she's 5. After I had her, things got worse. I developed something like a cyst, and they diagnosed me with a Bartholin's gland first. Erm, at the same appointment, I told my GP about these other symptoms – I was losing mucous, and I got to the toilet a lot. So they put me on mebeverine. I was referred to gynae with my cyst. I had an operation – marsupialisation – on that. Immediately after that operation I got so so poorly. Erm, and I came back up to urgent care, I came back up to A&E, and I saw the surgeon that did the intial surgery. And he said 'I can't understand why you're so poorly, everythings fine, everything appeared normal'. I was getting pain in my right bum cheek, erm, and I just felt like I wasn't being listened to. I went back to my gynae and she asked for an MRI, and another MRI, a more intense one, and she said 'this is beyond my knowledge'. That's when she realised it was connected to my bowel. So 'this is beyond my knowledge now, I don't know what to do with you'. So she referred me to Mr X – I don't know if you've met him, he's a general surgeon…I think he's a colorectal surgeon actually. And he…what did he do? I think it was March….so that was in 2014…the end of 2014. March 2015 he had me in and put setons in – he was the first person to ever mention Crohn's to me. He was like 'I'm 99.9% sure you've got Crohn's', so he referred me to gastro. It was really really quick. Like, I had to go for all the colonoscopies kind of stuff, erm, and in August time I was diagnosed with Crohn's. At the same appointment they told me I needed to have a stoma. So I've got a defunctioning colostomy. I had that done in 2015 – so I've had it for two years now. And that was basically to divert my bowel, to help the bottom end clear up….that' didn't help, I'm still really bad. Erm, they started me on azathioprine.errm…that was the beginning of 2016, and Infliximab at the same time. They've never managed to stablise my levels so they gave me double dose, then back to normal, then they put me on six-weekly trying to get my levels right. And now because of the last operation I've had, they've put me back on double dose – I'm due some infliximab next week. Erm, how many operations have I mentioned there, three?

I: You've mentioned your first operation with gynae, seton, stoma, and you had one done a few weeks ago.

P: Yeah. I've had five though. So I kept going back to Mr X, and he kept saying 'I think we just need to take everything away, all the badness, all the bad bowel away, sew me up, give me the bag permanently'. But then Dr Y, I'm under here, my gastro, he said – because I want more children – he doesn't want me to go to that final route yet. So he referred me to [teaching] hospital – I'm under [teaching] hospital. And I had Mr Y – he did an EUA and like scraped loads of badness away, replaced some setons, took some away...the maximum I've had is four at once. Like, rectovaginal as well all connected. He left me with a wound that was draining… or actually, did Mr X? There was a wound on my right bum cheek, basically where I sit, and it's been draining for two years. It's horrible, I hate it. It's worse than my bag. I can deal with my bag, that's easy. But this drain.. That's my worst symptom – pain and draining…constant draining from the fistulas around the setons and stuff. That operation that[teaching hospital] did, didn't help, my sypmtoms didn't change, in fact I was probably in more pain. So then, I've had loads of MRIs in between to check on it all. And the last one that they did, they just did a fistulectomy. So at the moment I'm having daily wound packing. It's horrible. It's the worst operation I've ever had, but I'm bouncing….the first two weeks after it I though I was dying. I've never been in so much pain – out of all the operations I've ever had, I've never been in that much pain, I just couldn't see the light. But I feel back to my normal self now, as close to normal as I can be. That's pretty much it.

I: That's quite a…

P: I see my consultant like every month – they know my face when I walk in reception, I don't even need to book in. That's how common I see them.

I: And this is all in three years?

P: Yeah, three years now.

I: You've had these problems with your bowels beforehand and…

P: Yeah, I did, but it's not down on paper because I just ignored my symptoms. It's not something you want to talk about. I'll talk about it now, I don't care. Obviously I was a bit younger and I didn't want to talk about bowel habits. And I'd just go through….like….constant bouts of diarrhoea/constipation/bad diarrhoea/constipation, losing mucous, losing blood…and I just ignored it. Which is why I think I'm so bad now.

I: And it was the gynaes that spotted that something wasn't quite right

P: Yeah, as soon as she saw it was connecting to the bowel, she was like 'this is beyond my knowledge'. She was dead honest with me.

I: So when she said this to you, did you go off and look on the internet?
P: Yeah.

I: So what sort of things did you go looking for?

P: Erm…I don't know, I can't remember. But people always ask me 'how do you deal with it?', but my head was already half way there because I'd researched my symptoms and my condition, and all that so much. I knew that a lot of people that was in the same situation as me ended up with a

bag. So I was already halfway there, I knew I was going to have it. I used to say to my mum, like when I was really poorly, that I was gonna end up with a bag. My mum told me like, stop being silly. I said I'm telling you now I'll end up with a bag And the same day I got my diagnosis was the same day that they told me. So, dunno. Obviously it was a bit of a shock still, but it's my normal now…easy to deal with.

I: So when you went looking, you looked for what your symptoms were and what they might be? And you were looking for what treatments people might give you, is that right?

P: Yeah, it was hard looking like…at the beginning…cause I didn't know what I was looking for. I didn't know what a fistula was. So yeah it was hard looking. But now I know what's wrong with me, I'm on so many support groups on facebook- there's so many people going through what I'm going through. It's crazy.

I: You saw Mr X, didn't you? He was your first general surgeon or colorectal surgeon. What do you remember about… you probably won't remember much because there will have been quite a lot happening, but do remember what he said about what he expected to find in the operation, or what might be involved?

P: Erm… I remember he first mentioned a bag, and he was like it's temporary, it's temporary. And I asked 'What's temporary?' and he said it could be six months, it could be six years. He said 'the longest patient I've got is seven years with a temporary bag'. So he did mention that a few times. I think he always knew where I was going to end up, like, even though my gastro consultant had sent me to [teaching hospital]…I can't remember who said it to me, I think it was Dr Y ' Mr X just thinks we are delaying the inevitable'. I'm probably going to end up with a bag for life, I'm gonna have everything taken away and be sewn shut, but he [Dr Y] wants to explore everything first. I think Mr X is dead matter of fact, like, he just says it how it is and he's dead stern and like…he just tells you straight [laughs].

I: So you've got one person saying 'this is a thing we should do' and another person saying 'we should look at everything else'. Where are you with that?

P: Initially….So Mr X tells me that it won't affect my fertility. If I had the – is it proctectomy? If I had the proctectomy, it wouldn't affect my fertility. And when I went to [teaching hospital] they said it would massively affect me having children in the future. That's all that's in the back of my mind, having more children [laughs]. So, then it's like what do I do? Do I just not take anymore treatment, try for a baby and then go for the proctectomy? Or do I just keep trying? I feel like I'm wasting my life now with these operations. My daughters five now. It's a big thing to me. And the surgeon I saw in [teaching hospital] said 'well what's more important? Your life or having more kids?'. Then it puts it in perspective doesn't it? So…

I: Having a bigger family is important to you, that's what I'm hearing. What other things matter to you here?

P: Quality of life. Definitely.

I: What does that mean for you?

P: Erm. Well I've have a constant draining fistula for over two years. It's horrible. I feel dirty all the time, even though I'm not. And now I'm having wound packing – it's gross. It obviously affects my sex life cause it's all closely linked isn't it. I feel like I can't walk very far because I'm in pain all the time. That's quality of life. And not having to take painkillers every day.

I: Are you working at the moment?

P: Yeah. I work here.

I: What kind of work do you do?

P: I work in a production unit in pharmacy, making up Chemo, stuff like that. Erm, so it varies sitting and standing. There was a point where I couldn't even sit like I'm sitting now – like – I used to have to sit like this [demonstrates], so things are better definitely. If I sit for too long, I'm in pain. If I stand for too long, I'm in pain. Work are really understanding, and they say 'if you need to change job, just tell me'. They are really understanding.

I: We'll get to the stoma in a minute – that's something I want to talk about. But if we could talk about the seton first. When that was done, it was put in, were you told what to expect with it?

P: No. I wasn't told anything when I was discharged. And, I was like…it was a cutting seton as well. So when I took the dressing off and looked in the mirror, I was like 'Oh my god, there is a massive hole in my bum cheek'. Like, it was this big, it wasn't deep but it was a big hole. I remember saying to my mum, you want to see this, it's huge. And she was like don't be silly. They didn't even tell me that I had a wound like. I don't think a lot of the nurses know a lot about it, so they didn't really know. I don't remember seeing the surgeon immediately after my operation. I didn't know about cleaning, care…didn't know anything.

I: People have mentioned things about setons before. Were there any side effects or problems you notices?

P: Draining. Definitely. It was just always wet, and it affects your skin. I was having to wear pads all the time. It' s gross, really gross. Erm, obviously that cost more cause of having the pads all the time. Cause of where it is, it's not easy to wear a dressing. It's just pointless, I was wearing a pad all the time, so that affects your quality of life, what you're wearing, stuff like that. Yeah they didn't really say anything on discharge.

I: Did you google anything about the setons?

P: Definitely, I google everything. It was hard to find stuff at the beginning, but now it's dead easy to find stuff that I need to find, it's just way more common that I thought.

I: From what you said, that was quite a quick move from having setons to a stoma, is that right?

P: Yes, March when Ihad the seton, and I must have been really unwell with loads of drainage. I remember there was one point before I got the setons… I had like 10 courses of antibiotics in the space of 6 months or something. It was ridiculous. That's when they didn't know what it was. My

GP was giving me co-amoxiclav all the time basically. But, yeah, erm, it was quite quick. The same day I got diagnosed was the same day they told me. It was about 2 months.

I: One of the things you've said is your stoma is probably temporary, but that's quite a big window from what you've said. Did they tell you anything else about the risks or benefits of having a stoma?

P: I understood that idea was to divert it, to reduce all the inflammation and stuff. But, it's easy for me to sit hear and say it's not helped me, but it has. It's stopped me from getting worse, but I still don't feel any better. But, I do remember before the stoma, after every bowel movement, I used to be in the most agonising amount of pain. And because I have Crohn's I go to the toilet quite a lot, so I was in pain all the time., I was in tears after every bowel movement, so it definitely helped there – that was a massive relief. Erm, yeah.

I: From the otherside, you said the bag doesn't bother you much now – did it bother you much at the start?

P: No. I handle it well really. I just get on with it, it's what I do.

I: You've talked about proctectomy, removal of the back passage, and you've told me a couple of things that matter to you about it. Have you gone and tried talking to other people about it?

P: Erm, yeah. It's a mixture. Some people have said you can have children, some people have said you can't. so… My consultant has once said to me 'well I'd be very surprised if you got pregnant because of how under pressure your body is anyway'. He'd be very surprised. People that don't understand around me are just like 'try for a baby', and I know I'd be stupid to put my self through that. I can barely look after my daughter and myself now, what am I going to be like with a new born? I'm not stupid.
I: The next thing I wanted to ask about. You mentioned about using support groups online, are they through facebook? Can we talk about those?

P: Yeah

I: I don't know what happens on them as they are closed aren't they? What sort of questions are people with fistulas asking?

P: Anthing, like, anything goes. People talk about sex, like anything. Any advice that you need it's a port of call. You'll get an answer because people have been through it. I've even helped people. I never imagined me. Even on the stoma sites I'm on, like, at the beginning, me asking all these silly little questions, now I can answer them for other people. It's like, you get to help other people. It's really nice, it's nice to be in it.

I: What do you think the two or three most common things people are asking about are?

P: Setons, definitely. Erm…

I: Is it what is a seton? Or?

P: If someone new comes on, they say I'm booked for this surgery, what can I expect? Cause they don't give you a lot to go on, and the nurses on discharge don't know much. Erm. Yeah, I think it really helps.

I: That's fine. And…just looking at my notes. Have you used youtube as well?

P: No…I could easily go on youtube and watch an operation that I've had done, but I'm just not ready to do that. Like, I can picture in my head what it would be like, but no, I'm not interested in that.

I: One of the things we've noticed on youtube is that sometimes patients go on and talk about their experiences – do you think it's useful to hear about other peoples experiences even if they are different to what you've had?

P: Yeah, on the stoma sites, a lot of people do Vlogs, like, so I've watched them before. There's some good ones that are helpful.

I: In an ideal world – you've told me that you don't think we give good information about operations two or three times – if we were going to talk to you about an operation, what are the main things you would want to know?

P: Aftercare, definitely. Like, because of this fistulectomy, I've had conflicting advice about showering daily. They didn't say anything on discharge about showering, I've been showering daily just before I get my dressing changed. And then the other day in clinic, a nurse said I shouldn't be showering because it affects healing. Well…I'm healing, no one has told me up to this point. How can I not shower? What am I supposed to do? So yeah, aftercare definitely. Dunno, signs of infection. I'd know that, maybe a lot of other people wouldn't. Like, I dunno, I'd like to think I'm quite wise when it comes to my health and that I know what to look out for. I know where to get help, but not a lot of people might.

I: Especially if you get someone who hasn't been to the doctors much before. I guess that was someone like you were?

P: Yeah, I'd never seen a doctor up until…I don't see my doctor now, I just see the consultants all the time rather than my GP. I never used to see my GP, then all of a sudden I was there every week. So yeah.

I:The bits of information we need to give to people, what' the best time and place to give it? And how should we give it?

P: Maybe at pre-op? I remember being at pre-op and asking questions and they just didn't know. A lot of my operations have come under EUA with plus or minus, so they never knew what they were doing until I was under, but…I dunno, I know it's a preop clinic and it's just general nurses, but if they were more like… theres so many operations that would go through there so it's impossible, but. I dunno, I even feel like my IBD nurse doesn't know much about it, so maybe she should read up on it…

I: It sounds like having a chat is a way you want information?

P: Yeah.

I: What about written stuff?

P: Yeah or a leaflet. Send me away with a leaflet, that would probably be better.

I: What about a website done by a hospital?

P: Yeah. That's a good idea.

I: If we were having a chat about stoma or proctectomy – this is usually down the line with treatment – when do you think we should talk to people about stomas, and when do you think we should talk to them about it?

P: You mean if the doctor thinks in their mind that it might come to that? I don't know. My doctor knew way efore he told me. I did too in the back of my mind. The stoma nurses are great here, so like they gave me all the information. It was really rushed with mine as well, because they gave me a date and I said I can't take that, my mums on holiday, so they gave me a date two weeks later. Then they called me up the day before my original operation and said 'I'm sorry, you can't have that date now, you'll have to come in tomorrow'. I literally broke down in tears. I left work and came up to the stoma nurses on their clinic. And they were good and calmed me down. I still had it done, even though my mum was away. Erm, so it was all very rushed then. I wasn't ready for it. But it all got changed dead quick. Like yeah, the stoma nurses were great.

I: I guess what I'm asking is: If we think a stoma is a good idea for someone, should we say that right at the start the first time we meet them? Or try other things?

P: Try other things. But I guess that if someone has Crohn's it'll always be in the back of their mind, having a stoma.

I: You think people might have thought about it anyway?

P: Yeah. Like me researching.

P: I think that's covered most of what I wanted to chat about. Is there anything important you think we haven't talked about?

I: No.

P: Thank you.

Appendix S: Ethical approval for questionnaire

NHS
Health Research Authority

London - Westminster Research Ethics Committee

23 August 2017

Dear Mr Lee,

Study title:	**Patient informational preferences in surgical therapies of perianal Crohn's disease**
REC reference:	**17/LO/1446**
IRAS project ID:	**230885**

The Proportionate Review Sub-committee of the London - Westminster Research Ethics Committee reviewed the above application on 22 August 2017.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Favourable opinion
On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

1) Please make the following changes to the Participant Information Sheet:

   a) Under the heading 'Why have I been chosen' change the word chosen to "invited".
   b) Under the heading 'Do I have to take part' being the first sentence with "No".
   c) Under the 'disadvantages and risks' section please insert the following sentence

'Participants can withdraw from the focus group at any point without giving a reason and care will not be affected in any way'.

2) Please make the following changes to the Invite Letter:

a) In the first sentence of the second paragraph insert "always" between the words "not" and "very good".

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

- Informed consent process and the adequacy and completeness of participant information

The member of the Sub-Committee requested minor changes to the Participant information sheet as detailed above.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Twitter advert]	1	14 June 2017
Interview schedules or topic guides for participants [discussion prompt sheet]	1	14 June 2017
IRAS Application Form [IRAS_Form_04082017]		04 August 2017
Letters of invitation to participant [Participant Invite letter]	1	14 June 2017
Non-validated questionnaire [patient questionnaire]	3	17 July 2017
Other [CV for co-investigator]		
Other [CV for co-investigator]		
Other [CV for co-investigator]		
Other [CV for co-investigator]		
Participant consent form [informed consent form]	1	14 June 2017
Participant information sheet (PIS) [Participant Information Sheet]	1	14 June 2017
Referee's report or other scientific critique report [Independent Scientific review]		
Research protocol or project proposal [Research Protocol]	2	13 July 2017
Summary CV for Chief Investigator (CI) [CV for CI]		

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

17/LO/1446	**Please quote this number on all correspondence**

Yours sincerely

PP Mr Robert Goldstein Chair

Email: nrescommittee.london-westminster@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Mr Luke Barron, Sheffield Teaching Hospitals NHS FT

Appendix T: Invitation letter to participants

Participant Invite Letter V1 14/06/2017 STH19994

IRAS ID: 230885

Dear Patient

This letter has been sent to you by surgeons at your local hospital, because you have been treated for an anal fistula (connection between the back passage and skin) related to Crohn's disease.

We know that surgeons are not very good at talking to patients about choices, and what operations help your fistula. We would like your help to change this, by designing a decision aid for patients. This questionnaire will help us to understand what information needs to be in this, and how it should be presented.

Enclosed is a questionnaire, which we have designed after interviewing patients about their experiences with Crohn's anal fistula. We would appreciated it if you could complete it – it should take no more than 15 minutes. We'd be grateful if you could send this back to us within a month of receiving it.

When you have completed it, please put in in the enclosed PREPAID envelope, and put it in a post box.

You do not have to complete this, and whether you complete it or not, it won't affect the care you receive. Each questionnaire has a code number– this means that we can tell your local hospital that one of their patients has completed the questionnaire, and they will get some research funding for this. All your responses come to the team in Sheffield, and we cannot identify you – this means no-one knows what you have said in your questionnaire.

We are not going to ask you to sign a consent form – if you complete and return the questionnaire, we will assume you are happy to participate.

If you have any questions, we would be happy to answer them. I

hope you are willing to participate in this study.

Yours faithfully

Mr Matthew Lee,

Research Fellow in General Surgery, Sheffield Teaching Hospitals
m.j.lee@sheffield.ac.uk

0114 243 43 43 (mobile via switchboard)

Appendix U: Final questionnaire

Perianal Crohn's Fistula – Surgical Treatment Preferences
Patient Questionnaire

Introduction

Thank you for helping us with this study.

The aim of our study is to find out what you thought about your surgical treatment for your anal fistula. We are interested in finding out how you wanted decisions about your treatment to be made, and what information and support you felt may have been of help to you at the time.

There are no right or wrong answers to these questions. We would like to hear about your personal experiences, views and opinions and so any information you provide will be of real value to us. All the information collected is anonymous. This questionnaire should take about 20 minutes to fill in.

By returning the questionnaire you are giving consent for your anonymised data to be used in this study. Whether you agree to participate or not, your care will not be affected and your doctors will not be told about your answers.

When you have finished, please return it to us in the pre-paid envelope. There is no need to use a stamp.

Thank you for your help.

Matthew Lee, Research Fellow in General Surgery

Section 1: About you

How old are you? Please write your age in years_____

Please indicate your sex below

Male _ Female

Other_____

Prefer not to answer_____

How long since you were diagnosed with Crohn's disease? Please write in years and months_____

What is the most recent operation you had for your fistula?

Operation	Please tick
Examination under anaesthetic only (examination of my bottom, with no other procedures performed)	
Placement of a seton (insertion of a band into the fistula to allow infection to drain)	
Advancement flap (moving part of the lining of the back passage to cover the inside hole of the fistula)	
Fistula plug (insertion of a plug to block the fistula)	
Formation of stoma (bringing the bowel to the tummy wall and using a bag to divert faeces away from the back passage)	
Proctectomy (removal of back passage)	
I'm not sure	
Other procedure not named above	

Please tell us about your level of education (please tick one)

I have one or more GCSEs	
I have one or more A-levels	
I have a Bachelors degree (e.g. BSc, BA)	
I have a Post-graduate degree (Masters/Doctorate)	
I do not have any qualifications	
Other	

(Optional) Which ethnic group do you belong to? Please tick one box only

White British	
Mixed or multiple ethnic groups	
Asian or Asian British	
Black, African Caribbean or Black British	
Prefer not to answer	
Other ethnic group (please specify below)	

Other_____

Section 2: What information did you use before surgical treatment?

In addition to information from doctors and nurses at the hospital, did you find any of the following information helpful when deciding on your treatment? Please tick all relevant answers. If you used an information sheet, please rate how useful this was from 1-9, with 1 being not helpful, and 9 being very helpful.

Information source	**Please tick if used**	**Usefulness 1-9 (1=not important, 9=essential)**
Discussions with my GP		
Internet forums/chat rooms		
Social media (e.g. Twitter, Facebook, Instagram, blog)		
Wikipedia		
Online videos (e.g. Youtube/Vlogs)		
Charity websites		
NHS Choices		
Leaflets/booklets provided by the hospital		
Friends or family		
Other (please specify below)		

Other:_____

When discussing treatments with you, which of the options below would be helpful in deciding about surgery? Please rate these from 1-9, with 1 being not important, and 9 being essential.

Information	**Importance 1-9 (1=not important, 9=essential)**
How long I would be in hospital	
Will the operation close my fistula?	
About risks of the operation	
How much pain I would have after the operation	
How 'invasive' the procedure was	
Whether I will need help with my wound when I go home from hospital	
Whether I would need to attend my GP practice/community clinic after my operation	
Whether I would need to attend hospital frequently after my operation	
Whether I would need further operations in the future	
Whether the treatment would stop discharge around my back passage	
Whether the treatment would affect my continence (i.e. would it cause leakage from my back passage?)	
Whether the treatment would affect my ability to work	
Whether the treatment affect my ability to sit down	
Whether the treatment affect sexual activity	
Whether I would still need to take medications to treat my fistula	

Section 3: How did you make decisions about your treatment?

When you discussed your fistula with the surgeon, did they offer you a choice of operations?

Yes, I was offered a choice of operations	
No, I was not offered a choice of operations	
I am not sure/don't know	

Please tick the box next to the statement that best describes the situation that ACTUALLY HAPPENED during your consultations. Please tick one only

I made the final selection about which treatment I had	
I made the final selection of my treatment after I had seriously considered my doctor/nurse's opinion	
My doctor/nurse and I shared the responsibility for deciding which treatment was best for me.	
My doctor/nurse made the final decision about which treatment was used, but seriously considered my opinion.	
My doctor/nurse made all the decisions regarding my treatment.	

Please tick the box next to the statement that best describes the situation that you believe would be IDEAL. Please tick one box

I prefer to make the final selection about which treatment I will have.	
I prefer to make the final selection of my treatment after seriously considering my doctor/nurse's opinion	
I prefer that my doctor/nurse and I share responsibility for deciding which treatment is best for me.	
I prefer that my doctor/nurse makes the final decision about which treatment will be used, but seriously considers my opinion.	
I prefer to leave all decisions regarding my treatment to my doctor/nurse.	

What information helped you decide on treatment? (Please tick)

	Yes	No	Unsure
I was helped by talking to the surgeons in surgical clinic			
I was helped by talking to the doctors in gastroenterology clinic			
I was helped by talking to the specialist nurses (e.g. IBD nurse or colorectal nurse)			
I found the written leaflets in hospital helpful			
I was helped by talking to other patients in person or on the internet			
I was helped by talking to support groups			

Were there other things you found useful? Please tell us what they were

_____

_____

_____

_____

Section 4: How would you like to make decisions about your treatment?

Did you feel that you had enough information to decide what treatment to choose? (Please tick one)

Yes, I had all the information I needed	
No, I would have liked more information	
Not applicable	

Whom would you prefer to talk to, about making a decision about your treatment? Please tick all that apply

A surgeon from the surgical clinic at the hospital	
A doctor from my gastroenterology clinic at the hospital	
A specialist bowel disease nurse from the hospital	
My GP or a practice nurse	
My family	
My friends	
Patients who have been through the same treatments	
No one	
Other (please specify)	

Other_____

We would like to know whether you were happy with your treatment decision

To what extent do you agree or disagree with the following statements about your treatment decisions?

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
It was the right decision					
I regret the choice that I made					
I would go for the same choice if I had to do it over again					
The choice did me a lot of harm					
The choice was a wise one					

Section 5: How would you like to be given information about treatment for your fistula?

How would you like to receive information to help you decide about Crohn's anal fistula treatment? Please tick all that apply

Booklet or leaflet	
DVD or video	
From others with experience of the condition/treatment	
Interactive website	
Webpage with information	
Face to face chat with a doctor/surgeon	
Face to face chat with a nurse	
I do not require/want this information	
Support Group	
Not sure	
Other (please specify)	

Other:_____

_____

_____

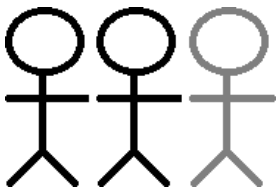
Do you have access to the internet? (Please tick one)

I have my own computer/smart phone and use the internet at home	
I can access the internet e.g. at someone else's house or at the library	
I cannot use a computer/smartphone myself but friends and relatives can use them for me	
I have no access to a computer/smartphone or the internet	
I do not want to use a computer/smartphone or the internet	

If information was available on the internet which could give you the pros and cons of your fistula treatment options, how likely would you be to use this?

Very likely	
Somewhat likely	
I'm not sure	
Somewhat unlikely	
Very unlikely	

Please tick the box next to your preferred way of being given this information

A statement in words: e.g. Anal fistula affects many people with Crohn's disease	
A number: e.g. 1 in 3 people with Crohn's disease will develop an anal fistula	
A percentage: e.g. 30% of people with Crohn's disease will develop an anal fistula	
A fraction: e.g. 1/3rd of people with Crohn's disease will develop an anal fistula	
A chart e.g. to show what fraction of people with Crohn's disease develop an anal fistula	
A graph to show what fraction of people with Crohn's disease develop an anal fistula	
Represented as a picture for example, 1 in 3 people with Crohn's disease will develop an anal fistula 	

We want to make any information we give to you relevant and interesting. The following are some suggestions of things that we can do. Please tick the relevant answer.

	Yes	**No**	**Unsure**
I would like to see/hear the stories of other patients who have had an anal fistula in Crohn's disease			
I like to see pictures of relevance to make the information more real and useful			
I prefer lots of factual information			
I prefer lots of diagrams			
I would like to see diagrams of what an operation involves			
I would like to see a video of what happens when you come into hospital for an operation			

Thank you for completing this questionnaire. Please return it in to us in the PRE-PAID envelope.

If you cannot find the pre-paid envelope, please return the questionnaire

to: Professor Brown's Secretary

Dept of General Surgery
First Floor Old Nurses
Home Northern General
Hospital Herries Road

Contact:

Mr Matthew Lee, Clinical Research Fellow, Sheffield Teaching Hospitals. Tel: 0114 243 43 43

Email: m.j.lee@sheffield.ac.uk

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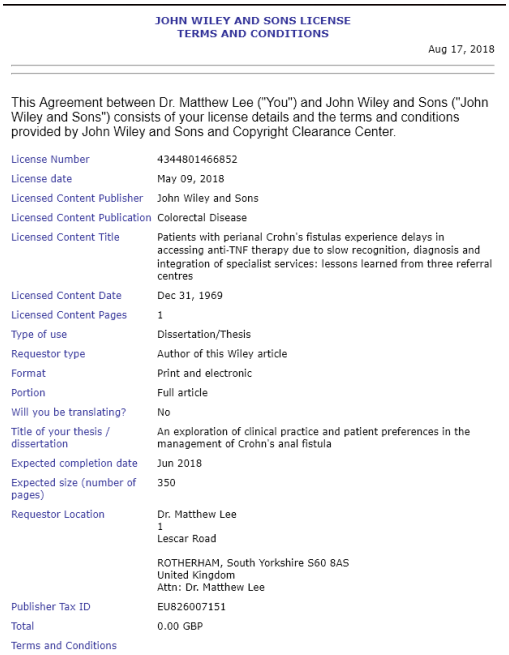
Lee MJ, Freer C, Adegbola S, Parkes M, Hart AL, Fearnhead NS, Lobo AJ, Brown SR. Patients with perianal Crohn's fistulae experience delays in accessing anti-TNF therapy due to slow recognition, diagnosis and integration of specialist services: lessons learned from three referral centres. Colorectal Diseases 2018 [in press]



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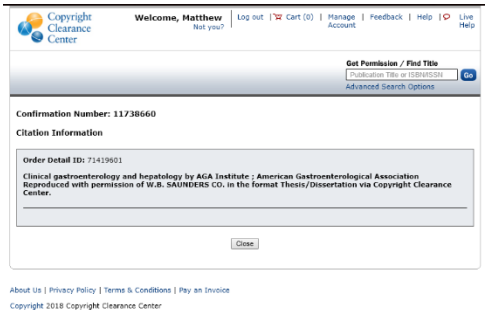
Lee MJ, Parker C, Taylor SR, Guizzetti L, Feagan BG, Lobo AJ, Jairath V. A systematic review and meta-analysis of medical therapies for fistulising Crohn's disease. *Clinical Gastroenterology and Hepatology* [epub ahead of print]



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Lee MJ, Brown SR, Fearnhead NS, Hart AL, Lobo AJ. How are we managing Fistulating Perianal Crohn's Disease? Results of a national survey of Consultant Gastroenterologists. *Frontline Gastroenterology* Published Online First: 23 September 2017. doi: 10.1136/flgastro-2017-100866. The author retains the right to reproduce the accepted article and constituent parts in as outlined in section 4 of 'rights granted to owners of the contribution' in the frontline

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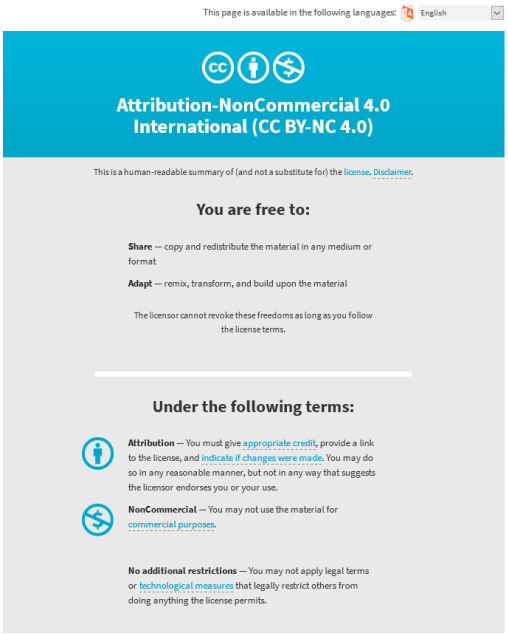
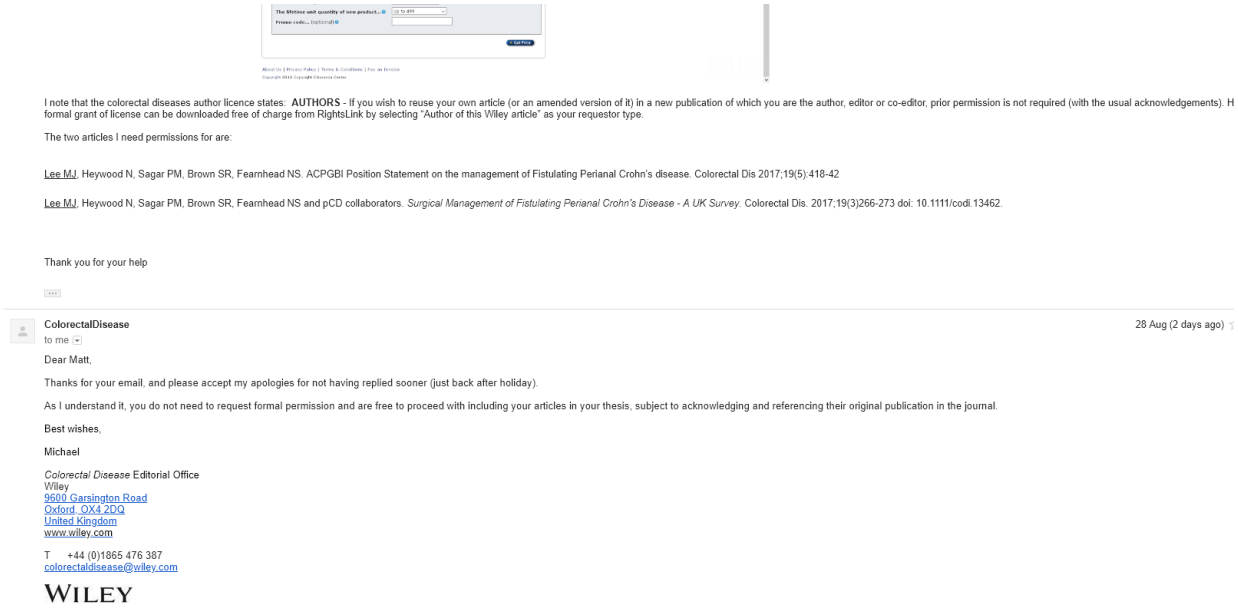
This article has been accepted for publication in Lee MJ, Brown SR, Fearnhead NS, et al How are we managing fistulating perianal Crohn's disease? Results of a national survey of consultant gastroenterologists Frontline Gastroenterology Published Online First: 23 September 2017. doi: 10.1136/flgastro-2017-100866 following peer-review. The definitive copyedited, typeset version is available at https://fg.bmj.com/content/9/1/16





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The two articles I need permissions for are:

Lee MJ, Heywood N, Sagar PM, Brown SR, Fearnhead NS. ACPGBI Position Statement on the management of Fistulating Perianal Crohn's disease. Colorectal Dis 2017;19(5):418-42

Lee MJ, Heywood N, Sagar PM, Brown SR, Fearnhead NS and pCD collaborators. *Surgical Management of Fistulating Perianal Crohn's Disease - A UK Survey*. Colorectal Dis. 2017;19(3)266-273 doi: 10.1111/codi.13462.

Thank you for your help

ColorectalDisease 28 Aug (2 days ago)
to me

Dear Matt,

Thanks for your email, and please accept my apologies for not having replied sooner (just back after holiday).

As I understand it, you do not need to request formal permission and are free to proceed with including your articles in your thesis, subject to acknowledging and referencing their original publication in the journal.

Best wishes,

Michael

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Lee MJ, Heywood N, Sagar PM, Brown SR, Fearnhead NS and pCD collaborators. *Surgical Management of Fistulating Perianal Crohn's Disease - A UK Survey*. Colorectal Dis. 2017;19(3)266-273 doi: 10.1111/codi.13462.

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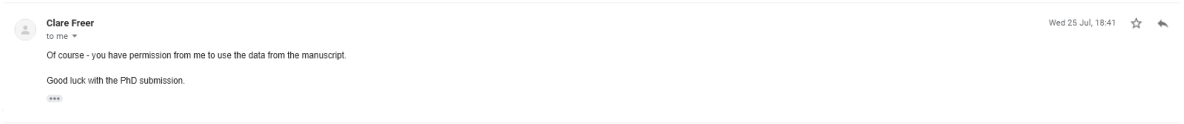

Clare Freer Wed 25 Jul, 18:41
to me

Of course - you have permission from me to use the data from the manuscript.

Good luck with the PhD submission.

miles.parkes@doctors.org.uk Mon 30 Jul, 18:13
to me

yes happy

Miles

HART, Ailsa (LONDON NORTH WEST UNIVERSITY HEALTHCARE NHS TRUST) Wed 25 Jul, 19:28
to me

Of course.

Good luck with the thesis – hope all well.

Best

Ailsa

From: Matt Lee [mailto:lee.mattjames@gmail.com]
Sent: 25 July 2018 10:51
To: HART, Ailsa (LONDON NORTH WEST UNIVERSITY HEALTHCARE NHS TRUST)
Subject: PhD Thesis

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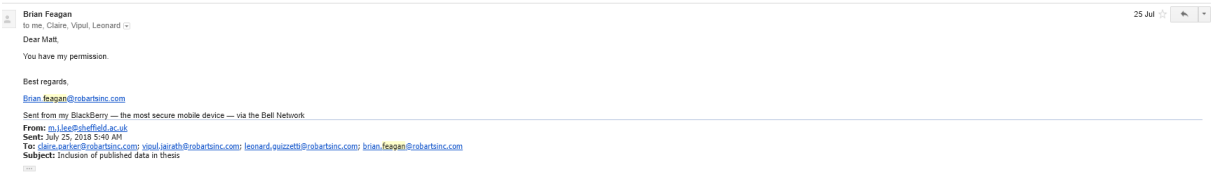

Brian Feagan 25 Jul
to me, Claire, Vipul, Leonard

Dear Matt,

You have my permission.

Best regards,

Brian.feagan@robartsinc.com

Sent from my BlackBerry — the most secure mobile device — via the Bell Network

From: m.j.lee@sheffield.ac.uk
Sent: July 25, 2018 5:40 AM
To: claire.parker@robartsinc.com; vipul.jairath@robartsinc.com; leonard.guizzetti@robartsinc.com; brian.feagan@robartsinc.com
Subject: Inclusion of published data in thesis

Claire Parker 25 Jul
to me, Vipul, Leonard, Brian

Permission granted

Claire Parker | *Scientific Writer*
Robarts Clinical Trials | 100 Dundas Street | Suite 200 | London, ON | CANADA N6A 5B6
Tel: 01 226 270 6781 | Cell: 01 519 933 6396 | Fax: +1 519 931 5705 | Email: Claire.Parker@RobartsInc.com
www.robartsinc.com

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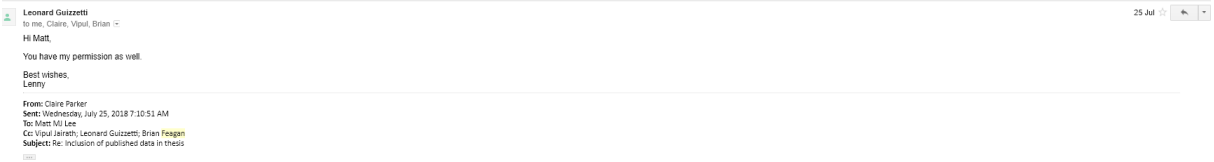


Leonard Guizzetti 25 Jul
to me, Claire, Vipul, Brian

Hi Matt,

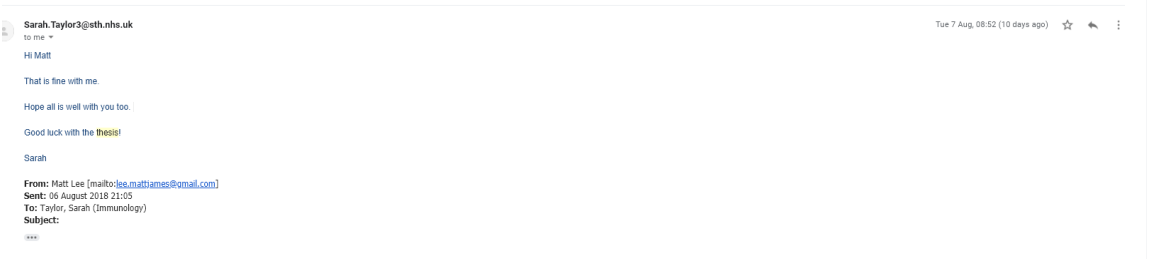
You have my permission as well.

Best wishes,
Lenny

From: Claire Parker
Sent: Wednesday, July 25, 2018 7:10:51 AM
To: Matt MJ Lee
Cc: Vipul Jairath; Leonard Guizzetti; Brian Feagan
Subject: Re: Inclusion of published data in thesis

Vipul Jairath 25 Jul
to Leonard, me, Claire, Brian

More than happy Matt- good luck!



Sarah.Taylor3@sth.nhs.uk Tue 7 Aug, 08:52 (10 days ago)
to me

Hi Matt

That is fine with me.

Hope all is well with you too.

Good luck with the thesis!

Sarah

From: Matt Lee [mailto:lee.mattjames@gmail.com]
Sent: 06 August 2018 21:05
To: Taylor, Sarah (Immunology)
Subject:

Nick Heywood
to me

Thu 26 Jul, 11:59

Hi Matt,

Absolutely this would be fine. Good luck with the VIVA

Regards

Nick Heywood
BMedSci BMBS MRCS MD
General Surgery & Colorectal Trainee
Northwest Deanery
Vice Chair of Northwest Research Collaborative

Kaps
to me

Wed 25 Jul, 20:33

Of course buddy

e. ks303@doctors.org.uk
m. 07725 810 141

Sent from my iPhone

Many thanks. | Thank you! | Thanks a lot!

Phil Tozer
to me

Wed 25 Jul, 16:52

Thanks for the message Matt.

Absolutely happy.

Good luck!

Phil

Sent from my iPhone

SAGAR, Peter (LEEDS TEACHING HOSPITALS NHS TRUST)
to me

Mon 30 Jul, 14:58

Hi Matt
Just back from family hols so apologies for slow response
Yes very happy for you to use this material and good luck !!
BW Pete

From: Matt Lee <lee.mattjames@gmail.com>
Sent: 25 July 2018 10:49
To: SAGAR, Peter (LEEDS TEACHING HOSPITALS NHS TRUST)
Subject: PhD Thesis
