Perianal fistula:

Improving diagnosis and understanding

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Thesis towards Doctor of Philosophy (PhD)

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Thesis Abstract

Perianal sepsis is poorly understood both in the literature and by patients and clinicians. This limits our ability to develop a clinical trial which would help determine best practice in perianal Crohn's disease. This thesis aims to establish the necessary background for a clinical trial in perianal Crohn's disease, to develop an improved understanding of the natural history of perianal sepsis and explores the use of novel imaging technology to improve evaluation, understanding and communication as to the nature of perianal fistulas.

(A) Epidemiology of perianal sepsis – understanding the origin

Perianal abscesses and fistulas are common and represent a significant caseload within the NHS. Current understanding of the relationship between abscess and fistula comes from often old, mostly single institution studies. The same can be said about the natural history of perianal fistulising Crohn's disease, where once again much of the epidemiological knowledge is derived from (sometimes historic) long-term population cohort studies, which are often single centre studies lacking therefore external validity and often lack the diversity of population.

Using Hospital Episode Statistics (HES) and a local hospital database we have established a new estimate for the rate of fistula formation following perianal abscess, using national data over a fifteen-year period, and quantified independent predictors of fistula following abscess which include inflammatory bowel disease, female gender and the location of the anorectal abscess.

(B) Assessing outcomes for perianal Crohn's disease

The lack of objective assessment tools for determining outcome following treatment of Crohn's anal fistula means that investigators often use multiple outcome measures, that these varies between studies, and that new measures are often created. This thesis describes the creation of a core outcome set for fistulising Crohn's disease. Core outcome sets are groups of outcome measures that have been identified through a systemic review and a Delphi process, and ratified by key stakeholders, which fundamentally includes patients. They are the outcomes which are thought most valuable and should, at the minimum, be reported in every study of that condition. We have developed an eight-domain outcome set for fistulising Crohn's disease after surveying 187 surgeons, gastroenterologists, nurses, radiologists and patients from across the UK.

(C) Creating a novel objective outcome measure

There is no standardized, reproducible measure for clinicians to use to assess the effect of medical treatment of Crohn's anal fistula. Currently the success of treatment is subjectively assessed clinically or radiologically. A local pilot study of specialist GI radiologist review of MRI scans before and after treatment with infliximab demonstrated that the radiologists were only in universal agreement on the status of a fistula around three-quarters of the time. This thesis has created the necessary background information to create a robust activity-based MRI score based on fistula volume calculation. The aim is that it will both serve as an objective adjunct to decisional algorithms, which also include clinical score and fistula anatomy, and to allow the development of predictive factors based on an objective assessment of response to treatment.

(D) Improved evaluation, understanding and communication of the nature of perianal fistulas.

Perianal Crohn's fistulas are complex and recurrence/reoperation rates are high. With each surgical intervention, scar tissue forms, distorting anatomy. Whilst conventional 2D pelvic MRI is effective at defining anatomy and guiding surgery, it remains difficult for surgeons to conceptualise complex fistula. Judicious surgery relies on knowledge of exact fistula morphology in relation to the anal sphincter; without this accurate appreciation of the anatomy, injudicious, imprecise or aggressive surgery can result in incontinence and/or recurrence.

This thesis describes a variety of different media of 3D reconstruction of the anorectum including the sphincter and the fistula tract(s), including the creation of 3D static images, digital animations, augmented reality platforms and 3D printed models. The 3D reconstructions have been created with the aim of improving conceptualization for trainees, patient understanding and surgical decision-making through the 3D modelling of perianal Crohn's disease.

Dedication

To my wife Jessamy, you have endured countless late nights, teleconferences and discussions about fistulas! I have subjected you to many a proof-reading exercise and you have never been anything but completely supportive and wonderful.

I dedicate this thesis to my wife (Jessamy), my sons (Leo & Jasper). This thesis is as much yours as it is mine. Jessamy, Leo, and Jasper thank you. You are both my everything and my driving force.

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My thesis would not have been possible without the support from my supervisors, collaborators but most importantly from my family and friends. I would like to thank the following people for guiding me through the past 3 years. The merits of this thesis as well as my other achievements would have been possible without their help and I would like to take this opportunity to thank them each in turn.

Professor Phillips has been a beacon of academic and pastoral wisdom throughout this thesis. Following his retirement his retirement, this mantle has been taken up by Mr Phil Tozer. Phil has been subjected to each and every first draft of everything I have written and allowed me to grow as an academic surgeon. His contribution to this thesis and my time at St Mark's is immeasurable and I am truly indebted. Professor Hart has been a fantastic supporter and facilitator of my thesis. I learnt a tremendous amount from her and she again has worked at developing my academic skill set. Professor Faiz's, acumen and critical appraisal skills are both attributes that I have benefitted from during this thesis. He has been an incredibly supportive influence and I am very grateful to him. Finally, Dr Phillip Lung's patience and perseverance has been invaluable. Together we have had the opportunity to explore a number of surgical technologies and without him this thesis simply would not have been possible. Through him I have not only developed specific expertise in imaging but also have become more confidence in research.

There are many internal and external collaborators who have helped me through my thesis. In particular, Samuel Adegbola has been a fellow researcher within the Robin Phillips Fistula Research Unit (FRU), who has provided sanity and guidance both

academically and personally. Alan Askari has been great source of inspiration and has helped me navigate my way through the world of academia. All the consultants at St Mark's have been incredibly helpful but Janindra Warusavitarne warrants a special mention. He has supported my academic career both within and outside this thesis, for which I am extremely grateful. Many of my external collaborators come from the ENiGMA collaborative within in the UK and I grateful to have been given the opportunity to work with all of them.

My wife (Jessamy) and my sons (Leo & Jasper) have had to endure countless telephone conferences and nights where I have been tied to my laptop. Jess, you are my best friend and all of you are my guiding lights.

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Lastly my thanks go to the IBD patients who have guided me through many of the projects in this thesis. The IBD patient panel at St Mark's, Azmina Verjee and Sue Blackwell guided me through a number of chapters and most importantly helped ensure that this thesis is patient centred and its results are relevant to patients.

Declaration of Originality & Contributions to this Thesis

This thesis and all studies contained represent my own original work under the guidance of my supervisors (Professor Phillips, Mr Phil Tozer, Professor Hart, Professor Omar Faiz and Dr Phillip Lung). Professors Phillips and Hart and Mr Tozer have played a key role in determining the direction of the thesis. Professor Faiz has provided expertise in the analysis of large datasets. Dr Lung has been instrumental in all the radiological based chapters and led the innovation aspect of the thesis.

All surgeries and MRI scans have been undertaken by the clinical staff at London NorthWest University Healthcare NHS Trust (St Mark's and Northwick Park General Hospital). All data analysis, interpretation and writing of the thesis has been carried out by myself. Mr A Askari assisted with retrieving and analysing the data from the Hospital Episode Statistic dataset. Dr P Lung Dr J Burn and Dr U Patel were the radiologists who performed the volumetric assessment for the MRI studies. In systematic reviews, Mr S Adegbola, Mr P Tozer, Mr M Lee and Mr N Heywood acted as second reviewers in the selection of the relevant articles and the wider ENiGMA collaborative, headed by Professor Ailsa Hart and Miss Nicola Fearnhead, reviewed the publication before submission. Dr Lung assisted me with segmentation to create 3D reconstructions and 3D prints. TouchSurgery created the 3D animations.

All other work contained within this thesis has been referenced accordingly. All my supervisors have helped in guiding the editing of the chapters and the thesis as a whole.

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Publications, Presentations, Prizes & Grants

Publications from this thesis:

Papers

1. **Perianal Abscess**
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   British Medical Journal, 2017; 356: j475

2. **Management of perianal Crohn's disease in the biologic's era.**
   Adegbola SO, **Sahnan K,** Tozer PJ, Faiz OD, Hart A.
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3. **The natural history of anorectal sepsis in England.**
   Sahnan K, Askari A, Adegbola SO, Tozer PJ, Phillips RKS, Hart AL, Faiz OD.
   British Journal of Surgery, 104: 1857–1865. doi:10.1002/bjs.10614

4. **Persistent fistula following anorectal abscess drainage – local experience of 11 years.**
   Sahnan K, Askari A, Adegbola SO, Warusavitarne J, Lung PFC, Hart AL, Faiz OD, Phillips RKS, Tozer PJ.
   Dis Colon Rectum 2018. *(accepted in press)*

5. **Developing a core outcome set for Fistulising Perianal Crohn's Disease**
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6. **Volume assessment magnetic resonance imaging technique for monitoring perianal Crohn's fistulas.**
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7. **Improving the understanding of perianal Crohn's fistula through 3D modelling.**
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   Ann Surg. 2018 Jun;267(6):e105-e107.

8. **Innovation in the imaging perianal fistula: a step towards personalised medicine.**
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9. **The use of 3D imaging to facilitate training during complex fistula surgery.**
   Sahnan K, Lung PFC, Adegbola SO, Shaikh S, Iqbal N, Hart AL, Warusavitarne J, Faiz OD, Phillips RKS, Tozer PJ.
   Colorectal Dis. 2019 Jan 9. doi: 10.1111/codi.14551.

10. **Medical-surgical combined approach in perianal fistulizing Crohn's disease (CD): doing it together.**
    Sahnan K, Adegbola SO, Farelerira A, Hart A, Warusavitarne J.
    Curr. Drug Targets 2019 May 19. Doi 10.2174/1389450120666190520103454.

Book Chapter

11. Management of perianal Crohn's disease in the biologics era.
    Adegbola SO, **Sahnan K,** Tozer PJ, Faiz OD, Hart A.

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5. **Sahnan K,** Tozer P, Adegbola S, Lee M, Heywood N, McNair A, Hind D, Yassin N, Lobo A, Brown S, Sebastian S, Phillips R, Lung P, Faiz O, Crook K, Blackwell S, Verjee A, Hart A, Fearnhead N and the ENiGMA collaborative. **Developing a core outcome set for Fistulising Perianal Crohn's Disease**.
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6. **Sahnan K,** Pellino G, Adegbola SO, Tozer PJ, Chandrasinghe P, Miskovic D, Hompes R, Hart A, Warusavitarne J, Lung PFC. **Development of a model of 3D imaging for the pre-operative planning of TaTME.** European Crohn's & Colitis Organisation. Poster Presentation, February 2018.

7. **Sahnan K,** Adegbola SO, Tozer PJ, Burling D, Gupta A, Warusavitarne J, Faiz OD, Phillips RKS, Hart A, Lung PFC. **Different platforms of 3D reconstructions in complex perianal Crohn's fistula disease**. European Crohn's & Colitis Organisation. Poster Presentation, February 2018.

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9. **Sahnan K,** Adegbola SO, Mitra A, Warusavitarne J, Faiz OD, Watfah J, Phillips RKS, Hart A, Tozer PJ. **Improving the diagnosis of Crohn's disease (CD) in patients presenting with perianal abscess to the emergency surgeons.** European Crohn's & Colitis Organisation. Poster Presentation, February 2018.

10. **Sahnan K,** Adegbola S, Tozer P, Gupta A, Warusavitarne J, Faiz O, Hart A, Phillips R, Lung P. **MRI fistulography**. European Crohn's & Colitis Organisation. Poster Presentation, February 2018.

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12. **Sahnan K,** Adegbola S, Mitra A, Tozer P, Warusavitarne J, Faiz O, Lung P, Watfah J, Hart A, Phillips R. **Improving the diagnosis of Crohn's disease (CD) through the selective use of faecal calprotectin with patients presenting with perianal abscess.** ESCP, Poster Presentation, September 2017

13. **Sahnan K,** Askari A, Adegbola S, Tozer P, Hart A, Phillips R, Faiz O. **Prediction of fistula formation following a Crohn's abscess**. ESCP, Poster Presentation, September 2017

14. **Sahnan K,** Askari A, Adegbola S, Tozer P, Lung P, Watfah J, Warusavitarne J, Faiz O, Hart A, Phillips R. **Abscess to fistula formation – local experience of 11 years.** ESCP, Poster Presentation, September 2017

15. **Sahnan K,** Adegbola SO, Tozer PJ, Burling D, Gupta A, Warusavitarne J, Phillips RKS, Hart A, Lung PFC. **3D modelling in complex perianal Crohn's fistula disease.** London Surgical Symposium, Poster presentation, September 2017

16. **Sahnan K,** Askari A, Adegbola SO, Tozer PJ, Oke S, Watfah J, Lung PFC, Hart AL, Faiz OD, Phillips RKS. **Rate of fistula formation after an anorectal abscess.** ACPGBI, Bournemouth. Oral Presentation, July 2017

17. **Sahnan K,** Adegbola SO, Allin BSR, Tozer PJ, Lee MJ, Heywood N, McNair AGK, Hinds D, Lobo AJ, Brown SR, Sebastian S, Phillips RKS, Lung PFC, Faiz OD, Crook K, Blackwell S, Verjee A, Fearnhead NS, Hart AL and the ENiGMA collaborators. **Developing a core outcome set for fistulating perianal Crohn's disease**. 'Overseas Bordeaux' meeting. Coloproctology Section; RSM, Oral Presentation, May 2017

18. **Sahnan K,** Lung PFC, Adegbola SO, Burling D, Burn J, Tozer PJ, Gupta A, Faiz OD, Phillips RKS, Hart AL. **An objective measure of response to treatment for patients with Crohn's perianal fistulas on anti-TNF treatment**. European Crohn's & Colitis Organisation. Poster Presentation, February 2017.

19. **Sahnan K,** Adegbola SO, Tozer PJ, Allin BSR, Lee MJ, Heywood N, McNair AGK, Lobo AJ, Brown SR, Sebastian S, Phillips RKS, Lung PFC, Faiz OD, Crook K, Verjee A, Blackwell S, Fearnhead NS, Hart AL. **A systematic review of outcomes reported in studies on fistulising perianal Crohn's disease**. European Crohn's & Colitis Organisation. Poster Presentation, February 2017.

20. **Sahnan K,** Adegbola SO, Tozer PJ, Burling D, A, Warusavitarne J, Faiz OD, Phillips RKS, Hart AL, Lung PFC. **Experience of 3D modelling in complex perianal Crohn's fistula disease and survey of international surgical interest**. European Crohn's & Colitis Organisation. Poster Presentation, February 2017.

21. **Sahnan K,** Adegbola SO, Mitra A, Tozer PJ, Warusavitarne J, Faiz OD, Watfah J, Hart AL, Phillips RKS. **Minimising diagnostic delay of Crohn's disease through the use of faecal calprotectin with patients presenting with a perianal abscess;** Innsbrucker Coloproktologie Wintertagung, Oral Presentation, January 2017

22. **Sahnan K. Perianal sepsis in the UK and improving the diagnosis.** John Nicholl's Prize presentation. Frontiers conference. St Mark's Hospital, Oral Presentation, November 2016

23. **Sahnan K**, Adegbola SO, Mitra A, Tozer PJ, Warusavitarne J, Faiz OD, Watfah J, Hart AL, Phillips RKS. **Improving the diagnosis of Crohn's disease through the selective use of faecal calprotectin with patients presenting with perianal abscess** 'John of Arderne' Prize Presentations. Coloproctology Section; RSM, Oral Presentation, October 2016

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25. **Sahnan K. 3D reconstructions of perianal fistula.** Frontiers conference. St Mark's Hospital, Course Convenor Prof Clark November 2016 (invited lecture)

26. **Sahnan K,** Mitra A, Adegbola SO, Tozer PJ, Warusavitarne J, Faiz OD, Phillips RKS, Hart AL, Watfah J. **Audit into the management of patients with perianal abscesses and risk stratification for Crohn's disease.** Surgical Symposium, Imperial College London. Poster Presentation. September 2016

27. **Sahnan K. Surgical Cases for live operating sessions with 3D MRI fistula reconstructions.** St Mark's Workshop on Anal Fistula. Oral Presentation, May 2016

28. **Sahnan K,** Askari A, Adegbola SO, Tozer PJ, Phillips RKS, Hart AL, Faiz OD. **Incidence and prediction of fistula formation in England.** European Crohn's & Colitis Organisation. Oral Presentation, March 2016

29. **Sahnan K,** Askari A, Adegbola SO, Tozer PJ, Phillips RKS, Hart AL, Faiz OD. **Abscess and Fistula in Crohn's disease.** European Crohn's & Colitis Organisation. Poster Presentation, March 2016

30. **Sahnan K,** Adegbola SO, Tozer PJ, Faiz OD, Phillips RKS, Hart AL. Novel use of **MRI volume measurement & 3D modelling in perianal Crohn's fistulas.** 'Global Health Innovator Competition', Institute for Global Health Innovation, Oral Presentation, March 2016

31. **Sahnan K,** Askari A, Adegbola SO, Phillips RKS, Hart AL, Faiz OD. **Abscess to Fistula, A natural history of anorectal sepsis in England.** 'John of Arderne' Prize Presentations. Coloproctology Section; RSM, Oral Presentation, October 2015

Prizes from this thesis

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2018	Selected for the Dukes' Club Top trainee presentation, ACPGBI 2018
2017	Royal College of Surgeons of England Research Fellowship
2017	Travelling Fellowship: Royal Society of Medicine, Coloproctology section

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For attendance at ECCO conference 2018

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MRI volume measurements for perianal Crohn's fistulas'

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Sahnan K
One-year research fellowship

2017 The Rolfe Charitable Trust (£1,000)
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Novel use of MRI volume measurements and 3D modelling in perianal Crohn's fistulas'

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Optimising management of fistulating perianal Crohn's

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3D printing of complex perianal Crohn's fistulas

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Novel use of MRI volume measurements and 3D modelling in perianal Crohn's fistulas'

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Sahnan K, Adegbola SO, Tozer PJ, Lung PFC, Faiz OD, Hart Al, Phillips RKS.
Novel use of MRI volume measurements and 3D modelling in perianal Crohn's fistulas'

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Incidence & prediction of fistula formation in England

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Abbreviations

2D	2-dimensional
3D	3-dimensional
5-ASA	5-Aminosalicyclic Acid
6-MP	6-mercatopurine
ACPGBI	Association of Coloproctology Great Britain & Ireland
AGA	American Gastroenterology Association
Anti-TNFα	Anti tumour necrosis factor-alpha
ASC	Adipose-derived stem cells
AZA	Azathioprine
BSG	British Society of Gastroenterology
BSGAR	British Society of Gastrointestinal & Abdominal Radiology
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CEA	Carcinoembryonic antigen
CI	Confidence Interval
COS	Core Outcome Set
CT	Computer Tomography
CTVC	Computer Tomography Virtual Colonography
DICOM	Digital imaging and communications in medicine
EAS	External Anal Sphincter
ECCO	European Crohn's & Colitis Organisation
ENiGMA	Evaluating goal-directed management of fistulising perianal Crohn's disease
ERAF	Endorectal advancement flaps
EUA	Examination under anaesthesia
FC	Faecal Calprotectin
FDA	Fistula drainage assessment
FiLaC	Fistula tract laser closure
GI	Gastrointestinal
GTN	Glycerine trinitrate
HES	Hospital Episode Statistics
IAS	Internal Anal Sphincter
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICC	intra-class correlation
ICHOM	International Consortium for Health Outcome Measurement
IMD	Indices of Multiple Deprivation

IQR	Inter quartile range
LIFT	Ligation of the intersphincteric fistula tract
LIS	Lateral Internal Sphincterotomy
MDT	Multidisciplinary team
MRI	Magnetic Resonance Imaging
NHS	National Health Service
OMERACT	Outcome Measures in Rheumatology
ONS	Office for National Statistics
OR	Odds Ratio
PACS	Picture archiving and communication system
pCD	Perianal Crohn's disease
pCDf	Perianal Crohn's disease fistula
PDAI	Perianal Disease Activity Index
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
R&D	Research and Development
RCT	Randomised Control Trial
RVF	Rectovaginal fistula
SD	Standard Deviation
SE	Standard Error
SPAIR	Spectral Attenuated Inversion Recovery
STL	Stereolithography
UC	Ulcerative Colitis
UK	United Kingdom
VA	Veterans Affairs
VAAFT	Video assisted anal fistula treatment

1

1 Introduction

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1.1 Perianal Crohn's disease

Crohn's disease (CD), affects between 4 and 250 people per 100 000 population worldwide and has a varied presentation.[1] Between a third and a half of all patients have perianal manifestations.[2] These are broadly classed as fistulising (encompassing abscesses and Crohn's perianal fistulas) and non-fistulising (fissures/ulcers, strictures/stenosis, skin tags).[3]

1.2 Manifestations of perianal Crohn's disease

This thesis concentrates on perianal Crohn's fistula but it is imperative to understand the wider context and the spectrum of other manifestations.

Anal Skin Tags

These fall into two types[4] in the American Gastroenterology Association (AGA) classification: (i) type 1 ("elephant ears") which are usually smaller, more compressible and tend to be painless, and (ii) type 2 which originate from a healed perianal lesion. Type 2 tags are often larger, and it is believed they form as a result of obstruction of the lymph system, hence their oedematous nature and greater degree of discomfort. They can

become acutely painful during flare episodes and can cause pruritus ani acting as a 'transporter' for faecal matter and mucus onto the perianal skin, and make it difficult to clean the area.[5]

1.2.1.1 Management

Keighley et al, demonstrated spontaneous healing in 32/75 patients with skin tags.[6] Surgery is best avoided in pCD due to the risk of unhealed wounds and the potential for scarring and stenosis. It is therefore best reserved for cases where malignancy is suspected or symptoms severe.[7]

Anal Fissures

Anal fissures are more common in patients with Crohn's disease[8] and the most frequent non-fistulising perianal lesion.[9] Retrospective series from Wolf and Lockhart-Mummery found incidence rates of 35% and 59% respectively.[10,11] A more recent study from the national Veterans Affairs (VA) administrative dataset found the prevalence to be 4% and non-gender specific. Fissures were more prevalent in the young age group (20-50 years) compared with older patients (60-90years), (7% vs. 1.5% p=0.0001) respectively.[8] They differ in aetiology from non-IBD fissures and are thought to be similar or secondary to ulceration driven by the inflammatory process, with hypertrophied edges. It is often said that fissures associated with Crohn's disease are less likely to be found in the traditional anterior/posterior positions, and instead are more often located in the lateral positions. However, it is probably more accurate to suggest that the fissures are often multiple, maybe eccentric and can occur anywhere, as series have shown posterior fissures can be as prevalent.[12, 13–15]

1.2.1.2 Management

The ten year follow-up of pCD patients from Buchmann et al. demonstrated that 81% of 53 patients' fissures healed over time.[16] Though the disease course is undoubtedly variable and with the natural inclination for patients to have looser stool in Crohn's disease, Crohn's fissures may cause fewer symptoms. Though, Fleshner et al. found 49/56 patients (84%) were symptomatic. They found that being of male gender, having a painless fissure and having an acute fissure were all predictive of successful medical treatment.[17]

It is estimated that non-surgical management (glycerine trinitrate (GTN) 0.4% or diltiazem cream) fails in about a third of Crohn's cases[12] and other treatments have demonstrated some response but the studies are often retrospective, with small sample sizes.[18] A retrospective review from two tertiary centres by Bougen et al. demonstrated that infliximab successfully treated 24 of 34 patients (70%) with fissures at a median follow-up of 3 years.[19] For non-IBD patients, the aim of treatment is to stop sphincter spasm, reduce tone, soften the stool and thereby allow healing. In pCD patients, concomitant luminal disease means any 'relaxation' of the sphincter increases the chance of soiling, and often renders stool softening unnecessary. In addition, wound healing is delayed which may exacerbate the problem.

If surgery is to be performed, a nuanced approach is advocated. Surgical options include fissurectomy,[14] advancement flap closure and lateral internal sphincterotomy (LIS). The role of LIS is difficult to ascertain in Crohn's disease as it is based on the non-Crohn's aetiology with high sphincter tone and hard stool, problems often absent in Crohn's patients, where an immunological basis seems more likely. There are successes as high

as 83% without any loss of continence when the existing literature of six retrospective series is pooled.[20] These data, however, are heterogenous and performed on a carefully selected group of patients. In general, the technique should be reserved for patients with persistent pain (note other forms of pCD maybe present and account for pain e.g. abscess/fistula at the base of the fissure), and in the absence of proctitis or other aspects of pCD. The most recent published series is from D'Ugo and colleagues, who demonstrated healing in two-thirds of patients (27/41 patients) with medical therapy with follow-up at a median of 37 months. The remainder of the cohort had some form of surgical intervention: Botox +/- fissurectomy with complete healing at 18 ± 5 days or LIS with complete healing at 25 ± 7 days. Of note, the overall complication rate was 57.1% (n = 8), with the most common complication being a non-healing wound (n = 4; 28.6%).

Anal ulcers

Anal ulceration is less common than other pCD lesions. Siproudhis et al, reported an incidence of 5% in a series of 101 CD patients with perianal sepsis referred to a tertiary institution[21], though other series report an incidence as high as 43%.[22] They can present with severe unremitting pain in up to 56% especially on defaecation.[21] Some patients also experience pruritus, discharge, and bleeding. They extend deep to the dermis and are large, oedematous and have irregular edges.[23] They can be found in the anal canal, the lower rectum and in some cases may extend to the surrounding peri-anal skin in aggressive disease.[24]

Anal ulcers are often associated with distal rectal inflammation and can predispose to other forms of pCD such as fistulas, abscess and anal stenosis. Cavitating ulcers are often more symptomatic and more likely to evolve into fistulas.[23]

1.2.1.3 Management

In the case of deep cavitating ulcers, the long term outcome is poor and nearly 50% of patients progress to anal stenosis.[25] Studies on symptomatic pCD, including patients with ulcers, have shown some benefit of topical treatments such as metronidazole (10%) ointment to improve symptoms.[26] Topical tacrolimus has been shown to improve the depth of the ulcer but studies are small and further, randomized evaluation is needed.[27,28] The evidence for systemic treatment is mostly from retrospective series. A benefit was demonstrated in 63% of patients after 3 intravenous infusions of infliximab at 2 months following the first infusion, assessed using a combination of functional scores and proctological examination.[29] Bougen et al, demonstrated complete response in 40 out of 94 patients (43%) at induction and complete response in 72% for ulcers after a median follow up of 3 years.[30]

Anal stenosis/Stricture

Anal stenosis is an abnormal narrowing of the anal canal that can cause proximal obstruction, and symptoms of discomfort and pain. It is commonly caused by surgery or inflammatory conditions such as Crohn's disease or following radiotherapy.

As many as half of Crohn's anorectal strictures are in the rectum, a third are in the anal canal and the remainder are anorectal.[31] Patients often have other forms of pCD such as

ulcers, fissures or fistula and it is the inflammatory process which leads to fibrosis and eventually to circumferential stricturing. It has a prevalence of 9-22%, is more commonly found in patients with colonic than ileocolonic disease[32] and approximately 96% of cases have associated proctitis.[23] Fields and colleagues, found more manifestations of pCD in a cohort of 70 CD patients with strictures compared to controls: perirectal fistulas (61% vs. 34%), peri-rectal abscess (50% vs. 17%) and anal skin tags (23% vs. 16%).[32]

Stricturing can be thought of as the end result of a severe inflammatory process, often following anal ulceration, and is a predictor of poorer outcomes, including proctectomy.[31] One study demonstrated that patients with anal stricture had a higher rate of temporary diversion (OR 3.90, 95% CI 1.18-15.8, p=0.03) and permanent stoma (OR 3.69, 95% CI 1.39-10.7, p= 0.01) on multivariate analysis.[33]

1.2.1.4 Clinical Presentation

Stricturing in patients without Crohn's disease causes constipation, straining, decreased stool calibre and tenesmus. On passage of the motion there can be some bleeding either associated with the trauma of defecation or digitation. Non-Crohn's strictures often present earlier than in Crohn's disease as these latter patients, often with associated luminal disease, usually including proctitis, may have looser stools and therefore get fewer symptoms from the stricture, presenting instead with other manifestations of perianal disease such as fistulas, which lead to detection of the stricture.[31,34]

A digital rectal examination may be impossible due to the degree of stenosis but where possible, the level and length of the stenosis should be noted in reference to the dentate line. The stenosis maybe short, annular, diaphragmatic and <2cm in length, or long and

tubular (suggesting the preceding inflammatory process occurred in the rectum).[35] Strictures secondary to 'defunction' atrophy represent a different aetiological group and present with different problems, since the faecal stream is diverted away. The principle problem for this latter group may be inadequate surveillance of the defunctioned but still 'cancer prone' colorectum.

1.2.1.5 Investigation

Ideally these patients should be assessed using a multi-disciplinary approach. Focused histories on current/past medical treatments and perianal disease, as well as the nature of the patient's bowel motion (consistency and frequency) should be undertaken. Following this, an examination under anaesthesia with biopsies to exclude malignancy should be performed. Imaging (usually MRI) is used to ascertain the morphology (the anatomical location, the length and extent of stricture and any associated perianal disease) of the strictured segment and examine for surrounding pathology such as perianal/perirectal sepsis or fistulas from organs above.

1.2.1.6 Treatment

Treatment can be determined in accordance with the severity of the presentation and the anatomical nature of the stenosis. The former is more useful as anatomical correlation with symptomatology is poor, although the ability to survey, regardless of symptoms, remains an important indication for intervention.

1.2.1.7 a) Non-surgical

Laxatives to alter the proximal pressure can be helpful in the short term if the stool is firm. In mild stenosis and if the patient is motivated and amenable, manual digitation (a single digit) or appropriately sized dilators can achieve prevention of deterioration of the stenosis or maintenance after surgical dilatation. Galandiuk and colleagues, found

patients with anal stricture who performed self-dilatation with Hagar dilators were less likely to require diversion.[33] This is more useful in shorter, more accessible strictures where it is easier for the patient to undertake. Topical treatments with steroids, 5 ASAs or metronidazole have been described[35].

1.2.1.8 b) Surgical dilatation

An examination under anaesthetic (EUA) and dilatation with Hagar dilators is usually warranted in mild-moderate stenosis even in cases of the severely scarred Crohn's anus[36]. Ideally, gentle progressive dilatation up to 22 to 26mm in diameter can be used in adults.[37] A coaxial balloon technique can also be applied for dilatation.[31] Some of the scarred tissue can be removed though this in itself may perpetuate further stenosis, without a sustained period of self-dilatation by the patient. Patients who self-dilate must be counselled appropriately and supported by specialist nurses and regular clinical contact as bleeding and sphincter damage have been reported with dilatation.[38]

1.2.1.9 c) Other surgery

Interposition flap procedures may be used in the absence of significant rectal mucosal disease though some studies have shown CD has a negative impact on healing in flap repairs.[39,40] Anal stricture in association with perianal sepsis is a poor prognostic feature and up to half require faecal diversion[31] and the risk of proctectomy is also increased. Galandiuk et al. found in a study of 356 patients with CD, the presence of both an anal stricture and colonic disease had a 30-fold increase in the likelihood of a permanent stoma vs. those patients with colonic disease without anal stricture.[33] Proctectomy should be considered when medical and surgical therapies have been exhausted but discussed early in patients, who sometimes welcome discussion of this radical option due to the severity of their symptoms.

Anal Cancer in the context of pCD

Epidemiological data regarding the cancer risk in pCD are scarce. This is due to the fact that the incidence of these cancers is likely very low, the natural disease course is long, and that studies reporting long-term follow-up data are lacking. Beaugerie and colleagues, recently demonstrated from an observational cohort of IBD patients (2911 patients) over a year (2004-5) and with median time of 35 months (IQR, 29-40 months), that patients with anal and/or perianal Crohn's disease have a high risk of anal cancer. This is not a true incidence but a point prevalence in an observational cohort. The corresponding incidence rates were 0.26 per 1000 patient-years for anal squamous-cell carcinoma (n=2), 0.38 per 1000 patient-years for perianal fistula-related adenocarcinoma (n=3), and 0.77 per 1000 patient-years for rectal cancer (n=6). Interestingly when the whole registry was analysed in a multivariate analysis to determine predictive factors for cancer, the presence of past or current anal and/or perianal lesions was the only significant factor (OR, 11.2; 95% CI, 1.18-551.51; P = 0.03).[41]

Often patients with chronic, complex disease are difficult to examine in the clinic and one should be mindful and perform EUAs and biopsies +/- imaging as necessary. Due to the relatively rarity of the condition, predictive factors are difficult to establish though Fornaro et al., hypothesised from a review of the literature that these might include: female gender, duration of pCD and duration of the fistula.[42] Kotze et al, in their review of the literature, suggested that one should be mindful of the diagnosis in patients with the presence of long-standing (>10 years) perianal fistulas and offer regular surveillance in terms of monitoring of CEA (carcinoembryonic antigen) levels and imaging (endoanal ultrasound, CT/MRI scan) with biopsy every 3 to 6 months in cases where malignancy is

suspected.[43] However, the value of CEA testing in fistula related cancers is entirely unknown.

1.2.1.10 Management:

As with all malignancies, patients should be managed by an oncology MDT and considered alongside non-IBD related cancers. Due to failure to recognise the malignancy, patients can present with advanced disease affecting prognosis, in particular with perirectal lymph node involvement.[44] Chemoradiotherapy may be appropriate depending on histological features but in our experience, abdominoperineal excision, usually extending beyond normal resection margins to become a wide excision or even an exenterative procedure is necessary. As with all perineal operations in pCD, patients often experience delayed wound healing, amplified in the presence of radiotherapy, and the morbidity is high.

Rectovaginal fistula

Rectovaginal or anovaginal fistulas (RVF) can occur in 10% of women with Crohn's disease and are classed as complex anal fistulas.[45] The majority occur in the middle of the rectovaginal septum and are thought to be secondary to an anterior rectal ulcer which erodes into the vagina.[35] As with perianal fistula they can occur secondary to an infected anal gland,[46] Bartholin's abscess,[47] malignancy or radiotherapy.[48] A more benign course is attributed to those originating from an infected anal gland[46]. RVF which are higher, associated with active rectal disease or originating from a Bartholin's abscess are associated with worse symptoms and prognosis[49,45,47].

Symptoms include intermittent vaginal flatus, discharge[50] and faecal incontinence.[35] Examination under anaesthesia, proctoscopy and vaginoscopy, augmented with hydrogen peroxide or methylene blue infusion per vaginal tampon, can be used in conjunction with contrast enemas or MRI to identify the tract. MRI may miss the fistula, particularly when it is short or epithelialised but provides information about inflammatory changes, ongoing sepsis, additional tracts and may delineate fistula morphology.

1.2.1.11 Management

Management of RVF is dependent on anatomical location, complexity and whether there is active inflammation in the rectum or distal colon. A multidisciplinary team should determine management options and reference must be made to severity of luminal as well as perianal disease, the presence of localized sepsis, sphincter function (through anorectal ultrasound and/or physiology studies) and treatment goals of the patient. Patients should be appropriately counselled that there is often no 'panacea' treatment and the risks of sphincter injury and recurrence, including a worsening of symptoms if the fistula diameter increases, should be explained.

The aim of immediate treatment is to control proctitis and drain any underlying sepsis. Surgical management is the mainstay but medical adjuncts are often used to alleviate the active inflammatory process.[51] The ACCENT II trial included 25 patients with Crohn's RVF who had infliximab infusions. Following induction infusions at zero, two and six weeks, 44% of fistulas were 'closed' at 14 weeks. The duration of closure was longer in the infliximab than the placebo group (median 46 vs. 31 weeks).[52] Lichtenstein and colleagues, demonstrated that infliximab reduced hospitalisation and operations in

fistulizing disease including a subgroup of RVF patients,[53] but it is less likely to be curative in RVF than perianal fistulas.[54]

Surgical options are indicated when there is endoscopic evidence of healed rectosigmoid mucosa[54] and include fistulotomy (rarely) if very superficial, anal/vaginal advancement flaps, Martius flaps,[55] gracilis interposition, omental interposition and direct repair with sphincter repair.[56]

Mucosal advancement flaps have been found to have highly variable rates of success ranging from 28% to 92%.[57,58,59] Makoweic et al, found that the recurrence rates were higher following advancement flaps for Crohn's RVF compared to anal fistulas (70%; 25%) at 2 year follow up.[57] In cases where proctitis cannot be managed medically, options for treatment include anocutaneous flaps,[60,61] defunctioning or protectomy.[45] Full sleeve/Soave-type advancements have a role if anal stenosis[62] is present or in cases where the fistula is very high, or has occurred at the site of an anastomosis.[63] Refractory fistulas can be managed with a diverting stoma with the aim of reducing vaginal discharge, whilst others may opt for a proctectomy. Whilst patients may need only one operation, closure rates no greater than 50% may be a reasonable expectation and women should be counselled appropriately, particularly where their symptoms are minimal.

Perianal abscess

Perianal abscesses are a common complication in Crohn's disease and one study found up to 62% of Crohn's patients will develop at least one during the course of the disease.[64] Two suggested aetiologies have been described including the cryptoglandular

hypothesis[65] and Hughes' theory that rectal inflammation leads to ulcers which evolve into fistulas.[66] More recent studies have also proposed the role of genetics[67,68,69,70,71] and an alteration in or unregulated response to the normal GI microbiota[72,73,74,75] in perianal Crohn's abscess/fistula.

Abscesses may present acutely with pain in the perianal region as a localized, erythematous swelling. Signs include a swollen tender lump with surrounding erythema. Abscesses are classified anatomically in relation to the anal sphincter. In a prospective series of 126 consecutive patients with pCD, just under half (48%) had at least one perianal abscess (mean follow-up, 32+/-17 months). In total, there were 110 episodes of an abscess with 145 anatomically distinct abscesses documented.[76]

Clinical examination often reveals the location of the abscess but in more complex presentations EUA is a useful diagnostic adjunct with a specificity of 91%.[77,78] Certain anatomical locations, such as intersphincteric further inside the anal canal,[79] are more difficult to assess clinically and imaging such as MRI or endoanal ultrasound[80] if tolerated, in combination with an EUA may be needed to identify the abscess. Abscesses appear as areas of high signal intensity in T2 weighted MRI scans and may be associated with a rim of inflammatory tissue.[81]

1.2.1.12 Management

Antibiotic therapy is used in cases of systemic sepsis and has been used in combination with the patient's normal immunomodulators,[82,83] but incision and drainage is usually required. Some authors suggest the insertion of a mushroom catheter in the case of larger cavities.

Clinically and in the literature, abscesses are sometimes referred to as 'acute fistulas' or fistulas as 'chronic abscesses' and although these descriptions may be incorrectly used, abscesses and fistulas may often coexist. Abscess is part of the natural history of the untreated anal fistula and although they may occur separately, both are more common in Crohn's than in the normal population and an underlying fistula should be sought when an abscess is found. Makowiec et al, found 73% of abscesses were associated with an 'ischiorectal' fistula and 50% with a transsphincteric fistula in a tertiary hospital[76]. Treating associated fistulas in the acute phase has reduced recurrence rates in idiopathic fistula[84] and whilst not all abscesses will develop into a fistula, patients with pCD are at high risk of recurrence, so seton placement where possible is advised. Whether this should be undertaken at the initial abscess drainage, especially when performed by junior or non-colorectal surgeons, is less clear and the risks of iatrogenic injury in the acutely inflamed anorectum mandate caution.

1.3 Perianal Crohn's fistula

Perianal fistulas occur in a third of all Crohn's disease patients.[85] They denote a distinct and aggressive phenotype,[86] with a higher risk of a severe and disabling disease course, relapse and the need for repeated operations. They cause pain and discharge and result in reduced quality of life.[87] In a population study, Schwartz et al. found the cumulative risk of at least 1 perianal fistula after 1 year was 12%, after 10 years was 21%, and after 20 years was 26%.[78]

Crohn's anal fistulas were first described in 1934[88] and it is known that they can precede luminal disease.[89] Anal fistulas are the initial manifestation and the presenting complaint

in 10% of Crohn's diagnoses.[90] Patients diagnosed with Crohn's before the age of 40 are at an increased risk of penetrating Crohn's disease, including anal fistula.[91] Anal fistulas are more common in men, non-Caucasians and Sephardic (as opposed to Ashkenazi) Jews.[91,92,46,86] Patients with colonic disease but specifically those who have active rectal disease are at greatest risk of developing fistulas.[49]

A number of classification systems exist for fistulas including Hanley's[93], Parks'[94] and the American Gastroenterological Association (AGA)[54] classification which describes fistulas as either simple or complex. Simple fistulas have one external opening and are low (below the dentate line; superficial, inter- or trans-sphincteric). Complex fistulas may have more than one external opening, be high (above the dentate line; inter-, trans-, supra-, or extra-sphincteric) or have extensions (a term denoting abscess/secondary tracts). Patients with Crohn's disease can present with either, but complex fistulas are more common in Crohn's than non-Crohn's patients. They have a tendency to recur and often require multiple operations.[95] With repeated surgery and episodes of sepsis the fistulas become harder to assess both clinically and radiologically due to an increase in scar tissue and distortion of the surrounding anatomy.[96] Assessment includes a focused history, examination including proctosigmoidoscopy followed by imaging, ideally with MRI or endoanal ultrasound to delineate the anatomy of the tracts themselves and their relation to the sphincter and levator plate, examination under anaesthetic with drainage of sepsis and seton placement and endoscopy to map the luminal disease where this is unknown.[97]

MRI is the gold standard for imaging anal fistula and has been shown to be superior to examination under anesthesia[95] and endoanal ultrasound.[98] A technical review by the American gastrointestinal association[54] found a diagnostic accuracy of 76-100% in

complex Crohn's fistula.[99,100,77,101,102,103,104] However, the location of the internal opening can be difficult to ascertain on MRI.[105] Schwartz et al, demonstrated in 32 patients with perianal Crohn's fistula that diagnostic accuracy could be improved if any two modalities (MRI, endoanal ultrasound, EUA) were used in combination.[102] Establishing the presence or absence of proctitis is fundamental and influences both treatment and prognosis. Proctosigmoidoscopy or formal endoscopy should be performed to determine this.[81]

Established treatment principles involve draining the sepsis and aggressively managing proctitis whilst treating the fistula medically, usually with a combination of antibiotics, thiopurines and anti-TNF therapies. In the Fistula Drainage Assessment, clinical response to treatment is defined as a 50% decrease in the number of external openings and/or a lack of discharge from these openings over two consecutive clinic visits.[106] Clinical remission or 'healing' is the complete cessation of drainage despite gentle finger pressure or the healing of all external openings. This subjective, clinical drainage assessment has been criticised for failing to appreciate the natural history of anal fistulas and failing to assess residual tracts which have been radiologically shown to heal a median of a year after clinical 'healing' by Tozer et al.[97]

Previous attempts to standardize radiological response, such as the van Assche score[107] have been criticised due to insensitivity to change in the long term[98] and weak correlation with PDAI (r=0.371, p= 0.036).[107] Currently, there is no universally accepted or reliable method of monitoring long-term radiological response to treatment. Clinical scoring systems such as the Perianal Disease Activity Index (PDAI) have been used, though they are highly subjective and not specific to fistulous disease; currently no widely accepted scoring system exists.[108]

Multi-disciplinary management of pCD should be standard of care[109] and an algorithm to approach these patients often helps the patient journey. **Figure 1-1** illustrates six key steps to be considered when treating these patients and these will be outlined in the subsequent sections.

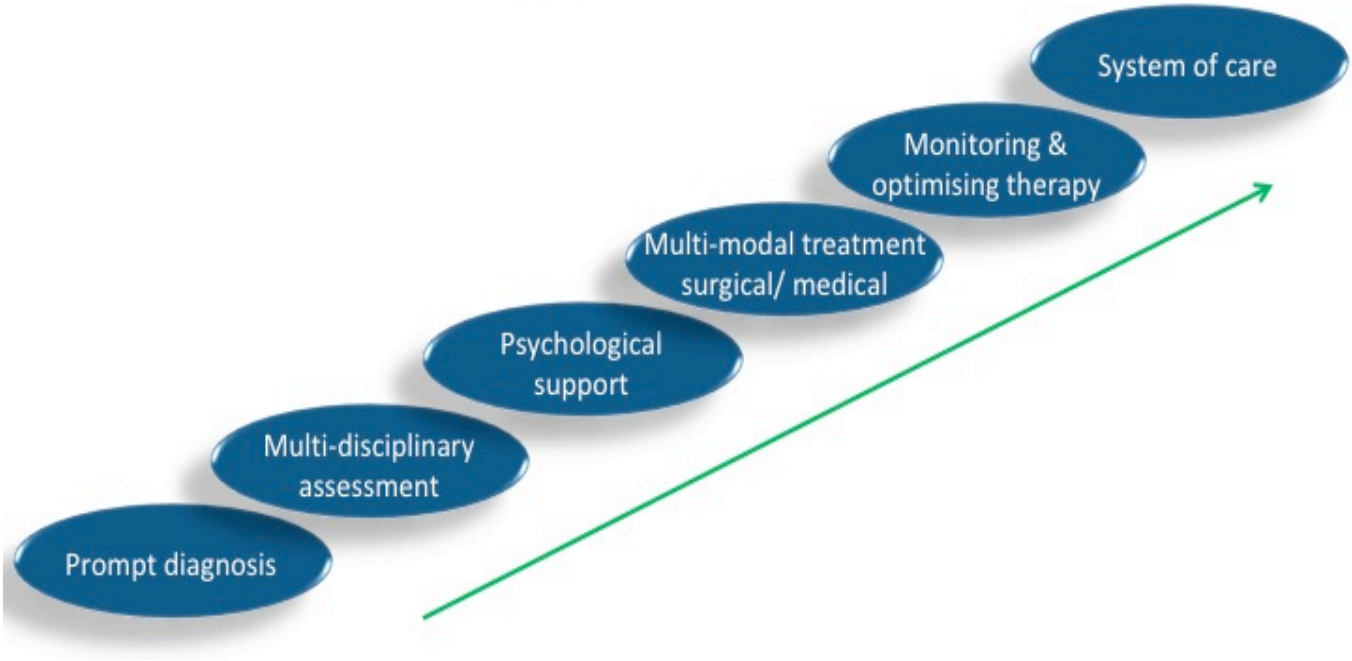


Figure 1-1. 6-steps to optimise the management of fistulising perianal Crohn's disease

Diagnosis

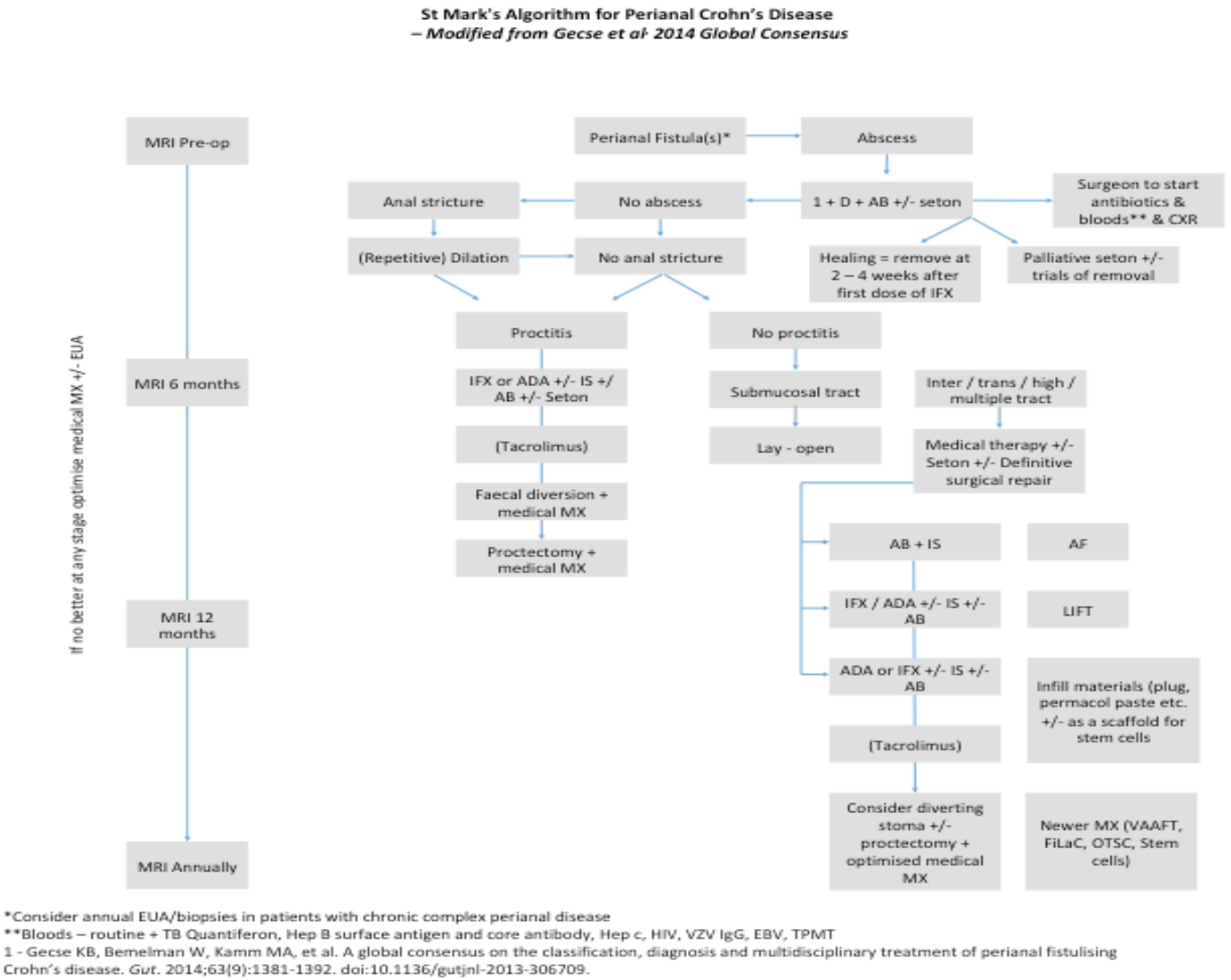
Perianal sepsis can be the presenting complaint in 10-25% of Crohn's diagnoses,[110,111] and may occur at least 6 months prior to luminal disease.[112] Perianal disease at presentation has been shown to be associated with a subsequent 5-year disabling disease course with more extensive (ileo-colonic) and complicated (stricturing and penetrating) disease behaviour.[1,89] Patients have an increased probability of repeated courses of corticosteroids (and risk of dependence), increased admissions to hospital, increased

surgical resections and a predisposition to chronic disabling symptoms.[89] In luminal disease, there is a benefit to initiating earlier biologic therapy in appropriate patients[113,114] and it has been shown to increase the remission rate.[115] In perianal disease, it is not known if the same is true but this 'top down' approach seems likely to be beneficial given that perianal CD represents a severe phenotype.

In a recent cohort study of emergency surgical practice in the United Kingdom, Pearce et al. found that only ~8% (10/128) of incision and drainage operations (in all perianal abscesses, mostly in the absence of Crohn's disease) were performed by consultant surgeons.[116] This is important as through a retrospective national dataset we have shown that 2·9 per cent of all patients presenting with a new abscess were subsequently diagnosed with Crohn's disease and that the median time to diagnosis was 14 months.[117] Clinicians should maintain a healthy suspicion of underlying Crohn's disease and there is an argument that more junior member of the surgical team may not be as well versed at identifying key findings at EUA which aid the diagnosis of Crohn's disease. In the pre-operative period, a full clinical history should be taken with relevance to salient points such as stool frequency and consistency, extra-intestinal manifestations and family history. In addition, at the time of the operation one should evaluate the anorectum for proctitis and where there is a high index of suspicion, diagnostic adjuncts such as faecal calprotectin assays, post-operative review in clinic or subsequent endoscopic assessment may be helpful. Trainees should be taught to consider IBD and when in doubt either to escalate to a senior colleague or seek advice from a gastroenterologist.

Multidisciplinary assessment

It is the author's view that where possible all complex fistulising disease should be discussed at an MDT. A survey of colorectal surgeons across the UK demonstrated that a multidisciplinary team was available to the vast majority (87.6%) but that only a quarter of the respondents routinely discussed patients with perianal Crohn's disease.[118] Whilst the initial management involves an examination under anaesthesia and drainage, the subsequent management strategy may be more complex and variable between individuals. At our institution we have adapted an algorithm from the ECCO consensus statement by Gecse et al,[81] **Figure 1-2.**



*Consider annual EUA/biopsies in patients with chronic complex perianal disease
**Bloods – routine + TB Quantiferon, Hep B surface antigen and core antibody, Hep c, HIV, VZV IgG, EBV, TPMT
1 - Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut*. 2014;63(9):1381-1392. doi:10.1136/gutjnl-2013-306709.

Figure 1-2. St Mark's Algorithm for perianal Crohn's disease (modified from Gecse et al)

Apart from the addition of more novel therapies published after the consensus exercise, the other major difference in our adaption is the frequency of MRI. In our tertiary centre, MRI scans are used for a number of reasons and to assess complex fistula over time. In particular they are used to: (i) assess the radiological response and specifically to look for reduction in fistula volume over time (ii) to distinguish between fluid and inflammation, which is particularly pertinent when deciding to (re)start biological therapies and (iii) to assess the fistula morphology to see whether complex fistula have been 'down-staged' sufficiently to allow and attempt at definitive surgical repair.

Many IBD institutions have joint clinics where complex IBD patients are reviewed by a gastroenterologist, IBD nurse and colorectal surgeon in the same room. These clinics can be an invaluable resource for patients who require complex decision-making, can avoid confusing or contradictory messages and allow patients to weigh options simultaneously. IBD nurses often have had the most interaction with patients through the infusion service or the advice line and can have a role as the patient's advocate. Traditionally, the need for surgery has been perceived as failure by patients, gastroenterologists and IBD nurses and it is important that patients understand that a combined approach is genuinely best. New and novel innovations can also be used to facilitate informed consent, such as the use of 3D modelling[119] or 3D printing[120].

Psychological support

Zhang et al[121] found that depression is the most significant predictor of poor quality of life in Crohn's disease and another study found self-reported depression in approximately 70%[122] of patients with fistulising pCD. Riss and colleagues[123] however,

found that IBDQ scores (Inflammatory Bowel Disease Questionnaire - a measurement of quality of life) were lower than in controls, but with no difference in mental health scores. This study included only 69 patients, and further evidence is required to draw robust conclusions. Furthermore, although there are many tools to measure quality of life in inflammatory bowel disease, they do not focus on areas specifically related to Crohn's perianal fistulas.[124] This is in part due to the paucity of evidence available on patient experience of perianal fistulas in CD. There is little perspective of living with the condition or indeed coping strategies in the face of futile treatment. Two exploratory studies describing qualitative techniques of assessment of the impact of the condition and of diagnosis, highlighted that the impact of perianal Crohn's fistulas extended far beyond restrictions on daily and sexual activity.[124,125] There is a burden of disease symptoms, (predominantly pain and discharge), a burden of chronic treatment (sometimes involving multiple surgeries, chronic medication with associated risks) and the burden of impact on physical, emotional and social wellbeing to consider in formulating an appropriate treatment plan.[126] These include the restrictive effect on sexual activity and enjoyment, social activities, career and future prospects. Often patients are diagnosed young, and there is usually a period of information gathering to improve understanding of the condition, and potential implications and goals of treatment. Patient sources of information and the psychological response to the diagnosis has a bearing on how patients perceive their fistulas. Trusted healthcare professionals (including specialist nursing care), support groups and online resources often help with building a positive experience[124] but sometimes these may be limited in patients' local hospitals. Early referral to tertiary centres is sometimes valuable, where support services may be more readily available, and teams may be better equipped to deal with patients needing increased support.

Treatment

Tozer et al. summarized the principles of treatment: to drain the underlying sepsis, aggressively manage proctitis and medically treat fistulas with a combination of antibiotics, immunosuppressants and anti-TNF therapy.[97] Simple fistulas, in the absence of proctitis, are sometimes managed by experienced surgeons in a similar fashion to those of cryptoglandular aetiology. However, the risks of impairment of continence, recurrence and poor wound healing, heightened in the Crohn's patient, lead to a preference for sphincter preserving techniques. Complex fistulas are notoriously difficult to manage with high rates of recurrence and wound failure, and necessitate a combined surgical and medical approach, with anti-TNF therapies as standard. Bell et al, working in the pre-anti TNF era, found complex fistulas in their cohort required a median of six procedures to heal and 50% ultimately went on to proctectomy.[127] Patients need to be assessed in an individualized fashion but a multi-disciplinary team, clear communication with the patient and management of expectations are fundamental.[127]

Definitive cure is challenging to achieve and when considering definitive surgical treatments there are a number of factors, which the operating surgeon needs to consider. These include (i) the morphology of the tract – the amount of sphincter involved and the number of tracts, (ii) the presence of proctitis – the presence of proctitis is a poor prognostic indicator[128] and a relative contraindication to most reparative surgical treatments, (iii) local expertise – consider referring to a specialist centre for multidisciplinary expertise or access to novel therapies,[129] (iv) perianal severity – this refers to induration from previous acute flares and surgical treatments, increased scarring alters anatomy and could make each subsequent procedure more difficult, and

(v) the patient's priorities – establish and understand which symptoms the patient is most concerned about. A continual dialogue with the patient is key in challenging cases.

1.3.1.1 Medical Treatment

Once surgical control of any sepsis has been achieved, early introduction of medical treatment is recommended.[130] An aggressive 'step up' approach is often employed, with the aim of achieving expedited control. There are a number of different medical options which will be discussed in further detail below.

1.3.1.1.1 Antibiotics

Antibiotics alone have failed to demonstrate long-term benefit in Crohn's anal fistula.[54] Adjunctive antibiotic therapies in the form of ciprofloxacin or metronidazole are used with some success. West et al. compared combined treatment of infliximab + ciprofloxacin with infliximab-alone in a double blind randomized control trial (RCT), and found 73% vs. 39% (p=0.12) fistula response respectively.[83] The ADAFI trial, a multicentre, double-blinded RCT, demonstrated that clinical response was observed in 71% of patients treated with adalimumab plus ciprofloxacin compared with 47% treated with adalimumab plus placebo (p=0.047).[131] Although both metronidazole and ciprofloxacin have demonstrated a benefit,[132] the side effect profile of ciprofloxacin is more favourable.

1.3.1.1.2 Immunomodulators

Despite widespread use, the evidence for immunomodulators (such as azathioprine and 6-mercaptopurine) inducing fistula healing is limited. A recent Cochrane review assessed immunomodulators vs. placebo for fistula healing and found a non-significant benefit (RR 2.0; 95% CI 0.67-5.93). However, the review only had a small number of patients and the studies included were over 40 years old.

Immunomodulators are often used as an adjunct to anti-TNF agents, partially in the hope of reducing antibody production. However, a recent meta-analysis by Jones et al. found anti-TNF monotherapy was equivalent to concomitant use of immunomodulators and anti-TNF therapy.[133] This of course is a controversial statement and the true answer as to the interaction many believe is based on whether the patient was anti-TNF naïve before commencement of therapy/ies. As such the role of these agents needs addressing in prospective trials.

1.3.1.1.3 Biological therapies

Anti-TNFα therapies have enhanced our management of pCD and a number of different agents exist.[134] Of the biologic agents, the anti-TNFα agents infliximab (*an IgG1 murine-human chimeric monoclonal antibody*), adalimumab (*a fully humanised, anti-TNF monoclonal antibody*) and certolizumab (*humanised, PEGylated, Fc-free anti-TNFα monoclonal antibody*) have been shown to be effective for patients with fistulising pCD[135,136,137,138,139–141] and combination therapy with thiopurines is associated with better outcomes.[142] Potential advantages of combination therapy with thiopurines are decreased antibody formation and decreased clearance of the anti-TNFα medications.[143]

The ACCENT II trial, a double blind RCT, demonstrated the benefit of infliximab maintenance treatments in fistulising Crohn's disease.[136] A maintained partial response was shown in 64% of initial responders at 54 weeks and a complete response was shown in 36% vs. 19% in the placebo maintenance group. In addition, there was a 50% reduction in the rate of hospital admissions and operations, and there is increasing evidence that infliximab improves health related quality of life.[53,144] In general, the better the initial response to infliximab the lower the fistula recurrence rate.[145]

The combination of anti-TNFα therapy and seton insertion has been assessed recently in a multicentre observational study from Brazil, which demonstrated that combination therapy lead to efficacious and durable results.[146] Both utilization of infliximab prior to surgery[147,148] and seton insertion prior to infliximab have demonstrated benefit.[149]

The search for clinical factors which can predict response to therapy and relapse rate is a focus for current research.[150] The role of antibodies and trough levels of the anti-TNFα agents have also been explored and both may guide therapy.[151]

Continuing with the first anti-TNFα agent is usually recommended unless there is a loss of response. The CHARM study showed benefits to both the Anti-TNFα naïve patients and those who had switched to adalimumab. In this study, patients who had received infliximab or any anti-TNFα antagonist other than adalimumab, greater than 12 weeks before screening, could be enrolled. This was provided they did not exhibit initial nonresponse to the agent (i.e. no clinical response to first injection as judged by the investigator). Fistula response was found in 41% of patients at 56 weeks.[138] Of all those patients who had fistula response (including those in the placebo group), 90% had maintained response following 1 year of open-label adalimumab therapy, for at least an additional year.[152] The role of adalimumab following lack of response to infliximab has been considered in several studies. The GAIN study found no difference between adalimumab and placebo as a second line agent.[153] The CHOICE trial found complete fistula closure in 34/88 (39%) treated with adalimumab after loss of response to infliximab.[154] Echarri et al. reported complete response in 50% (n=8) after four weeks of whom 87.5% remained in remission after 48 weeks of treatment.[155] A recent retrospective review of 46 patients assessed the role of adalimumab in anti-TNFα naïve

patients and found complete remission in 41% at 12 months, which was defined clinically and radiologically with good correlation between both.[90] Of note, Legue et al. recently published a series of 45 patients with pCD who discontinued their anti-TNFα therapy, and found that the cumulative probabilities of perianal relapse (surgical drainage) was 24% at 1 year and 55% at 5 years.[156]

Certolizumab Pegol, another anti-TNF therapy, was compared against placebo and assessed at 26 weeks in the PRECISE 1 and 2 trials. The results were not statistically significant (54% vs. 43%, p=0.069) for the protocol definition of fistula closure (≥50% closure at two consecutive post-baseline visits ≥3 weeks apart at week 26).[157] Though the authors found of the 55 patients with perianal fistula, the closure rate was superior with Certolizumab compared to placebo (36% vs. 17%, p=0.038).

The evidence base regarding the use of vedolizumab (an $\alpha_4\beta_7$ integrin monoclonal antibody) and ustekinumab is small and currently confined to small retrospective series.[158,159,160,161,162]

1.3.1.2 Surgical treatment

The surgeon's initial role is predominantly to assess and drain the fistula complex prior to medical management. Due to the risks of impairment of continence, recurrence and poor wound healing, fistulotomy is rarely appropriate in Crohn's disease. Sphincter preserving treatments may be considered and data on drainage procedures (long term loose seton), disconnection procedures (advancement flaps, the LIFT procedure [Ligation of the intersphincteric fistula tract], infill procedures (glues, plugs) and ablative

procedures (Fistula tract laser closure' [FiLaC] and 'Video assisted anal fistula treatment' [VAAFT], whilst mostly limited to case series, have shown feasibility in Crohn's disease.

When examining long-term outcomes following fistulising pCD surgery, Graf et al. found that of the 119 patients with a median follow-up of 7.1 years, 52% had healed fistulas, defined clinically as the absence of fistula symptoms, skin healing and no evidence of the fistula on clinical examination. Of these, fourteen healed after one procedure with the remaining 48 patients taking a median of 4.0 (2–20) further procedures to achieve healing.[128] At best, patients can hope for approximately 50% fistula healing rates despite advances in medical and surgical therapies.[163]

1.3.1.2.1 Seton

In the context of rectal inflammation and a complex fistula, a long term loose seton in combination with medical therapies can be effective.[164,165.] Cutting setons are less widely used and many argue that they cause pain and sphincter injury.[37] A long–term loose seton is an acceptable management strategy in some patients and may only need to be changed in the case of persistent inflammation (which suggests they are not fulfilling the function of a conduit for suppuration and that further drainage may be needed), snapping or calcification. More commonly the loose seton is placed to ensure full drainage of all perianal sepsis prior to medical therapy.

The primary aim of using a seton is to facilitate drainage and 'control' any sepsis. The secondary aims include (i) allowing the secondary extensions to drain and subsequently heal (ii) aiding the creation of a single tract i.e. rationalising the fistula complex to create

a single draining tract and (iii) reducing 'volume' of the tract, allowing for definitive treatment in the future.

Once biological treatment is well established, removing the seton can be considered to allow fistula closure. Traditionally and empirically seton removal has been after the second or third infliximab infusion however more recent evidence suggests decreased fistula recurrence rates when setons are left in place longer. [166,167] There is no consensus as to the optimum time to remove the seton[81] and the ongoing PISA trials attempt to address this issue.[168] Setons may be used as a bridge between draining the initial sepsis and optimizing the patient medically before an attempt at definitive surgical treatment.

1.3.1.2.1.1 Infill strategies

'Infill strategies' such as glues and plugs have been employed with varying success. The closure rate for fibrin glue was 57% at 23.4 months in one study of fourteen patients.[169] A systematic review found a 55% fistula closure rate in a pooled analysis of 42 patients.[170] The initial success for infill strategies has not been replicable in other centres and limited long-term data are available in pCD.[170] Two GETAID randomised controlled trials have addressed these questions. Glue in pCD fistula was found to be superior to placebo but follow up was very short (assessed at 8 weeks) and this study does not counter the balance of evidence suggesting a lack of efficacy overall, including in Crohn's patients.[171] The GETAID plug RCT was more robustly performed and demonstrated no benefit of the fistula plug over placebo in Crohn's disease.[172]

There are however potential uses for these materials as scaffolds for newer therapies such as stem cells and local pharmaceuticals. Indeed a phase II multicentre study of

complex fistula (14 patients out of 49 had pCD), compared glue vs. glue and expanded adipose-derived stem cells (ASCs) and reported healing in 16% vs. 71% respectively, with a one year recurrence of 17.6% in the ASCs group.[173] Whilst mesenchymal-derived stem cells (MSCs) are now administered without a scaffold, the utility of various scaffolds is being assessed with a view to future combined treatments, utilising a surgical repair with local pharmaceutical and/or biological augmentation. Importantly, as with all SPPs, patients can have these procedures repeatedly without risk of sphincter damage.

1.3.1.2.2 Advancement flap

Endorectal advancement flaps (ERAF) for anorectal and RVF have been used in Crohn's disease with variable success. They warrant consideration in trans- sphincteric or supra-sphincteric tracts. The surrounding mucosa in the rectum must be healthy and creating a tension free anastomosis is key.[35] Patients with perineal descent and/or internal intussusception are often better suited to advancement flaps and surgeons may choose between mucosal, partial or full thickness flaps. In a series of 36 Crohn's fistulas, there was an 11% primary failure rate and recurrence rate of 31%.[57] Solanti et al, performed a review of the literature in which 10 studies featured pCD with a 64% success rate and a 9.4% incontinence rate[174] but multiple attempts at advancement flap were permitted. A retrospective review from the Cleveland clinic identified 28 patients with pCD and a higher recurrence rate was found compared to idiopathic (57.1% vs. 33.3%, $p<0.04$).

1.3.1.2.3 Ligation of the intersphincteric tract

'Ligation of the intersphincteric tract' (LIFT) is best reserved for thin, long trans-sphincteric tracts without any intersphincteric complexity. Many of the earlier studies excluded pCD however Gingold et al, found in 8 out of 12 patients (67%) had LIFT site healing at 12 months in their prospective trial.[175] However, the same group then

published long term data (median follow up of 23 months), including the original patients, in a retrospective chart review and found an overall success rate of 48% (n -23). [176] In patients without perineal descent it is an alternative to an advancement flap. Complexity in the intersphincteric space and high fistula (difficult surgical access, proximity to rectal and/or vaginal wall) are relative contraindications.

1.3.1.2.4 Novel therapies

A recent systematic review of eighteen early phase studies (all case series) assessed the efficacy of three novel fistula therapies, VAAFT, FiLaC™ and OTSC®.[129] The conclusion was that all of these treatment modalities show promise of success (64-100%) but studies included in the review were heterogeneous in terms of technique, outcomes and follow-up, and an historical perspective, particularly considering other 'novel therapies' such as glues and plugs, warns surgeons to use success rates of early series, often produced by originators or enthusiasts, with great caution.

The evidence for FiLaC™ is particularly sparse but the factors thought to support success in idiopathic fistula may follow suit, namely a long, narrow unbranched tract. In addition to closure of tracts, VAAFT has additional utility. For example, for curettage of collections, or seton placement into tracts, which are high or difficult to reach, one may consider using VAAFT[177].

Stem cell therapy (autologous or allogenic) is a novel technique that has been assessed through a number of studies including multicentre randomised controlled trials, and relatively long term follow up is now available.[178–184] De la Portilla et al. performed an open-label, single-arm clinical trial in six Spanish hospitals, of 24 patients with pCD. At

24 weeks, 56.3% of patients achieved complete closure of the tract, with 30% achieving closure of all existing tracts; defined clinically and radiologically as the absence of collections.[180] A Phase II trial in Korea reported complete fistula healing (defined clinically) in 27/33 patients (82%) at 8 weeks[178] and the same group have recently reported their 2 year outcomes in which in modified per protocol analysis 75% had complete healing at 2 years defined clinically.[185] A longer follow up was found by Ciccocioppo et al. who found a fistula free survival of 88% at 1 year, 50% at 2 years, and 37% at 4 years.[186] Panes et al. recently published the long-term outcomes from their phase III RCT (Admire CD, n=212) which compared a single dose of 120 x 10^6 locally injected MSCs vs. 105 patients who received placebo injection with the same fistula treatment as the treatment arm (fistula curettage, surgical drainage, and closure of the internal orifice). At 1 year follow up they demonstrated clinical healing rates of 56.3% in the MSC arm vs. 38.6% in the placebo arm (p= 0.01).[184] The interesting points on analysis of this study are (i) is the given definition of 'healed,' a collection assessed radiologically as being <2cm sufficient to be described as 'healed' (ii) how does one explain the high rates of remission in the placebo arm.

The unanswered questions for stem cell treatment include: (i) further elucidation of the correct treatment regime (pre-injection tract preparation, dose and type of stem cells, whether scaffolds are beneficial), (ii) whether repeated treatments are beneficial after failure, or needed to sustain healing after success (iii) what prognostic factors predict success and lastly, (iv) cost-effectiveness.

1.3.1.2.5 Faecal diversion and proctectomy

Despite all available treatment modalities, a proportion of patients still require faecal diversion and no change in this rate has yet been seen since the advent of biological therapies.[187,188] Faecal diversion can take the form of defunctioning colostomy or ileostomy. A meta-analysis of 16 studies (556 patients) found that approximately two-thirds of patients (63.8%; 95% CI: 54.1-72.5) undergoing defunctioning ostomy for refractory pCD had early clinical response [188] and others have demonstrated improvements in quality of life scores.[189] Diversion is often viewed as a temporary manoeuvre to allow the acute Crohn's perineum to 'cool' as the patient is optimised with medical therapies, however, the same meta-analysis found that restoration of bowel continuity was only attempted in roughly a third of patients (34.5%; 95% CI: 27.0-42.8) and was only successful (without relapse of symptoms or need for additional surgery) in 17% of patients.[188] The authors concluded 42% of patients undergoing restoration of bowel continuity, go on to require proctectomy due to relapse of symptoms. A persistent perineal sinus occurred in 30% (33/145) of patients after proctectomy for Crohn's disease in one study[190], with 25–50% of these patients requiring coloplastics input post-operatively in another.[191] Other post-operative complications include recurrent abscess and fluid collections in the 'dead space' created, and damage to pelvic nerves. Proctectomy has traditionally been and often continues to be seen as a failure of management but in a few patients with very severe perianal disease and/or proctitis, it can be a life changing intervention, and the implication of failure, from the patients' point of view, is both inaccurate and unhelpful.

Decision-making in relation to IBD can be extremely difficult due to issues including predicting responsiveness to treatment, the morbidity associated with treatment options

and the fact that the symptom burden to patients, and their perceptions of its acceptability, change over time. It is often difficult for patients to determine what will give them the best chance of the best outcome. An area to be explored is the quality of life experienced by patients prior to and following proctectomy. A significant and prolonged impact on quality of life negates the need for the theoretical argument about tissue damage outlined above; an earlier proctectomy is valid in its own right if it produces a sustained and marked improvement in quality of life. It would be useful to quantify the change in quality of life following proctectomy, as well as how these manifests in terms of decisional regret following proctectomy. Few quality of life studies exist in this area, particularly exploring the relative importance of living with chronic symptomatic fistulas (with or without various other features of perianal Crohn's disease) compared to living with a permanent stoma and, in some patients, an unhealed perineal wound. Qualitative work would also help to establish what patients are willing to 'trade' for a good quality of life following treatment for established perianal Crohn's disease.[192] Whilst this information would be offered to patients in counselling them regarding surgery, it would ultimately be the patient's own decision to undergo or defer surgery. In some centres, patients are seen in a joint clinic with both a colorectal surgeon and a gastroenterologist, when they are able to obtain advice from the multi-disciplinary team (MDT) directly, including a full discussion of the risks and benefits different treatment options offer, at the same consultation. With this approach surgery may be less likely to be seen as a failure of treatment, but as a treatment choice, and concepts such as faecal diversion may be brought into the conversation on the long-term pathway earlier.

1.3.1.2.6 Crohn's disease and pregnancy

A recent retrospective review of all deliveries from 1998-2009 found patients with pCD were more likely to have a caesarean section compared to those patients with non-CD perianal disease (83.1% vs. 38.9%, p<0.001).[193] Multivariate analysis was performed to identify independent risk factors of 4th degree lacerations. Crohn's disease alone was not a risk factor (OR 1.18; 95% CI, 0.8-1.8, p 0.4) whereas perianal disease was (OR, 10.9; 95% CI, 8.3–4.1; $p < 0.001$) but a distinction between pCD and non-CD perianal disease was not made.[194] The European Crohn's and Colitis Organisation (ECCO) guidelines recommend normal vaginal delivery as safe for all patients except those with active perianal disease, and to avoid episiotomy where possible.[195]

Monitoring therapy

Escalation or switching of treatment can be efficacious and should be guided by clinical response and through drug monitoring. Insufficient trough levels would prompt an escalation in dose or shorter interval between doses and the presence of serum antibodies may prompt a switch.[196] The evidence for switching biological therapies in pCD is sparse[197] and a concern is that a significant time period may elapse during the course of multiple switches.

Yarur et al. recently demonstrated in a cross-sectional survey of 117 patients that those with fistula healing had significantly higher median serum infliximab levels when compared to those with active fistulas [15.8 vs. 4.4 µg/mL, respectively (P < 0.0001)]. The group also found that there was an incremental gain in fistula healing with higher infliximab levels. The authors concluded that dose optimisation of infliximab

≥10.1 mcg/mL in patients should be part of a treat-to-target strategy.[198] Davidov and colleagues echoed these findings in their retrospective study and went on to suggest that high trough levels during induction are predictive of response.[199] This makes intuitive sense, with clinical evidence suggesting that the better the initial response to infliximab the lower the fistula recurrence rate.[145] More data, perhaps even registry data would help elucidate the optimum dosing regime,[163] and help to identify poor responders (apart from those with antibodies) who may benefit from dose augmentation or an alternative treatment strategy.

System of Care

It is important that patients' have the ability to access the IBD service not only for administrative reasons, such as dates for infusions and organising investigations but also for non-elective access to care. Patients should be counselled as to what symptoms to be aware of such as perianal pain or discomfort or a new external opening and should be able to access either a gastroenterologist or a colorectal surgeon quickly. Often this is co-ordinated by an IBD nurse but both specialities must also have capacity in terms of clinic or theatre slots to assess and manage patients. At our institution, there is a VAAFT (video assisted anal fistula treatment) service which the patients are able to access and recent evaluation of this service found it improved quality of life in terms of pain and discharge.[177] The VAAFT procedure in these cases was used primarily to wash out and debride the tracts and thus acts as a less invasive drainage/curettage procedure. As with a number of chronic diseases with a young age of onset, patients with IBD become well versed with their condition and management plans. This is probably truer of patients with perianal manifestations due to the aggressive nature of the disease and the fact that

they need/access IBD services more. IBD as a speciality has a promising future with better understanding of patient reported outcome measures along with a young, educated patient base who are able to perform home testing[200] and hence become empowered. Future digital innovations and e-patient records are likely to make patients true members of their own multidisciplinary team.

Conclusion

There are a number of factors which influence patients' goals, such as the duration of their fistula, the severity of symptoms, experience of previous unsuccessful treatments and how much the symptoms interfere with their life. Wong et al. demonstrated that often a surgeon's perception of success is distinctly different to that of the patients.[192] They illustrated that whilst surgeons felt that the most important quality of life considerations were continence, leakage, pain, cure and sepsis; patients felt somewhat differently and chose independent activity, pain, continence, psychological health and leakage as their five most important quality of life factors. Similar findings were demonstrated in the first Delphi round for the development of a core outcome set for fistulising pCD where colorectal surgeons, gastrointestinal radiologists, IBD nurses and patients were asked to prioritise the outcome measures they felt to be the most important.[201]

However, despite advances in diagnosis, medications and surgical techniques, surgery for complex pCD remains challenging.[202,203,204,147,205] Recurrence and reoperation rates are high and proctectomy may ultimately be required in 10-18% of cases.[164,64,206,165] Complex fistulous disease may never be cured and for some patients a palliative approach is currently the only option. Communication with the patient and an understanding of their

goals of treatment are crucial. For example, an appreciation that patient goals of treatment will vary through the disease course is important and should be fundamental when planning definitive treatments and (de)escalating therapies.

1.4 Thesis Hypothesis, Aims & Objectives

Designing a clinical trial of fistulising perianal Crohn's disease is currently undeliverable due to lack of epidemiological data, consensus on outcome reporting and objective outcome measures. Patient involvement in decision making is limited by patient understanding of their own disease and fistula morphology.

Aim

The aim of this thesis is to identify the necessary epidemiological data, establish consensus on which outcomes we should report and develop an objective outcome measure. In addition, to investigate innovation in imaging to allow better communication of complex perianal disease.

Thesis Objectives

1. Investigate the role of the precursor lesion (abscess) and subsequent fistula formation.
2. Establish consensus for a core outcome set.
3. Develop an objective measure of response
4. Investigate different innovations of imaging to facilitate comprehension of complex fistulous disease.

1.5 Thesis Structure

This thesis has been structured into four main sections (sections A-D)

1. **Chapter 1 – Introduction**

1.1.1 Section A – Epidemiology of perianal sepsis

2. **Chapter 2 – Abscess to Fistula – The natural history of anorectal sepsis in England:** National data from Hospital Episode Statistics (HES) dataset will be used to determine the rate of fistula formation following presentation with an anorectal abscess. In addition, predictive factors of fistula formation will be determined as will the role of Crohn's disease in the cohort. **(Objective 1)**

3. **Chapter 3 – Persistent fistula following anorectal abscess drainage – local experience of 11 years:** Data from a local hospital database over 11 years will be interrogated to validate the findings of the national data. The rate of fistula formation as well as the predictive factors of developing a fistula will be established. **(Objective 1)**

1.1.2 Section B – Assessing outcomes for perianal Crohn's disease

4. **Chapter 4 – A systematic review of outcomes reported in studies on fistulising perianal Crohn's fistula:** A systematic review of contemporary prospective studies will be performed to identify the outcome measures currently

used to assess the efficacy of interventions for perianal Crohn's disease. **(Objective 2)**

5. **Chapter 5 – Developing a core outcome set for fistulising perianal Crohn's disease:** Candidate outcomes derived from a systematic review and patient interviews will enter into a modified Delphi process to establish consensus on which outcomes should be used universally in interventional studies for perianal Crohn's disease. **(Objective 2)**

1.1.3 Section C – Developing an objective outcome measure

6. **Chapter 6 – Volume assessment MRI technique for monitoring perianal Crohn's fistulas:** The current standard of care of radiological assessment will be compared in this pilot study looking at MRI volumes as a potential objective outcome. MRI volumes will be created using open source segmentation software. **(Objective 3)**

1.1.4 Section D – Novel imaging strategies to better understand complex perianal disease

7. **Chapter 7 – Improving the understanding of perianal Crohn's fistula through 3D modelling:** A number of different media of 3D reconstruction will be shown here to illustrate the intuitive advantage of 3D over 2D representation. These include, static images, animations and a system that can be accessed using an app. **(Objective 4)**

8. **Chapter 8 - Innovation in the imaging of perianal fistula: a step towards personalised medicine:** Here the process of creating 3D printed models for complex fistula will be discussed as well as MRI fistulography, a computerised animation taking forward the principle of virtual colonoscopy. **(Objective 4)**

1.1.5 Thesis Discussion & future work

9. **Chapter 9 – Thesis Discussion & Future work:** The overall findings of the thesis will be discussed as well as expanding on future directions for the work.

Section A – Epidemiology of perianal sepsis

When proposing to conduct a clinical trial on a condition it is imperative to know and understand the epidemiology of that condition and of the comparator. In this case, of both fistulising perianal Crohn's disease and the comparator cohort of cryptoglandular/idiopathic fistula.

Section A will look at the role of the anorectal abscess as a precursor lesion in forming a fistula both at a national and a local level. Predictive factors of fistula will be established as well as the role of Crohn's disease in those patients presenting initially with an anorectal abscess. Such efforts being key to better understand the natural history of anorectal sepsis and facilitate future epidemiological studies.

2 Abscess to Fistula – The natural history of anorectal sepsis in England

This chapter has been published in the British Journal of Surgery and in part in the British Medical Journal. Permission for the reuse of this article has been given by Wiley, 4305921154674 and the British Medical Journal publishing group 4305920164030 respectively.

2.1 Abstract

Introduction

Progression from anorectal abscess to fistula is poorly described and it remains unclear which patients develop a fistula following a preceding abscess. We aim to assess the burden of anorectal abscess and the risk factors of subsequent fistula formation.

Methods

The Hospital Episode Statistics database was used to identify all patients presenting with new anorectal abscesses. Cox regression analysis was undertaken to identify factors predictive of fistula formation.

Results

159,052 patients in England with first-time abscesses presented from 1997-2012 with an incidence of 20.2/100,000. Fistula formation rate following an abscess was 16.0% (25,530/159,563) in idiopathic cases and 41.5% (4,407/10,613) in IBD cases (27%

coded concurrently as ulcerative colitis (UC); 47.0% coded as Crohn's disease (CD)). Of the total patients who developed a fistula, 67.0% did so within the first year.

Independent predictors of fistula formation following perianal abscess were; *IBD*, in particular *CD* (HR 3.51, p<0.001), *UC* (HR 1.82, p<0.001), *female gender* (HR 1.18, p<0.001), age *41-60 years* (HR 1.85, p<0.001, compared to the <20 age group); and *intersphincteric* (HR 1.53, p<0.001) or *ischiorectal* (HR 1.48, p<0.001) abscess locations (compared to perianal).

Some 2.8% of all patients without a diagnosis of IBD at the time of presenting with a new abscess were subsequently diagnosed with CD (median 14 months).

Conclusion

This population study demonstrates that the burden of anorectal sepsis is high, with subsequent fistula formation nearly x3 times higher in CD than idiopathic disease. Female gender is a novel, independent predictor of fistula formation following abscess drainage and most fistulas are diagnosed within the first year. Risk stratification can guide management and follow-up.

2.2 Introduction

Anorectal abscesses are common with 18,000 patients affected each year in England.[116] They are a costly condition to the NHS and result in approximately 12,500 operations a year.[207] A recent Swedish cohort study estimated the incidence at 16.1 per 100,000.[208] The true incidence may be even higher, since many patients are treated with antibiotics in the community and some abscesses regress or spontaneously discharge.[208,209]

Abscesses are primarily treated by incision and drainage performed in the operating theatre by a general surgeon. A proportion of patients will subsequently develop a fistula; however, the proportion is difficult to ascertain. The incidence of fistula alone is also difficult to accurately denote, and current evidence is inconsistent. Sainio and colleagues derived the incidence of anal fistula from operating room data in Helsinki and found the incidence of anal fistula in a single institution to be 8.6 per 100,000 population/year (12.6 for males and 5.6 for females) between 1969 and 1978.[210]. Zanotti demonstrated a higher incidence but this is estimated from data from a single year. They reviewed European databases and described higher incidences of 1.84/10,000 in the United Kingdom (UK) (2003-4) and of 2.32/10,000 in Italy (2002).[211]

There is no definitive means of preventing or predicting fistula occurrence or formation following abscess drainage. Previously, it was thought that the isolation of enteric organisms from the perianal abscess was associated with a higher risk of subsequent fistula formation.[212] However, in a recent case series of 164 patients, no significant association was demonstrated between the presence of gut-derived organisms and the development of a fistula (odds ratio = 0.48; 95% confidence interval = 0.17-1.37) or recurrence of perianal abscess (odds ratio = 1.66; 95% confidence interval = 0.46-

6.01).[213] Evidence from a multicentre, double-blinded randomised trial demonstrated that antibiotics during an acute episode offer no protective effect against subsequent fistula formation.[214]

Around 90% of idiopathic or non-IBD sepsis occurs due to infection of the cryptoglandular glands.[215,216] The majority of abscesses occur posteriorly and in the intersphincteric space, where the anal glands are located.[217] Abscesses are classified as superficial or deep in relation to the anal sphincter. If the infection penetrates through the external sphincter, it will form an ischiorectal abscess. If it spreads laterally on both sides it can form a collection of sepsis which forms a 'horseshoe' around the sphincters. Superior extension (supralevator abscess) beyond the puborectalis or the levators is rare and may represent iatrogenic injury. There is no evidence to support the theory that abscesses are related to personal hygiene or sedentary lifestyles.[218]

The cryptoglandular hypothesis indicates that infection of an intersphincteric gland via an internal opening leads to fistulation out to the perianal skin. However, not all anorectal abscesses lead to persistent fistulas. Oliver and colleagues found that 83% of a series of 200 abscesses had an internal opening when examined by an experienced proctologist. They found treating fistulas in the acute phase yielded a reduced recurrence rate (5% vs. 29%),[84] demonstrating that not all of the abscesses identified to have an internal opening then presented with a fistula. Abcarian and colleagues similarly found that 40% of abscesses progress to fistula formation but other studies have found this rate to range from 26% to 87%.[219,220,221,222,223,224,225] This is even the case in studies in which all included patients had an internal opening (acute fistula).[226,227] This means that some patients with abscesses associated with an internal opening would never present with a

persistent fistula.[228] Treating the fistula in the acute phase also risks iatrogenic injury, either to the sphincter or by the creation of new tracts.

It would be helpful to risk stratify which patients presenting with an abscess are likely to present with a persistent fistula.[109] Other than Crohn's disease, there are few reliable clinical factors that predict which abscesses will develop into fistulas.[229] It is important for clinicians to be able to predict which patients presenting with abscesses are likely to fistulate so clinicians can make informed follow up plans. Follow-up after an abscess is clinician dependent, with most simple abscesses not followed up at all. Understanding which patients are more likely to fistulate will allow clinicians to follow-up patients they suspect are at high risk of forming fistulas and prevent complications.[109]

Between 28% to 38% of patients with Crohn's Disease suffer from perianal disease.[46,230] Perianal Crohn's disease is associated with a higher rate of fistula recurrence following treatment and a shorter median time to recurrence[2,3]. It represents a distinct and aggressive phenotype[231] and is one of the most disabling manifestations of Crohn's disease[232] with 12% to 39% undergoing proctectomy for intractable proctitis, often associated with perianal fistula or anorectal stenosis.[233,234,235,165] Early identification of patients with perianal Crohn's disease is important to try and avoid complications.

Our population-based study is the largest to date with the longest follow up investigating demographic and diagnostic predictive markers of fistula formation. We aim to assess the burden of new diagnosis of anorectal abscess and the risk factors that lead to subsequent fistula formation.

2.3 Methods

Ethical Approval

Ethical approval was obtained through the National Research Ethics Service (NRES), Project ID 134045, Research Ethics Committee (REC) reference 13/LO/1235 and local Research & Development (RD) permission was sought (RD reference: 13.051) from London North West Hospitals NHS Trust.

The Hospital Episode Statistic dataset

The Hospital Episode Statistics (HES) dataset is an administrative dataset encompassing almost complete capture of all hospital episodes in England since its inception in 1987. The dataset provides information on patients and their specific admission episode. For the purposes of this chapter, the HES dataset was linked with Office for National Statistics (ONS), providing date of death for all patients where appropriate. Incidence and age-standardised rates were calculated in accordance with the ONS website (http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Mortality+Rates). Within the dataset, diagnoses are coded according to the World Health Organisation's (WHO) ICD-10 (International Classification for Disease version 10) classification. The diagnostic and operative codes used to identify abscess, fistula and inflammatory bowel disease (IBD) are presented in **Table 2-1.** Patients were identified according to these codes capturing inpatient/outpatient/emergency attendances. The HES dataset was analysed over a 15-year period from April 1997 to March 2012. The first patient admission with an abscess code was taken as the index abscess admission. Patients who had an admission for an anal abscess or fistula before or at the same time as their index abscess admission were excluded from the study.

1

ICD-10 codes

	Abscess		Fistula
K61.0	Perianal abscess	K60.3	Anal fistula
K61.1	Perirectal abscess	K60.4	Rectal fistula
K61.2	Anorectal abscess	K60.5	Anorectal fistula
K61.3	Ischiorectal abscess		
K61.4	Intrasphincteric abscess		

	Inflammatory Bowel Disease		Diabetes
K50	Crohn's Disease	E10	Type 1 diabetes mellitus
K51	Ulcerative Colitis	E11	Type 2 diabetes mellitus

OPCS codes

	Abscess		Fistula
H58.1	Drainage of ischiorectal abscess	H55.1	Laying open of low anal fistula
H58.2	Drainage of perianal abscess	H55.2	Laying open of high anal fistula
H58.3	Drainage of perirectal abscess	H55.3	Laying open of anal fistula NEC
		H55.4	Insertion of seton into high anal fistula and partial laying open of track HFQ
		H55.5	Fistulography of anal fistula
		H55.6	Probing of perineal fistula
		H55.7	Repair of anal fistula using plug
		H31.1	Image guided percutaneous occlusion of colorectal fistula
		H31.2	Image guided transluminal occlusion of colorectal fistula
		H41.4	Perianal mucosal proctectomy and endoanal anastomosis

2

3 **Table 2-1. ICD-10 and OPCS codes used to identify patients with abscess, fistula, IBD & diabetes mellitus**

4

Age and social deprivation data (using the Indices of Multiple Deprivation (IMD*)- a measure of relative levels of deprivation, ranging between Quintiles 1-5 (Q1-5); with Q1 being the most affluent and Q5 the most deprived)*) were also obtained. This scoring system is used by the ONS and takes account of a number of factors including: income, health deprivation and disability, education skills and training, barriers to housing and services, crime and living environment. Pre-existing comorbidity was calculated using the Charlson Comorbidity Index **Table 2-2**. The time in months from admission with an abscess to the development of a fistula was calculated. Censoring of patients was carried out as follows: in patients in whom the event (forming fistula following abscess drainage) occurred, the admission date for the first episode with a fistula after an abscess episode was taken as the censor date. Patients who did not have a fistula episode were censored by date of death (if applicable) or by the date of 31st March 2012 (the last admission date on the dataset). Mortality data was linked to our dataset and originated from the ONS.

No Comorbidity	0 Points
Myocardial Infarction Peripheral Vascular Disease Dementia Cerebrovascular Disease Chronic Lung Disease Connective Tissue Disorder Ulcer Chronic Liver Disease Diabetes	1 Point
Hemiplegia Moderate or severe kidney disease Diabetes with end organ damage Tumour Leukaemia Lymphoma	2 Points
Moderate Liver Disease Severe Liver Disease	3 Points
AIDS Metastatic Cancer	6 Points

Table 2-2. Charlson Comorbidity Index (original weighting)

Statistical Analysis

Groups were compared using Kruskal-Wallis analyses. Binary logistic regression and Cox proportional hazard regression models were developed to determine factors associated with progression from abscess to fistula. Variables were initially individually tested against the outcome (progress to fistula from abscess). Those variables that demonstrated a significance of $p \leq 0.001$ were considered significant and entered into a multivariable (adjusted) regression model. At multivariable analyses, factors demonstrating a significance of $p \leq 0.05$ were considered statistically significant. All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 21.0, IBM.

2.4 Results

Baseline demographics

A total of 159,052 patients had an episode of new abscess formation between 1997 and 2012. The median time of follow up for the whole population was 60 months (IQR 17-115). The majority of patients were male 72.6% (n= 115,579) and the most commonly coded abscess type was perianal 89.2% (n= 141,936).

Abscesses were most commonly identified in the 41-60 year age group and the median age was 46 years. The majority of fistula episodes were in male patients (66%). Within our cohort 7.5% (n= 11,929) had a diagnosis of diabetes before their first admission with an abscess and 4.8% (n = 7,708) had a diagnosis code for Crohn's Disease at some point within the study period **Table 2-3.**

	Perianal (*n* = 136 021)	Perirectal (*n* = 3221)	Anorectal (*n* = 805)	Ischiorectal (*n* = 17 267)	Intersphincteric (*n* = 1399)	Total (*n* = 158 713)	*P*†
Age at time of first abscess (years)							< 0·001
< 20	12 687 (9·3)	165 (5·1)	56 (7·0)	995 (5·8)	39 (2·8)	13 942 (8·8)	
21–40	59 798 (44·0)	749 (23·3)	270 (33·5)	6383 (37·0)	588 (42·0)	67 788 (42·7)	
41–60	46 076 (33·9)	1116 (34·6)	272 (33·8)	6587 (38·1)	561 (40·1)	54 612 (34·4)	
> 60	17 460 (12·8)	1191 (37·0)	207 (25·7)	3302 (19·1)	211 (15·1)	22 371 (14·1)	
Sex							< 0·001
M	95 629 (70·3)	2011 (62·4)	518 (64·3)	10 837 (62·8)	1017 (72·7)	110 012 (69·3)	
F	40 392 (29·7)	1210 (37·6)	287 (35·7)	6430 (37·2)	382 (27·3)	48 701 (30·7)	
Diabetes							< 0·001
No	126 085 (92·7)	2913 (90·4)	739 (91·8)	15 492 (89·7)	1326 (94·8)	146 555 (92·3)	
Type 1	2326 (1·7)	50 (1·6)	6 (0·7)	379 (2·2)	10 (0·7)	2771 (1·7)	
Type 2	7610 (5·6)	258 (8·0)	60 (7·5)	1396 (8·1)	63 (4·5)	9387 (5·9)	
IBD							< 0·001
No	127 487 (93·7)	2792 (86·7)	715 (88·8)	16 040 (92·9)	1252 (89·5)	148 286 (93·4)	
Crohn's disease	6252 (4·6)	258 (8·0)	58 (7·2)	895 (5·2)	108 (7·7)	7571 (4·8)	
Ulcerative colitis	2282 (1·7)	171 (5·3)	32 (4·0)	332 (1·9)	39 (2·8)	2856 (1·8)	
Social deprivation*							< 0·001
Q1 (affluent)	57 639 (42·4)	1515 (47·0)	357 (44·3)	7450 (43·1)	661 (47·2)	67 622 (42·6)	
Q2	42 792 (31·5)	978 (30·4)	251 (31·2)	5341 (30·9)	422 (30·2)	49 784 (31·4)	
Q3	24 111 (17·7)	503 (15·6)	130 (16·1)	3064 (17·7)	208 (14·9)	28 016 (17·7)	
Q4	9608 (7·1)	179 (5·6)	55 (6·8)	1193 (6·9)	87 (6·2)	11 122 (7·0)	
Q5 (deprived)	1871 (1·4)	46 (1·4)	12 (1·5)	219 (1·3)	21 (1·5)	2169 (1·4)	
Charlson Co-morbidity Index score							< 0·001
0	117 174 (86·1)	2366 (73·5)	664 (82·5)	14 151 (82·0)	1221 (87·3)	135 576 (85·4)	
1–3	17 830 (13·1)	720 (22·4)	128 (15·9)	2883 (16·7)	169 (12·1)	21 730 (13·7)	
> 3	1017 (0·7)	135 (4·2)	13 (1·6)	233 (1·3)	9 (0·6)	1407 (0·9)	
Abscess progressed to fistula							< 0·001
No	113 760 (83·6)	2741 (85·1)	672 (83·5)	13 151 (76·2)	1040 (74·3)	131 364 (82·8)	
Yes	22 261 (16·4)	480 (14·9)	133 (16·5)	4116 (23·8)	359 (25·7)	27 349 (17·2)	

Values in parentheses are percentages. *Based on Indices of Multiple Deprivation score. IBD, inflammatory bowel disease. †Kruskal–Wallis test.

Table 2-3. Baseline demographics for all abscess presentations

Incidence

The crude incidence rate (CIR) of *first-time* admission to hospital (within the study period) with an abscess was 20.4 per 100,000 (over a 15-year time period in England). Census data from the Office of National Statistics (ONS) were used to establish population size and hence an Age Standardised Rate (ASR) of 20.2 per 100,000 (CI 95% 20.1- 20.3). The Age Standardised Rate does not include the significant number of patients who have recurrent abscesses, or those cases performed in the private sector.

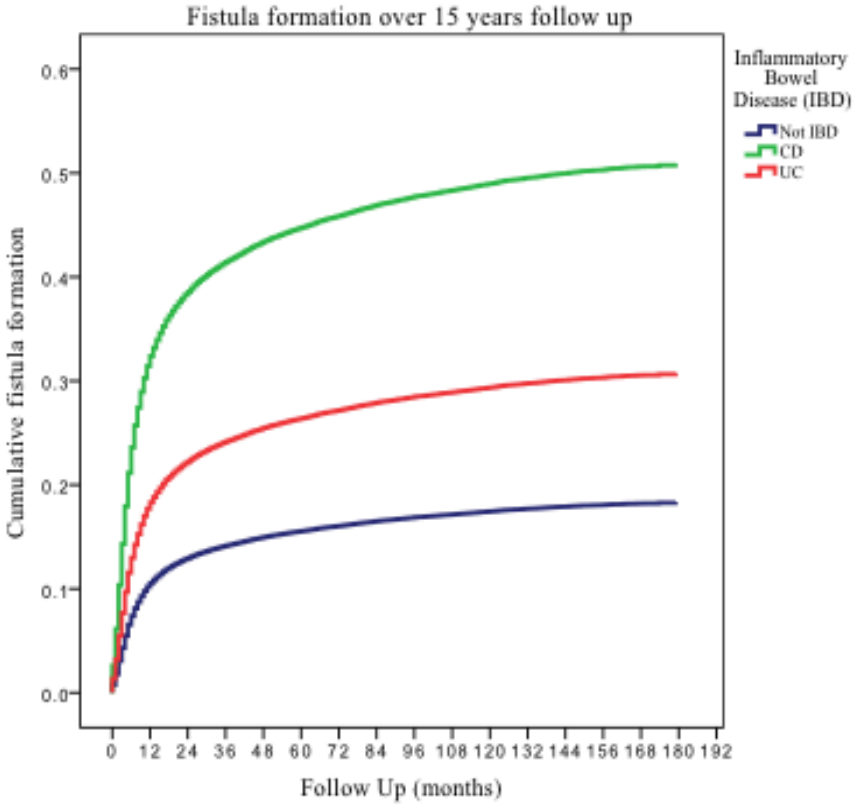
Incidence and time of fistula diagnosis following abscess drainage

Within the 15-year time period, the overall rate of fistula formation, as defined by the ICD-10 and the OPCS codes, following anorectal abscess was 17.0% (27,038/159,052). Sub-classification revealed the rate of subsequent fistula formation following an abscess was 16.0% (25,530/159,563) in idiopathic cases and 41.5% (4,407/10,613) in IBD cases.

Of those patients who did progress from abscess to fistula, the overall rate was most pronounced within the first 12 months (67.0%). This was stratified; 52.0% of idiopathic (95% CI 51.8- 53%, $p<0.001$), 65.0% of ulcerative colitis (95% CI 61.4- 68.1%, $p<0.001$) and 84.0% of Crohn's disease (95% CI 81.9- 85.6%, $p<0.001$) cases progressed within the first 12-months.

Timing of fistula diagnosis

The median time to first episode (inpatient, outpatient or accident and emergency) for fistula following abscess drainage was seven months (Inter-quartile range (IQR) 3-20; range 0-174) for the entire study population, **Figure 2-1.**



		Number of Years Follow Up														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Not IBD	Not Progressed	14,101	10,314	9,481	9,176	8,697	8,506	8,223	7,901	7,495	7,158	6,942	6,945	6,889	6,954	6,453
	Progressed abscess to fistula	15,623	3,145	1,395	857	534	412	328	239	150	128	98	49	34	17	3
	At Risk	29,724	13,459	10,876	10,033	9,231	8,918	8,551	8,140	7,645	7,286	7,040	6,994	6,923	6,971	6,456
Crohn's Disease	Not Progressed	438	289	278	273	269	256	251	265	234	251	251	249	220	251	220
	Progressed abscess to fistula	2,309	485	216	148	110	82	80	39	26	27	20	18	6	6	2
	At Risk	2,747	774	494	421	379	338	331	304	260	278	271	267	226	257	222
Ulcerative Colitis	Not Progressed	287	179	164	158	137	150	124	129	137	106	121	111	110	103	76
	Progressed abscess to fistula	537	88	40	30	19	12	7	5	5	11	4	2	3	0	0
	At Risk	824	267	204	188	156	162	131	134	142	117	125	113	113	103	76
Whole Population	Not Progressed	14,826	10,782	9,923	9,607	9,103	8,912	8,598	8,295	7,866	7,515	7,314	7,305	7,219	7,308	6,749
	Progressed abscess to fistula	18,469	3,718	1,651	1,035	663	506	415	283	181	166	122	69	43	23	5
	At Risk	33,295	14,500	11,574	10,642	9,766	9,418	9,013	8,578	8,047	7,681	7,436	7,374	7,262	7,331	6,754

Figure 2-1. Fistula formation for IBD and non-IBD cohort

Of all those patients who were diagnosed with a fistula within one-year, the median time to diagnosis of fistulation was 7 months (95% CI 6.9- 7.1) for the idiopathic cohort and 5 months for the ulcerative colitis (95% CI 4.7- 5.2,) and Crohn's Disease cohorts (95% CI 4.5- 5.5), **Figure 2-2.**

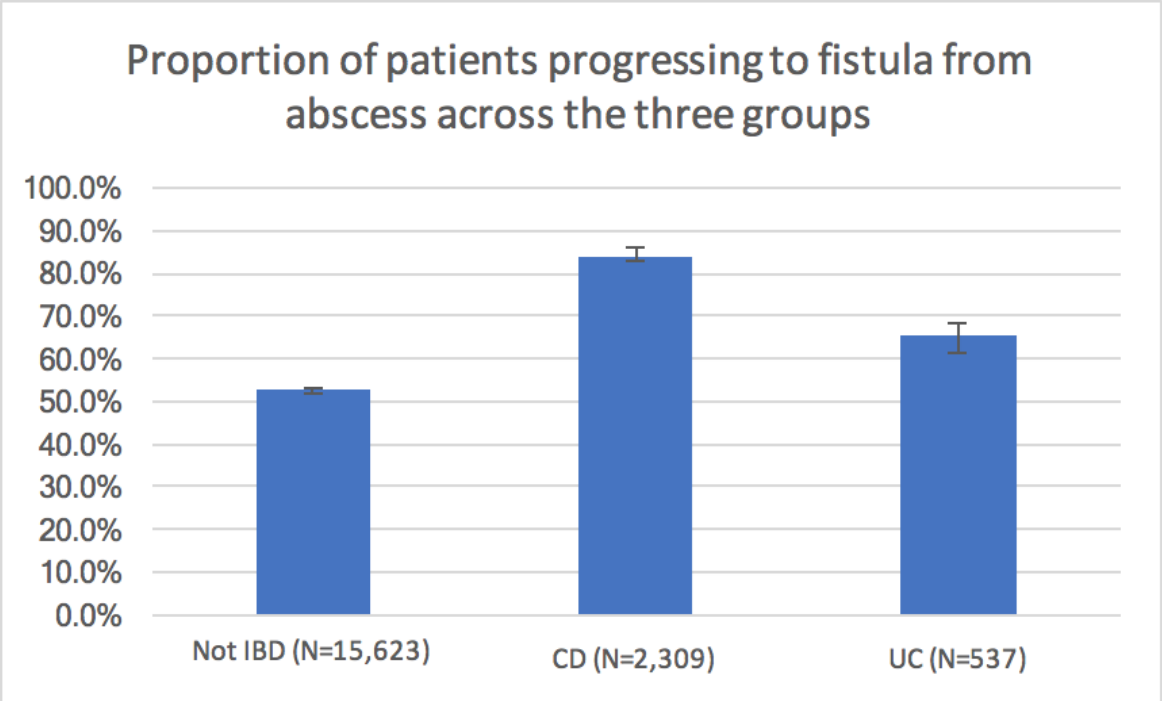


Figure 2-2. Proportion of patients developing a fistula following abscess drainage, who did so within the first year following abscess drainage.

Factors associated with a fistula

Cox proportional hazards regression analyses **Table 2-4** was undertaken to identify factors associated with subsequent diagnosis of a fistula from first admission with an abscess. Independent predictors of fistulation were found to be female gender (HR 1.18, 95% CI: 1.15-1.21, p<0.001), age 41-60yrs (HR 1.85, 95% CI: 1.76- 1.95, p<0.001) and location of the initial abscess as ischiorectal (HR 1.48, 95% CI: 1.43- 1.53, p<0.001) or intersphincteric (HR 1.53, 95% CI: 1.38- 1.70, p<0.001).

	Unadjusted *P*	Adjusted analysis	
		Hazard ratio	*P*
Age at time of first abscess (years)	< 0·001		
< 20		1·00 (reference)	
21–40		1·69 (1·61, 1·78)	< 0·001
41–60		1·85 (1·76, 1·95)	< 0·001
> 60		1·64 (1·54, 1·74)	< 0·001
Sex	< 0·001		
M		1·00 (reference)	
F		1·18 (1·15, 1·21)	< 0·001
Diabetes	< 0·001		
No		1·00 (reference)	
Type 1		0·42 (0·36, 0·48)	< 0·001
Type 2		0·76 (0·71, 0·82)	< 0·001
IBD	< 0·001		
No		1·00 (reference)	
Crohn's disease		3·51 (3·38, 3·63)	< 0·001
Ulcerative colitis		1·82 (1·69, 1·96)	< 0·001
Social deprivation	< 0·001		
Q1 (affluent)		1·00 (reference)	
Q2		0·92 (0·90, 0·95)	< 0·001
Q3		0·84 (0·82, 0·87)	< 0·001
Q4		0·80 (0·76, 0·84)	< 0·001
Q5 (deprived)		0·73 (0·65, 0·82)	< 0·001
Charlson Co-morbidity Index score	< 0·001		
0		1·00 (reference)	
1–3		0·92 (0·88, 0·97)	< 0·001
> 3		0·83 (0·68, 1·00)	< 0·001
Abscess type	< 0·001		
Perianal		1·00 (reference)	
Perirectal		0·87 (0·79, 0·95)	< 0·001
Anorectal		0·94 (0·80, 1·11)	0·499
Ischiorectal		1·48 (1·43, 1·53)	< 0·001
Intersphincteric		1·53 (1·38, 1·70)	< 0·001

1

2 **Table 2-4. Cox Regression analysis of fistula formation**

The presence of inflammatory bowel disease was strongly associated with progression to fistula (ulcerative colitis (HR 1.82, 95% CI: 1.69- 1.96, p<0.001), Crohn's disease (HR 3.51; 95% CI: 3.38-3.63, p<0.001) compared to the non-inflammatory bowel disease population.

Diabetes, an existing comorbidity, or a social deprivation score less than Q1 were not associated with an increased risk of fistula formation.

Diagnosis of Crohn's disease in relation to anorectal sepsis

Of our cohort across the entire study period, 4.8% (n=7708) of patients had a diagnosis of Crohn's disease at some point. An established diagnosis of Crohn's disease before their first admission with an anorectal abscess on the dataset was observed in 42.2% (n-3254) of the Crohn's group. A further 16.5% (n-1272) were diagnosed with Crohn's disease within the same admission as their first abscess. The remaining 41.3% (n-3182) of patients had a diagnosis code for Crohn's disease after their first abscess, at a median of 14 months (IQR 4-40).

Of the 3,182 patients, who had a Crohn's disease diagnosis after their abscess admission, 53.0% (n-1, 683) went on to develop a fistula within our study period. The median time to diagnosis of the 973 patients who were diagnosed with CD after the fistula admission was 5 months (IQR 2-10). This described in **Figure 2-3.**

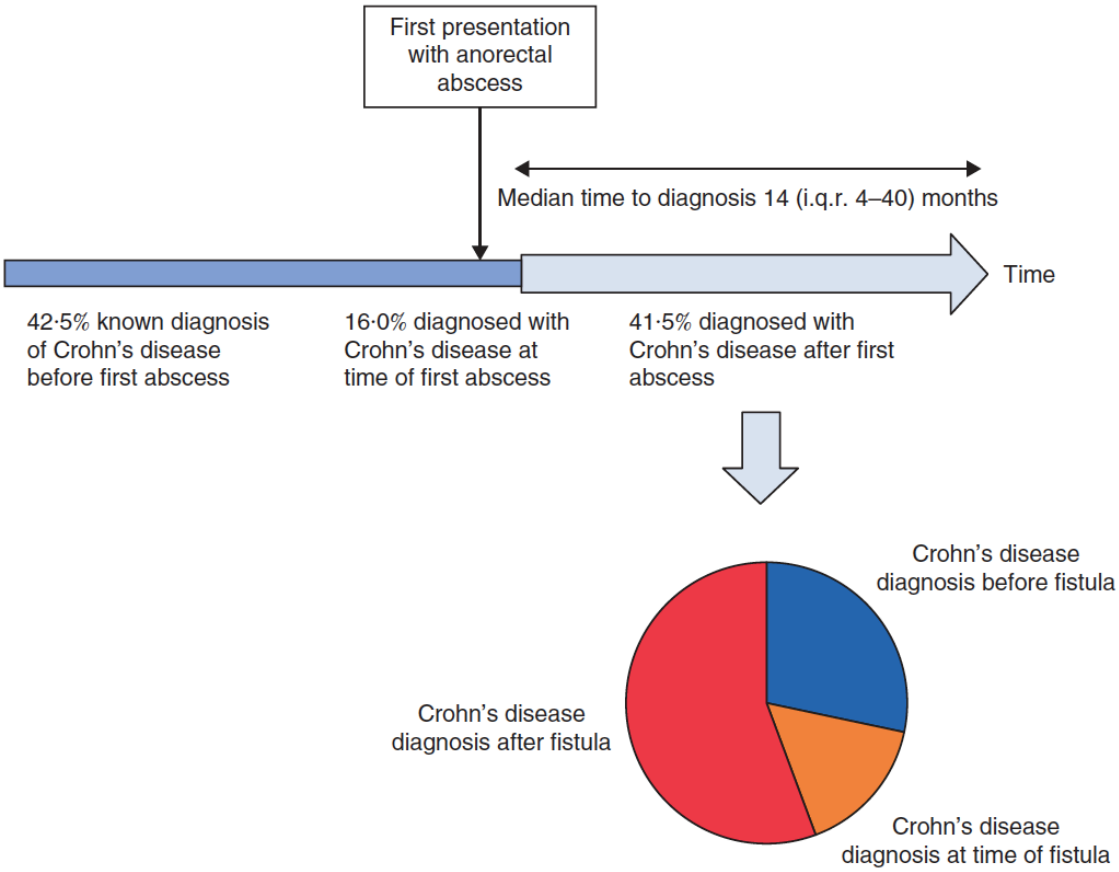


Figure 2-3. Diagnosis of Crohn's disease following abscess presentation and subsequent fistula formation

Of the 155,798 patients presenting with an anorectal abscess who did not have a diagnosis of Crohn's disease on admission, 2.8% (n=4,454) were subsequently diagnosed with Crohn's disease, either at the time of the admission or after.

Fistula formation in the Crohn's population

Of the known 7,708 patients presenting with a new CD abscess, 54.0% were female. Subsequent presentation with anal fistula occurred in 47%. In this sub-group, Cox regression analysis (**Table 2-5)** revealed independent predictors of fistula formation were: ischiorectal abscess (HR 1.30 vs. perianal abscess, CI: 1.18- 1.42, p<0.001); and female gender (HR 1.11, CI: 1.04- 1.19, p<0.001). Neither type 1 (HR 0.41, CI 0.21- 078,

p=0.007) nor type 2 (HR 0.87, CI 0.68- 1.13, p=0.308) diabetes was associated with subsequent fistula diagnosis.

		Unadjusted	Adjusted		
		p=	HR	95% CI	p=
Gender	Male	<0.001	1 (Ref)		
	Female		1.11	1.04-1.19	**0.001**
Age at time of first abscess	<20 yrs	<0.001	1 (Ref)		
	21-40 yrs		0.97	0.89-1.06	0.522
	41-60 yrs		0.78	0.70-0.87	**0.001**
	>60 yrs		0.71	0.71-0.83	**0.001**
Diabetes status	No Diabetes	<0.001	1 (Ref)		
	Type I Diabetes		0.41	0.21-0.78	**0.007**
	Type 2 Diabetes		0.87	0.68-1.13	0.308
Social Deprivation (Indices of Multiple Deprivation score)	Q1-Affluent	0.119	1 (Ref)		
	Q2				
	Q3				
	Q4				
	Q5-Deprived				
Comorbidity (Charlson Score)	No Comorbidity	0.036	1 (Ref)		
	1-3		0.99	0.86-1.13	0.830
	>3		0.52	0.13-2.07	0.351
Abscess Type	Peri-anal	<0.001	1 (Ref)		
	Peri-rectal		0.79	0.64-0.97	**0.025**
	Anorectal		0.79	0.52-1.21	0.278
	Ischiorectal		1.30	1.18-1.42	**<0.001**
	Intersphincteric		0.78	0.57-1.06	0.107

Table 2-5. Cox regression analysis - predictors of fistula formation

2.5 Discussion

This observational population study has reported the incidence (Age Standardised Rate) of *first-time* admissions with an abscess as 20.2 per 100,000 in England. Anorectal abscesses are common with approximately a sixth of all patients with an abscess going on to develop a fistula. The majority of fistula diagnoses occur within the first year of the preceding abscess and this is most pronounced in patients with Crohn's disease. Nearly half of all patients with Crohn's abscesses develop a fistula.

The true incidence of both abscess and fistula is poorly defined in the literature.[109] Our incidence is an accurate reflection for new abscesses in England but does not include recurrent abscesses, those managed purely in the community or those presenting to the private sector, although we predict that this latter group is small. Current understanding suggests that the male population has a higher incidence of idiopathic abscess and fistula[236] with a male: female ratio in the order of 2:1. We found that an annual incidence of 10,708 *new* diagnoses of abscesses occur in a population of 53.01 million.[237] From the *new* abscess diagnoses, an overall incidence of fistula of 3.4/100,000 can be derived. This however underestimates the true burden, as it does not include any recurrent presentations with abscesses. Of our patients with abscesses, 70% were male with a median age of 47 years. Of those who went on to develop a fistula, two-thirds were male.

Our data demonstrated that whilst both abscesses and fistula were more common in men, women were more likely to develop a fistula following an abscess. A similar association was found in a study of 146 patients, with a higher incidence of fistula formation in females, particularly for anterior abscesses. However, the study only contained 44 female patients and regression analysis was not applied. The authors also

found that there was no difference in bacterial growth by gender.[238] They hypothesise that anatomical differences might explain the higher incidence for anterior abscesses. Other hypotheses include inadequate incision and drainage in the first instance (although it is not clear why this should affect men more than women) or higher rates of anal digitation, but these need prospective validation. Perhaps more compelling hypotheses might be either that factors which lead to fistula persistence (as opposed to initial abscess formation) are more common or potent in women, or that men are more likely to develop abscesses which fall outside cryptoglandular aetiology.

Sub-classification between the inflammatory bowel disease and non-inflammatory bowel disease cohorts revealed that almost half of patients with Crohn's abscesses (47%) and a quarter of patients with ulcerative colitis (27%) went on to be diagnosed with a fistula. Following an abscess, the majority of subsequent fistula presentations occurred within the first year. Our data do not allow us to calculate the incidence of anorectal disease in IBD but do confirm that IBD patients who develop an abscess are more likely to develop a perianal fistula. The exact pathogenesis of fistulas is less clearly defined in inflammatory bowel disease. The cause is likely multifactorial and includes genetic, immunological and microbiological factors. In addition to suppuration from anal glands, other aetiological theories have been proposed such as fistulas arising as a result of a deep penetrating ulcer in the anorectum.[232] Patients with known Crohn's disease (and UC) had an accelerated diagnosis of fistula, with the median time to diagnosis reducing from 7 to 5 months, perhaps because these patients are generally under careful and regular follow up from clinicians expecting a fistula to appear.

Whilst the high chance of an underlying fistula in the Crohn's cohort may be expected, an interesting observation is the rate of fistula formation within the ulcerative colitis population. For the purpose of interpretation and in an effort to mitigate the argument that some UC patients actually had Crohn's disease and were misdiagnosed as ulcerative colitis, if a patient was coded with Crohn's disease at any point during the study period, then this was the final IBD diagnosis recorded. Nevertheless, misdiagnosis remains a possibility and the development of perianal disease in a patient with a known diagnosis of UC should prompt clinicians to review the IBD status and investigate the patient to consider whether Crohn's is the true diagnosis.

Perianal disease in ulcerative colitis has been described by Zabana et al, who found concomitant perianal disease in 5% of patients.[239] Another explanation may be that it is a combination of the systemic nature of the disease and immunosuppressant medications that might lead to an increase in the formation of cryptoglandular-type fistulas but this is unknown.

The majority of the abscesses were coded as perianal, however the anatomical classification of abscesses in this study is determined by the operating surgeon. This is often a junior trainee, who may use "perianal" as an umbrella term in place of anorectal. We found that fistula development was higher in patients who presented with ischiorectal and intersphincteric abscesses. Given the significant preponderance of abscesses coded as perianal in the present study, this result must be interpreted with caution. However, Sozener et al, also found ischiorectal (OR 7.82) and intersphincteric abscesses (OR 3.35) conferred a higher risk of progression to fistula compared to perianal abscesses.[214]

Patients in Q1 (affluent) had both a higher proportion of perianal sepsis and a greater tendency to fistula formation, following an almost linear trend, Q1-5. This raises the question as to how socioeconomic status might be related to abscess or fistula presentation? From our data we are not able to draw any conclusions, but the greater tendency reported could conceivably be related to behavioural patterns and/or access to healthcare.

Perhaps unsurprisingly, diabetes was not associated with fistula formation - diabetes being a precursor to cutaneous infections, which might be less likely to be associated with a subsequent fistula than those which arise from a cryptoglandular origin. In fact, patients with type 1 diabetes were less likely to present with a fistula after drainage of an abscess. Hamadani and co-workers found non-diabetic patients had a two-fold increased risk of recurrence compared with diabetics. This finding was confined to univariate analysis.[240] Whilst no data exist on diabetes and fistula formation, Yano et al. found that diabetes was not a risk factor for recurrence of abscess.[241]

Anal sepsis has been found to be the initial manifestation and the presenting complaint in 10-25% of Crohn's diagnoses.[90,46] A more recent population based cohort study found that up to a fifth of patients develop perianal disease at least 6 months prior to luminal disease.[242]

Our study demonstrates that approximately three in every 100 patients presenting with an anorectal abscess will go on to a diagnosis of Crohn's disease. The median time to diagnosis is just over a year. We have demonstrated that over half of patients who are not yet diagnosed with Crohn's at the time of their abscess admission, develop a subsequent

fistula. In luminal disease, there is a benefit in initiating earlier biologic therapy in appropriate patients[113,114] and this has been shown to increase remission rate.[115] In perianal disease, the impact on outcomes of a delay in diagnosis is not known but is likely to be detrimental given that perianal Crohn's disease represents a severe phenotype. A combination of a significant rate of undiagnosed Crohn's disease (~3%) within a common presentation (anorectal abscess) in a disease with an historically delayed diagnosis, represents an opportunity to improve the speed of diagnosis for this group of patients.

2.6 Limitations

Though studies have demonstrated high diagnostic accuracy of routinely collected clinical dataset[243], as with any retrospective administrative study there is a potential for coding error. Specifically, this may be a problem particularly in determining the site of abscess i.e. perianal, perirectal etc. Furthermore, in this study the first admission with an abscess was taken as an index admission for abscess and it was assumed that neither fistula nor abscess had occurred before. It is possible that some patients (especially those with an index admission at the beginning of the dataset, i.e. those admitted in 1997) might have had a prior abscess/fistula that would not be captured by our data. The Hospital Episode Statistics database does not contain other confounders such as smoking status or the role of drugs such as anti-TNF agents and immunosuppressants. Our study determines the incidence of fistula arising from an abscess in the English National Health Service healthcare system, but this will be different to countries where there is not universal healthcare access or where the management of perianal abscess differs.

The issue of complete data is also a limitation. This dataset only looks at hospital admission but does not account for diagnosis in a primary care setting. With respect to establishing co-morbidity, diagnosis codes were derived from the dataset to allow the Charlson Comorbidity Index to be used, which predicts 10-year survival. This scoring system can be described as outdated (1987) and doesn't account for the improved survival advantages seen in the data period we studied, such as in AIDS. In efforts to mitigate bias with analysis from the HES dataset, the question asked needs to be unambiguous and considered, which I believe is the case with this project. The HES dataset also fails to capture factors which might influence the rate of fistula following abscess drainage. For example, the use of antibiotics, smoking status and medical treatment in Crohn's patients.

2.7 Conclusion

Our population-based study is the largest to date with the longest follow up investigating demographic and diagnostic predictive markers of fistula formation. We report a large number of observations, over fifteen years with almost complete data capture, which makes these findings reflective of the population. A representative incidence of new abscess admissions has been derived. Independent predictors of fistula development from preceding abscesses have similarly been described and the role of inflammatory bowel disease has been explored. The current study also demonstrates that the majority of fistulas are diagnosed within the first 12 months following abscess drainage.

Our study illustrates the difference in rate and time taken to fistulate amongst inflammatory bowel disease and non-inflammatory bowel disease cohorts.

Approximately a sixth of all patients develop a fistula following an abscess, surprisingly women have the greatest risk, although both abscess and fistula are more common in men. Independent predictors of fistulation were found to be female gender, age 41-60yrs and location of the initial abscess as ischiorectal or intersphincteric. Nearly half of all patients with Crohn's abscesses develop a fistula, with the majority occurring within the first 12 months. Some 2.8% of patients with an anorectal abscess but without a diagnosis of Crohn's disease will be found to have the disease after a median of 14 months.

3 Persistent fistula following anorectal abscess drainage – local experience of 11 years

This paper has been accepted by Diseases of the Colon and Rectum but it yet to be published. As per the author agreement by Wolters Kluwer Health Inc, as the primary author I have permission to reuse the content in this chapter.

3.1 Abstract

Introduction:

The characteristics of patients who develop a fistula-in-ano following an anorectal abscess are unclear. Our study explores this relationship and patient factors associated with fistula development.

Methods:

The study was conducted in a district general hospital for patients with anorectal abscess admitted to our institution between 2004 and 2015. ICD-10 (International Classification of Disease, 10th revision) and OPCS (Classification of Interventions and Procedures, version 4) codes were used to identify all patients with a primary anorectal abscess. Multivariable analysis was used to identify factors predictive of fistula formation.

Results:

A total of 1,970 abscess patients were identified; 70.0% (n=1,379) were male and 7.3% (n=144) had Crohn's Disease. Fistulas occurred in 16.2% (n=319) at a median of 7

months (IQR 3-7). Patients with Crohn's Disease were more than twice as likely to develop a fistula than non- Crohn's Disease patients (32.6% vs. 14.9%, OR 2.5, 95% CI: 1.7-3.7, p<0.001).

Crohn's patients with a fistula were more likely to be women (55.3% vs. 34.6%, p=0.007) and aged under 30 (51.1% vs. 24.3%, p<0.001) than non-Crohn's patients with a fistula. At multivariable analysis of the entire cohort, male gender (OR 0.7, 95% CI: 0.5-0.9, p=0.005), and diabetes mellitus (OR 0.5, 95% CI 0.3-0.9, p=0.027) were associated with a reduced likelihood of developing a fistula following abscess formation.

Conclusions:

Abscesses are more common in men but progression to fistula is more likely in women. The rate of fistula progression in Crohn's disease is twice that in non-Crohn's patients. Identification of patients *"at risk",* may help delineate those who will benefit from a more conservative surgical approach, enhanced follow up or investigation after abscess drainage.

3.2 Introduction

In the previous chapter, 17.2% (27,349 of 158,713) of patients who presented with an anorectal abscess were subsequently diagnosed with a fistula in the HES dataset. This rate rose to nearly one in two amongst patients with Crohn's disease.[244] The heterogeneity in reported rates from the literature (26% to 87%.[219,220,221,222,223,224,225]) probably reflects differences in diagnosis, follow up and comorbidity, including the presence of Crohn's disease. In any event, in order to validate our findings from the HES dataset, this chapter aims to establish the incidence of fistula following abscess drainage from a local hospital database. In particular, we aimed to confirm the findings of the population study, which identified an increased risk of persistent fistula after abscess drainage for women, patients with Crohn's disease and based on abscess location.

Surgeons have long questioned which factors predict a persistent fistula after drainage of anorectal abscess. Bacteriology and the presence of an internal opening have been cited, but with inconsistent results.[212,213,245] Clinical factors associated with persistent fistula formation after abscess drainage have also been examined. In the population based study described above, the single largest predictor of subsequent fistula formation was Crohn's disease (CD) (HR 3·51, 3·38 to 3·63, p<0·001).[244] It is likely that a combination of genetic, microbiological and immunological factors predispose patients with CD to this elevated risk.[246] The other patient factor that is most associated with progression to fistula is the location of the abscess, specifically ischiorectal and intersphincteric abscess locations compared to those coded as perianal abscesses, although coding error may bias this finding.[244,214] Determining the anatomical location of an anorectal abscess is dependent on the operating surgeon and it should be noted that

incision and drainage operations are rarely performed by experienced proctologists. An observational study from the UK revealed that only 7.8% (10/128) of incision and drainage operations were performed by consultant surgeons, whereas 85.2% were performed by junior surgical trainees.[116]

Contrary to the findings of our population based study, being of male gender has recently been demonstrated as a risk factor for developing a fistula (OR = 3.11; CI, 1.31–7.38 and p = 0.010) in a prospective randomised control trial (RCT) of 307 patients.[247] An improved understanding of the overall rate of further perianal sepsis or persistent fistula formation after abscess drainage, and the risk factors that are associated with fistula, are important to enable stratification of patients at the time of abscess drainage, to determine both the operative plan and surgical follow-up.[248]

The aims of this paper are to interrogate the database of a busy district general hospital, to identify the patients with anorectal abscess, and determine the risk factors that are associated with subsequent fistula formation.

3.3 Methods

ICD-10 (International Classification of Disease, 10th revision) and OPCS (Classification of Interventions and Procedures, version 4) codes (**Table 3-1**) were used to identify all patients with primary anorectal abscess, those with progression to anal fistula and to note the presence of Crohn's disease (CD). The same codes were used in the previous chapter. Patients were treated at Northwick Park General Hospital, a busy urban district

general hospital with a diverse population, between March 2004 and November 2015. The data for adult patients (>16 years) were obtained from the coding department at the hospital. The data were interpreted and analysed by the Fistula Research Unit at St Mark's Hospital, the adjacent tertiary referral centre. The abscess diagnosis was present prior to the fistula diagnosis, but the diagnosis of Crohn's disease, where present, occurred at any point in the patient pathway. Pre-existing comorbidity was calculated using the Charlson Comorbidity Index. Demographic and disease data were analysed and compared between the CD and non-CD populations, and between those who did and did not develop a persistent fistula. Multivariable analysis sought to identify factors predictive of fistula formation.

ICD-10 codes

	Abscess		**Fistula**
K61.0	Perianal abscess	K60.3	Anal fistula
K61.1	Perirectal abscess	K60.4	Rectal fistula
K61.2	Anorectal abscess	K60.5	Anorectal fistula
K61.3	Ischiorectal abscess		
K61.4	Intrasphincteric abscess		

	IBD		**Diabetes**
K50	Crohn's Disease	E10	Type 1 diabetes mellitus
K51	Ulcerative Colitis	E11	Type 2 diabetes mellitus

OPCS codes

	Abscess		**Fistula**
H58.1	Drainage of ischiorectal abscess	H55.1	Laying open of low anal fistula
H58.2	Drainage of perianal abscess	H55.2	Laying open of high anal fistula

H58.3	Drainage of perirectal abscess	H55.3	Laying open of anal fistula NEC
		H55.4	Insertion of seton into high anal fistula and partial laying open of track HFQ
		H55.5	Fistulography of anal fistula
		H55.6	Probing of perineal fistula
		H55.7	Repair of anal fistula using plug
		H31.1	Image guided percutaneous occlusion of colorectal fistula
		H31.2	Image guided transluminal occlusion of colorectal fistula
		H41.4	Perianal mucosal proctectomy and endoanal anastomosis

Table 3-1. ICD-10 and OPCS codes used to identify patients with abscess, fistula, IBD & diabetes mellitus

Statistical Analysis

For comparison of groups, Chi Squared analyses were undertaken. Binary logistic regression analyses were carried out to determine factors associated with progression to fistula from baseline anorectal abscess. All variables were tested for association with the outcome separately. A $p<0.010$ was considered significant and the variable was included in a multivariable model. During multivariable analyses, variables with a $p<0.05$ were considered statistically significant and independently associated with the outcome. All analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 21.

3.4 Results

Over this 11-year period, the median follow up was 45 months (Interquartile Range [IQR] 11-94) and a total of 1,970 patients had 2,797 episodes of anorectal abscess. Of the total population, 70.0% (n=1,379) were male and 7.3% (n=144) had a diagnosis of CD (**Table 3-2**). Across the population, the most commonly coded abscess type was perianal (85.6%), followed by ischiorectal (10.4%), intersphincteric, peri-rectal and anorectal.

		n	%
Gender	Female	591	30.0%
	Male	1,379	70.0%
Age	<30 yrs	594	30.2%
	30-50 yrs	925	47.0%
	>50 yrs	451	22.9%
Abscess Type	Perianal	1,686	85.6%
	Peri-rectal	28	1.4%
	Anorectal	14	0.7%
	Ischiorectal	205	10.4%
	Intersphincteric	37	1.9%
Comorbidity Status	No Comorbidity	1,663	84.4%
	One or more comorbidity	307	15.6%
Diabetes Status	Not Diabetic	1,808	91.8%
	Diabetic	162	8.2%
Formation of anorectal fistula status	Didn't form anorectal fistula	1,651	83.8%
	Formed anorectal fistula	319	16.2%
CD Status	Idiopathic	1,826	92.7%
	Crohn's Disease	144	7.3%

Table 3-2. Population demographics (n=1,970)

The rate of persistent fistula following abscess drainage was 16.2% (n=319) amongst the entire study population. However, patients with CD were more likely to present with a fistula after their initial anorectal abscess drainage compared with the non-CD population (32.6% vs. 14.9%, p<0.001). The median time to fistula formation was 7 months (IQR 3-7) overall, and was similar in the Crohn's (8 months, IQR 3-14) and non-Crohn's (6 months IQR 3-11) groups (p=0.064).

When comparing the Crohn's and non-Crohn's patient who presented with an initial abscess (**Table 3-3**) the abscess location was similar. However, there were a higher proportion of women in the CD group than the non-CD group (45.1% vs. 28.8%, p<0.001). The median age at first abscess formation was lower in those with CD than those without (33yrs old, IQR 24-39 vs. 38 years old, IQR 28-50, p<0.005). Rates of diabetes and comorbidity were also lower in the CD group than the non-CD population.

		Non CD		CD		p
		n	%	n	%	
Gender	Female	526	28.8%	65	45.1%	**<0.001**
	Male	1,300	71.2%	79	54.9%	
Age	<30 yrs	533	29.2%	61	42.4%	
	30-50 yrs	856	46.9%	69	47.9%	**<0.001**
	>50 yrs	437	23.9%	14	9.7%	
	Perianal	1,562	85.5%	124	86.1%	
	Peri-rectal	24	1.3%	4	2.8%	
Abscess Type	Anorectal	12	0.7%	2	1.4%	0.425
	Ischiorectal	193	10.6%	12	8.3%	
	Intersphincteric	35	1.9%	2	1.4%	
Comorbidity	No Comorbidity	1,528	83.7%	135	93.8%	**<0.001**
	>1 Comorbidity	298	16.3%	9	6.2%	
Diabetes Status	Not Diabetic	1,666	91.2%	142	98.6%	**0.002**
	Diabetic	160	8.8%	2	1.4%	
Fistula Formation	Not formed Fistula	1,554	85.1%	97	67.4%	**<0.001**
	Formed Fistula	272	14.9%	47	32.6%	

Table 3-3. Demographics for patients with abscess (n=1,970)

Amongst the patients who developed a fistula (n=319), a higher proportion of patients were female (55.3% vs. 34.6%, p=0.007) and young (<30 years old 51.1% vs. 24.3%, p<0.001) in the CD group than the non-CD population (**Table 3-4**). There were no differences in comorbidity or diabetes status between the CD and non-CD groups in the patients that formed a fistula.

		Non CD		CD		p
		n	%	n	%	
Gender	Female	94	34.6%	26	55.3%	**0.007**
	Male	178	65.4%	21	44.7%	
Age	<30 yrs	66	24.3%	24	51.1%	
	30-50 yrs	131	48.2%	20	42.6%	**<0.001**
	>50 yrs	75	27.6%	3	6.4%	
Comorbidity	No Comorbidity	242	89.0%	42	89.4%	0.937
	>1 Comorbidity	30	11.0%	5	10.6%	
Diabetes Status	Not Diabetic	259	95.2%	45	95.7%	0.875
	Diabetic	13	4.8%	2	4.3%	

Table 3-4. Demographics for patients with fistula (n=319)

Regression analysis was undertaken to determine factors associated with progression from anorectal abscess to persistent fistula (**Table 3-5**). At univariable analysis, gender, existing comorbidities, a diagnosis of CD and diabetes were associated with progression from abscess to fistula. At multivariable analysis, men were less likely to develop a fistula following abscess drainage than women (OR 0.7, 95% CI: 0.5-0.9, p=0.005), as were those with a diagnosis of diabetes mellitus (OR 0.5, 95% CI 0.3-0.9, p=0.027). Patients with CD were more than twice as likely to develop a fistula following abscess drainage than the non-CD population (OR 2.5, 95% CI: 1.7-3.7, p<0.001).

		Univariable	Odds Ratio (OR)	Multivariable 95% Confidence Interval (CI)	p
Gender	Female Male	**0.001**	(Ref) 0.7	0.5-0.9	**0.005**
Age	<30 yrs 30-50 yrs >50 yrs	0.347			
Comorbidities	No Comorbidity 1 or more	**0.014**	(Ref) 0.8	0.48-1.30	0.344
Crohn's Disease	No Yes	**<0.001**	(Ref) 2.5	1.7-3.7	**<0.001**
Diabetes	No Yes	**0.014**	(Ref) 0.5	0.3-0.9	**0.027**
Previous Fistulas	Yes No	0.996			
Abscess Type	Peri-anal Peri-rectal Anorectal Ischiorectal Intersphincteric	0.175			

Table 3-5. Factors associated with formation of anorectal fistula following a diagnosis of anorectal abscess (n=1,970)

3.5 Discussion

We studied consecutive patients presenting with anorectal abscess to a district general hospital over an 11-year period. Men were more likely to present with an abscess overall and regardless of the presence of Crohn's disease, but women were more likely to develop a persistent fistula following anorectal abscess drainage. One in seven patients

developed a fistula following anorectal abscess drainage overall, rising to just under a third of patients with CD. Crohn's disease increased the risk of persistent fistula after anorectal abscess drainage more than twofold. Patients with diabetes developed persistent fistula after abscess drainage less commonly than those without diabetes. Location of the anorectal abscess, comorbidity and patient age were not associated with an altered risk of fistula.

The strength of this study is that the rate of, and risk factors associated with, fistula formation are in line with our previous administrative dataset study in England, corroborating the findings from the Hospital Episode Statistics (HES) database for perianal sepsis. In addition, it confirms our previous finding that female gender is a risk factor for developing a fistula, contrary to the findings of other studies, and surgical dogma. The accuracy of clinical data is continually improving and a systematic review demonstrated the overall median accuracy (routinely collected data sets compared with case notes) was 83.2% (IQR: 67.3-92.1%).[249]

Abscess and fistula can co-exist. Indeed, some surgeons consider an abscess to be an 'acute fistula', and a fistula to be a 'chronic abscess.' This relates to the role of intersphincteric sepsis and a distinction between pathogenesis and persistence.[250] Further, acute abscesses often contain internal openings,[84] but not all abscesses with an internal opening end up developing a fistula.[227,226] Our data suggest that men are at a greater risk of abscess formation, but not of persistent fistula. Hypotheses for this include that men either develop abscesses that are of an aetiology less likely to progress to fistula (superficial, skin-based sepsis rather than cryptoglandular sepsis, for example), or they

are protected from persistence by an absence of factors that drive this, compared to women. That diabetes is associated with a lower risk of persistent fistula following abscess drainage supports the former hypothesis; if diabetes-related persistence factors were the key, one might expect the diabetic patient to have an increased or at least equivalent risk of fistula, whereas diabetes is likely to predispose to superficial perianal infections, as it does elsewhere, and these might be less likely to lead to fistula formation than infections of cryptoglandular origin.

A Cochrane review of six RCTs concluded that treating the fistula in the acute setting reduced the risk of persistent abscess and the need for repeat surgery.[251] However, the majority of primary, non-Crohn's abscesses with an internal opening will never develop into a fistula.[226,227,84] Also, there is a considerable risk of iatrogenic injury in the hands of inexperienced surgeons. Whilst there is likely to be global disparity, a recent observational study from the UK demonstrated that more than 85% of incision and drainage operations are performed by junior trainees, usually during daytime hours.[116] It is not implausible to hypothesise that inexperienced trainees often make smaller, more conservative incisions and as such do not adequately drain the pus, which may lead to undrained collections which fistulate. Identification of 'at risk' patients could influence operative factors such as the level of supervision for these patients, and the nature and urgency of their surgical follow up and investigations.

We have considered some demographic factors that might influence fistula persistence following anorectal abscess drainage, prompted by our previous study at the national administrative dataset level. Furthermore, the aetiological processes underpinning

fistula formation and persistence following development of an abscess remain poorly understood. A fistula can be thought of as a "chronic abscess", which has persisted after the majority of acute abscesses simply resolve. The factors leading to persistence, or in other words, the factors which determine why one patient's abscess resolves when another's becomes a fistula, are not fully understood, but are thought to be separate to the original pathology which sparked the acute abscess, generally accepted to be cryptoglandular infection, at least in non-Crohn's patients.[250]

3.6 Limitations

The use of coding data and the retrospective nature of this study are both limitations. The coding of abscess location is particularly suspect. It is our view that 'perianal abscess' is used as a catch-all term by junior surgeons who are unfamiliar with the more nuanced classification of anorectal abscess used by experienced proctologists or are unable to employ it in the acute setting. This limits the present study's ability to identify any association between abscess location and persistent fistula, an association one might expect to see based on the cryptoglandular hypothesis. However, in general, the volume of cases, the long data collection period and the similarity to the HES database outcomes, make the findings credible and generalizable.

There are a number of factors that have not been evaluated: such as the role of smoking, use of antibiotics, use of immunodulators, obesity (BMI) and post-operative packing, which may have a role in subsequent fistula development. In addition, not all co-morbidities are encompassed within the Charlson Comorbidity Index and whilst

imperfect, this scoring system has been used widely in the medical literature, as discussed in the previous chapter. Another limitation of this study is the difficulty in determining how to categorise the Crohn's patients. Patients were labelled as having Crohn's if they were identified with a diagnosis of Crohn's at any time point. It is therefore possible that certain patients (particularly those with short follow up) have been labelled as having a Crohn's abscess/fistula even though at that point in time they had not manifested Crohn's yet. However, it is known that diagnosis in Crohn's disease often occurs sometime after symptoms have begun and also that Crohn's perianal fistula can predate the diagnosis of luminal Crohn's.

3.7 Conclusion

Future studies into the microbiological, immunological, molecular and wound healing factors that predispose to fistula formation may yield biomarkers that would help predict which patients will develop a persistent fistula following abscess presentation.

Section B – Assessing outcomes for perianal Crohn's disease

There are currently a number of different treatment regimes, both medical and surgical, for perianal Crohn's disease. Often, this plurality of options suggests that there is no good way to treat the condition, and a nuanced management strategy with defined outcomes is necessitated. Further, identification of the current 'gold standard' treatment is challenging to ascertain. The lack of standardised outcomes hampers effective analysis and comparison of data when comparing treatments in fistulising perianal Crohn's disease (pCD) in an effort to try to determine relative efficacy of treatment techniques and strategies. Development of a standardised set of outcomes would resolve these issues.

This section describes the process of developing a core outcome set over two chapters. The first chapter will explore the existing literature through systematic review, to identify the current outcome measures being used. The second chapter will describe the acquisition of other candidate outcomes from patient interviews and describe how a Delphi process was used to establish consensus on a core outcome set for fistulising perianal Crohn's disease.

Application of the COS will reduce heterogeneity in outcome reporting, thereby facilitating more meaningful comparisons between treatments in future studies, enable data synthesis and ultimately benefit patient care.

4 A systematic review of outcomes reported in studies on fistulising perianal Crohn's fistula

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4.1 Abstract

Introduction

Treatment of fistulising perianal Crohn's disease (pCD) is challenging and it can be difficult to ascertain gold standard interventions from the literature. One factor limiting development of a robust evidence-base, is heterogeneity in outcomes reported, leading to a risk of reporting bias and making meta-analysis difficult. In order to produce a long list of candidate outcome measures for a subsequent Delphi consensus to develop a COS in pCD, we conducted a systematic review of studies assessing medical, surgical and combined medical/surgical treatment of fistulising pCD to evaluate the outcomes used.

Methods

MEDLINE and EMBASE were searched from 1980-2016 for eligible studies in adult patients with fistulising pCD. Our primary aim was to list the type and frequency of outcomes measured in each study. Our secondary aim was to assess the quality of outcome reporting.

Results

In total, 49 studies were included which reported a median of 6 (IQR 3-7) outcomes. The three most commonly reported outcomes were: ≥50% tracts not draining on clinical examination (22 studies; 45%); Perianal Disease Activity Index (20 studies; 41%); and the Crohn's Disease Activity Index (19 studies; 39%).

The primary outcome was clearly stated in 73% (36 studies) and defined in 76% (37 studies). Secondary outcomes were clearly stated in 57% (28 studies) and defined in 63% (31 studies).

Definition of 'fistula healing' was particularly heterogeneous with only 12 of 49 studies (24%) reporting sustained healing on ≥2 clinical visits.

Conclusion

There is heterogeneity of outcome reporting in fistulising pCD studies. This review represents the first step in informing a Delphi consensus with the aim of developing a Core Outcome Set for fistulising pCD.

4.2 Introduction

The incidence of Crohn's disease is 5.9-11.7 per 100,000 in the UK and is increasing worldwide.[252] Anal fistulas occur in a third of all Crohn's patients.[85] They denote a distinct and aggressive phenotype,[1,2] with a higher risk of a severe and disabling disease course, relapse and need for repeated operations. They cause pain and discharge, resulting in reduced quality of life.[87] In a population study, Schwartz et al. found the annual cumulative risk of one perianal fistula was 12%, and after 20 years was 26%.[230]

Prior to the introduction of biologic therapies, treatment was aimed at reducing fistula drainage to improve the patient's quality of life. Complete and lasting cessation of drainage was rarely achieved, with approximately 20% of patients requiring proctectomy because of refractory symptoms.[253] The introduction of anti-tumour necrosis factor-alpha (anti-TNFα) agents provided clinicians with therapies that could facilitate complete cessation of fistula drainage in some patients with Crohn's perianal fistulas, and even lead to complete healing in a minority.[106] In addition, surgical innovation has led to an increase in the number of sphincter-preserving procedures now available.

While the introduction of these treatment modalities has offered benefits, definitive cure is still an elusive goal. Establishing the gold standard treatment is challenging. This is partly due to the difficulty in appraising, and in particular comparing, these new (and existing) modalities as a result of the varied definitions of 'success'. Critical appraisal of the literature requires synthesis of data and heterogeneous outcome measures do not allow for this. Core outcome sets (COS) are a research tool, which aim to reduce the

heterogeneity of outcome reporting. The overall objective of this systematic review was to identify outcomes currently reported in studies comparing treatments for fistulising pCD, as the first stage in the development of a fistulising pCD COS.

4.3 Methods

A systematic review of studies assessing medical, surgical and combined (medical/surgical) treatment of fistulising pCD was performed in accordance with a prospectively registered protocol (PROSPERO CRD42016039019) and the Core Outcome Measures in Effectiveness Trials (COMET) initiative (www.comet- initiative.org).[254]

Search Strategy

The OVID SP version of MEDLINE (1950 to 2016) and Embase (1980 to 2016) were searched using validated terms for 'Crohn's disease,' 'anorectal fistula,' and 'randomized controlled trials or prospective studies' separated by the Boolean operator 'AND' (**Appendix** This was supplemented with a free text search of the same databases, using relevant keywords/terms (including synonyms and variants), also separated by the Boolean operator 'AND'. The search was limited to studies conducted in human adults aged ≥ 18 years old and to papers published between 01/01/2010 – 12/07/2016, in order to ensure that identified outcomes were contemporary and currently applicable.

Inclusion and exclusion criteria

Prospective studies (including cohort comparisons, case controls and case series), or studies in which there was an explicit statement that data was collected prospectively, were included. Systematic reviews were included, and the individual studies reviewed

were searched to ensure complete capture. Evaluation of luminal studies not primarily targeted at perianal fistulas were included where a sub-group analysis was presented for patients with fistula.

Studies were eligible for inclusion if they:

- Reported on outcomes on an intervention (medical, surgical, combination) for patients with fistulising pCD
- Included ≥10 patients receiving an intervention for fistulising pCD

And excluded if:

- The fistulas were of a non-Crohn's aetiology or were not perianal e.g. rectovaginal, rectourethral and pouch fistulas
- Sole abstract and conference reports
- Not published in the English language

Study Selection & Data Extraction

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

The following data were extracted from all studies: study design, year of study, year of

publication, interventions investigated (medical, surgical, combination), total population investigated, size of study population (number of patients with perianal Crohn's fistula who received treatment), outcomes reported (primary and secondary), time-points at which outcomes were measured and the quality of the outcome reporting.

Outcome description and the quality of reporting

Our primary aim was to list the type and frequency of outcomes used in each study. The median number of outcomes reported per study was calculated and similar outcomes were grouped into one common term prior to analysis by three independent reviewers (KS, SOA, PJT) and a patient representative (AV).

According to our secondary aims, the same reviewers assigned the outcomes to the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter 2.0[255] (adverse events; life impact; resource use; pathophysiological manifestations; and death), a tool used to categorise outcomes across specialities. The quality of reporting was assessed using the five core questions proposed by Harman's criteria[256]:

1. Is the primary outcome clearly stated?
2. Is the primary outcome clearly defined so that another researcher would be able to reproduce its measurement?
3. Are the secondary outcomes clearly stated?
4. Are the secondary outcomes clearly defined?
5. Do the authors explain the use of the outcomes they have selected?

In all cases conflicts were resolved by discussion, with recourse to a senior investigator (NSF, AH) where necessary.

4.4 Results

A total of 2857 titles were identified, of which 949 were duplicates and the remaining 1908 were screened. Of these a further 1654 studies were excluded based on title and abstract review. Following full-text review, a further 205 papers were excluded, for the following reasons: only the abstract could be found, non-prospective study design, non-English language publications and not having a sufficient number of patients with Crohn's fistula receiving treatment. This resulted in 49 included studies, **Figure 4-1**. No additional papers were identified from systematic reviews or other trials. In total, 18 of the studies (37%) were prospective cohort studies (including two studies where data were retrospectively analysed from a prospectively collected database), 18 (37%) were systematic reviews and meta-analyses, nine (18%) were randomised controlled trials and the remainder were non-randomised studies. The median number of study participants with Crohn's perianal fistula who received treatment was 29 (IQR 17-68).

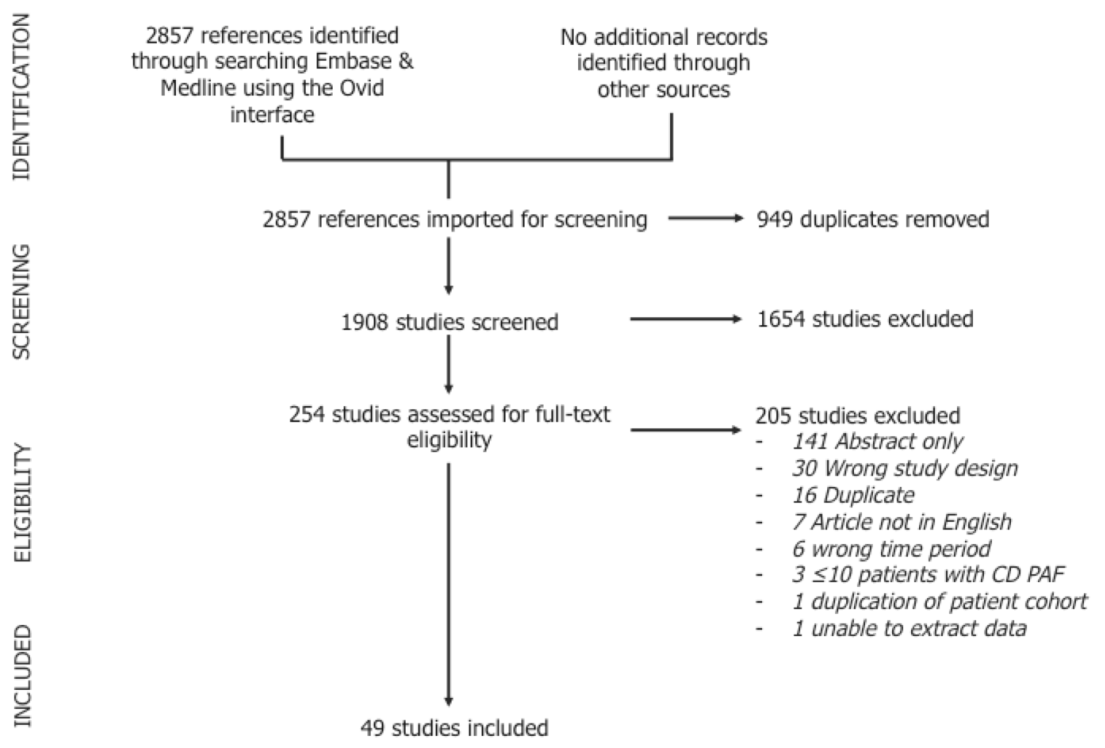


Figure 4-1. PRISMA (Preferred Reporting Items for Systematic Reviews) diagram of studies considered for the systematic review.

Outcome measures identified

There were 295 different clinical outcomes reported, with studies reporting a median of six (IQR 3-7) outcomes, these are summarised in **Table 4-1** and **Appendix B.** Included studies were analysed and similar terms were merged to form 89 unique outcome domains, specific to assessing treatment effect of perianal fistula. The unique outcome domains are presented in **Table 4-2** and have been assigned to one of the core areas of the OMERACT filter 2.0. Details regarding how the terms were grouped and consensus agreed are described in **Appendix C.** Unique outcome measures following grouping

	Randomised Studies (n=10)	Non-Randomised Studies (n=39)
Year		
2010-11	2	15
2012-13	2	11
2014-16	6	13
Intervention		
Medical	5	18
Surgical	4	14
Combination	1	7
Number of patients with fistula		
<50	3	22
50-100	5	4
>100	1	3
NR*	1	9
Number of outcomes measures		
<5	3	18
5-10	6	20
>10	1	1
Meets all core criteria for completeness of outcome reporting	50.0%	12.80%

Table 4-1. Number of outcomes reported and completeness of outcome reporting in perianal Crohn's fistula studies

ADVERSE EVENTS	*LIFE IMPACT*	*RESOURCE USE*	*PATHOPHYSIOLOGICAL*	*DEATH*
Surgical complications specific to the surgical procedure (e.g. plug extrusion)	Tolerability of treatment	Surgical re-intervention	Development of new fistulas since intervention	Death
Grading system for complications e.g. Clavien-Dindo	Decisional regret of treatment choice	Faecal diversion and/or proctectomy	Perianal abscess on clinical assessment after intervention	
Safety (adverse events) and toxicity	Lifestyle alterations (Pain/restriction of activities)	Use Anti diarrhoeal drugs	Development of other forms of perianal features (other than fistula)	
Allergic reaction	Unable to attend to school/work	Feasibility of technique	Extraintestinal manifestations of Crohn's disease	
Cardio-respiratory complications	Limitation to moderate activities (e.g. light housework)	Dietary supplements as oral intake low	Abdominal pain/discomfort/bloating	
Neurological complications	Limitation to vigorous activities (e.g. running, lifting heavy objects, participating in strenuous sports)	Time to loss of response to medical treatments	Abdominal mass	
Urinary complications	Physically restricted in self care	Cost-effectiveness	Increase frequency of loose stool	
Nausea and vomiting	Change in general health - physical	Crohn's related hospitalisation	C-reactive protein (CRP)	
Wound infection	Change in general health - psychological		Non-inflammatory blood markers	
Rash or other skin/hair problems	Comparison with other individuals (luminal)		Objective blood markers of inflammation	
Fever	Lethargy and Fatigue		Haemorrhage	
Anal pain	Social interaction avoidance - *Stop leaving the house unless you have to (work but not friends)*		A validated score to assess perianal disease activity e.g. Perianal Disease Activity Index (PDAI)	
Anal bleeding	Change in lifestyle based on toileting needs		Complete fistula healing assessed clinically	
	Anxiety & worries		Partial fistula healing assessed clinically	
	Feeling Depressed & down and hopelessness		Closure of all the external openings on clinical examination	
	Restriction of sexual activity		Closure of the internal opening	
	Felt irritable, frustrated and angry		Clinical assessment of drainage either spontaneously or on gentle finger pressure	
	How often have you felt worried about further intervention		≥50% tracts not draining on clinical examination	
	Difficulty getting a good nights sleep due episodes of getting up to toilet/wound care		Local perianal inflammation/induration assessed clinically	
	Faecal urgency - Inability to defer defaecation for 15 minutes		Duration of healing/improvement	
	Length of time off work/study after intervention		Decrease in size of fistula	
	Wearing a pads for continence/leakage		Time to recurrence	
	Wearing a plug for continence/leakage		A validated Crohn's disease activity score	

1

2 **Table 4-2. Unique outcomes following grouping and assigned to the core areas of the OMERACT filter 2.0**

The three most commonly reported outcome measures in the studies were: ≥50% of tracts not draining on clinical examination (22 studies; 45%); Perianal Disease Activity Index (PDAI) (20 studies; 41%); and Crohn's Disease Activity Index (CDAI), **Table 4-3**.

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

Table 4-3. The most common outcomes reported

The definition of 'fistula healing' from each study was analysed to determine how many studies assessed fistula healing on more than two clinical visits, a key component of the fistula drainage assessment (FDA) used in the ACCENT studies that evaluated long-term remission with biological therapy.[257,258] The definitions of 'fistula healing' were particularly heterogeneous and only 12 of 49 studies (24%) reported sustained healing on more than two clinical visits. Individual definitions are described in **Table 4-4.**

Definition From Text
Complete response was defined as the absence of discharge between two consecutive visits and a partial response was defined as either closure of >50% in the number of externally draining fistulas, or a marked reduction in drainage of all fistulas together, sustained for at least two consecutive visits[1]
Number of fistulas without active drainage. Partial response - cessation of secretion and induration in at least 50% of fistulas presented at baseline[2]
Clinical remission - (i) absence of drainage spontaneously or on compression (graded 0-5) (ii) Absence of pain (graded 0-3) (iii) no abscess; Clinical response - ≥50% of tracts not draining[3]
Clinical response was defined as a closure of ≥50% of fistulas that were draining at the baseline evaluation. Remission was defined as the absence of perianal drainage despite gentle finger compression[4]
Clinical response - closure of all external openings and cessation of fistula drainage for more than 3 months. Partial response - a reduction in the size, number, drainage or discomfort associated with a fistula[5]
Systematic review - success undefined[6]
Fistula healing was defined as complete closure of all fistula tracts, as verified by probe exploration performed independently by two of the authors[7]
Outcomes were long-term continence, complications which were assessed by a Wexner's score along with a complementary questionnaire[8]
Remission when fistula tracks appeared closed (i.e. inability to insert a cannula through the external opening and no drainage despite finger compression), or as 'improvement' when the number of draining fistulas was reduced by at least 50% from baseline and/ or when no discharge upon finger compression was present[9]
Systematic review/Meta-analysis - Studies did not provide remission as an end point and all gave reduction in fistula drainage as an outcome so these data were synthesized[10]
Complete response - closure of all draining fistulas (a fistula was considered to be closed when it no longer drained despite gentle finger compression); partial response - a reduction of at least 50% of draining fistula[11]
Clinical remission was defined as the absence of any draining fistulas at clinical examination according to present criteria within 2 months of the MRI evaluation and the absence of self-reported drainage episode by the patient within the same period of time. Clinical response was defined as a reduction of 50% or more from baseline in the number of draining fistulas at the examination or in case of absence of any draining fistula by persistent patient self reported drainage episodes[12]
Fistula closure was defined as the absence of drainage on gentle compression at any two consecutive post-baseline visits at least 3 weeks apart (>50% closure of fistulas open at baseline and 100% closure of fistulas open at baseline); (ii) maintenance of fistula closure, defined as at least 50% closure of fistulas at any two consecutive post-baseline visits (>3 weeks apart) at any time during the study and at least 50% or 100% closure at week 26; (iii) fistula closure based on the pre-specified definition in the PRECiSE 2 study (closure of ‡50% of fistulas at any two consecutive post-baseline visits >3 weeks apart)[13]
Healing undefined[14]
Complete fistula healing, defined as complete closure of all fistulas that were draining at baseline[15]
Percentages of patients with closed fistulas[16]
Systematic review - Included RCTs analysed individually for fistula outcomes (Response: reduction of 50% or more of draining fistula; Complete response: absence of draining fistula) at two or more consecutive visits[17]
Complete Response - signified complete fistula closure with no further discharge expressed on digital pressure on two consecutive clinic visits, at least 4 weeks apart. Partial Response was defined as reduction in the size or the number of fistulae, reduction in the amount of discharge or improvement in perianal pain[18]
Complete response - complete closure of fistula with no drainage on gentle finger pressure; Partial response - (i) decrease in size, (ii) decrease in the number of fistulae, (iii) reduction in the amount of discharge as reported by the patient, (iv) improvement in perianal pain[19]
Systematic review - Success was defined as closure of all secondary openings, an absence of fistula drainage, and an absence of abscess formation[20]
Clinical remission was defined as cessation of drainage on history, absence of perianal drainage to gentle finger compression of all external openings and surrounding tissues, and absence of spontaneous drainage between two consecutive visits. Clinical response was defined as 1) closure of 50% in the number of externally draining fistulas, or 2) marked reduction in drainage of fistula(s) together with less pain and induration as reported by the patient, sustained for at least two consecutive visits compared with baseline evaluation[21]
Complete closure of the fistula track, and internal and external opening without drainage or signs of inflammation[22]
Fistula closure is defined as the absence of suppuration of the fistula through the external orifice, both spontaneously and upon application of pressure, with complete re-epithelization of the external orifice during clinical evaluation and absence of collections >2 cm, in three axis, directly related to the fistula tract treated, as measured by MRI. Fistulas were evaluated at two consecutive visits[23]
Complete healing was defined as complete closure of fistula tract and internal and external openings, without drainage or any sign of inflammation. Secondary endpoints were the fraction of patients with a decrease in drainage of more than 50%[24]
Success was defined as closure of both internal and external openings, absence of drainage without further intervention and absence of abscess formation[25]
Systematic review - Remission: complete closure of all fistulas[26]
Clinical response was defined as ≥70 point reduction in Crohn's Disease Activity Index (CDAI) from baseline in luminal disease and a reduction in active fistulas of ≥50% from baseline in fistulising disease. Clinical remission was defined as an absolute CDAI score of ≤150

Table 4-4. Fistula healing: definitions

Harman's criteria were used to assess the completeness of outcome reporting. The primary and secondary outcomes were clearly stated in 73% (36 studies) and 57% (28 studies) respectively and defined in 76% (37 studies) and 63% (31 studies) of a total of 49 studies. Authors explained the rationale for using the outcomes they selected in 33% (16 studies). Assessment of each study by Harman's criteria is detailed in **Appendix B.** Included studies

4.5 Discussion

This systematic review demonstrates the heterogeneity of outcomes used in fistulising pCD studies. Outcomes are categorised into analogous concepts and used to inform the development of a core outcome set, forming the basis of the initial long list of candidate outcomes to be included in the consensus exercise. Eighty-nine unique outcomes across 49 studies were identified. Of note, no outcome was reported universally. Both reporting and defining of secondary outcomes were less robust than for primary outcomes and only a third of authors explained their rationale in the choice of outcomes. Heterogeneity in the definition of healing was particularly marked and only one in four studies used at least two time points to measure this. Our review has demonstrated that the most common scoring tools used are: ≥50% tracts not draining on clinical examination[160] (part of the fistula drainage assessment), PDAI[259] and CDAI[152]. All are subjectively assessed and there remains no universally accepted objective measure of success in this field.

Within the field of fistulising pCD, there is a paucity of widely used, reproducible, objective and sensitive measures available for clinicians to assess the effect of treatment. The concept of 'healing' in fistulising pCD is open to criticism and difficult to describe

clinically or radiologically. The most widely accepted definition of clinical healing comes from the ACCENT II trial, which uses the FDA. The FDA defines remission as complete cessation of drainage from all fistula openings present at baseline despite gentle finger pressure, on at least two occasions over at least a four week period, and improvement as a 50% reduction in the number of external openings present or draining, assessed in the same way.[160] As fistulising pCD is a chronic relapsing and remitting disease,[260] patients describe the discharge and other symptoms as sporadic. This means the goal of 'healing' or clinical remission, cannot be determined at a single time point but must be sustained over a defined period of time to be valid. In addition, closure of an external opening does not equate to healing of internal tracts, or mitigation of symptoms causing reduced quality of life. It has previously been shown that deep tissue healing, assessed on MRI, lags behind clinical remission by a median of a year in those patients who achieve it.[261] In addition, there is no accepted radiological definition for a healed fistula on MRI. As a result of these difficulties, many of the systematic reviews in our included studies report on interventions with heterogeneous outcomes. This variability of outcome reporting results in an inability to synthesise data from the studies, thus hampering effective meta-analysis and limiting the establishment of a robust evidence base. Subsequent to the completion of the search, the ADMIRE CD group published the first randomised controlled trial on fistulising pCD.[262] A composite primary endpoint containing both clinical remission (closure of all treated baseline external openings) and radiological remission (the absence of collections greater than 2cm in at least two of three dimensions on MRI scans) was measured at week 24. The inclusion of a radiological element is beneficial, limiting the criticism regarding the use of a short follow up period, as it seeks to demonstrate healing across the whole track not just at the level of the external opening. The exact definition of radiological 'remission' remains unclear and the

volume of undrained sepsis that necessitates further intervention is unknown. Allowing such a large volume of high signal is probably inadequate as a radiological measure of success. Moreover, neither endpoint gives weight to the patient's views.

The lack of objective assessment tools means that investigators often assess multiple outcomes and new measures are regularly created. Standardising the outcomes measured by developing a core outcome set is an effective and established approach to improve the ability to pool data and draw meaningful conclusions. The OMERACT filter 2.0 was originally described for patients with Rheumatoid arthritis, and, whilst not disease specific, serves as a useful guide for the development of a COS. In our study, all core areas of the OMERACT filter 2.0 were encompassed through the included studies. A COS would create homogeneity of outcome reporting within the field of fistulising pCD. They are devised through a Delphi process, and ratified by key stakeholders. They are the outcomes which are thus determined to be the most valuable and should, at the minimum, be reported in every study of that condition,[263] but are not restrictive and investigators may also choose supplementary outcomes. They contain relevant, contemporary outcomes, which aim to reduce reporting bias, allow meta-analysis of data and enhance overall transparency within a given field of research.

4.6 Limitations

The strengths of this review are the use of prospective study designs and the inclusion of luminal studies, which report fistula response as a secondary outcome measure, without which, many studies reporting outcomes in the medical treatment of pCD would have been lost. Retrospective designs were excluded, which may raise the limitation of the list

of outcomes not being exhaustive. A significant amount of studies were excluded due to retrospective study design and one may argue that sampling has therefore been too exclusive and not representative of studies in the field. Studies with both curative and palliative intent as well as those containing patients with both simple and complex fistula were also included. This gives rise to another potential limitation in that the goals of treatment may therefore be different across different patient groups. However, this is likely to represent the spectrum of treatment goals and likely outcomes experienced by patients with fistulising pCD through their lifetime. This spectrum may explain some of the heterogeneity in outcomes seen and reflect the chronicity of disease. In addition, the outcomes identified by this review, when taken in isolation, do not account for the views of other stakeholders, such as other healthcare professionals and, most importantly, patients. While many outcomes tried to capture impact on patients, there was no validated patient-reported composite outcome measurement used in any of the studies.

4.7 Conclusion

There is heterogeneity of outcome measure reporting in fistulising pCD studies. In particular, there is a lack of a standardised definition of fistula healing and a pressing need for a validated patient-reported outcome tool. This systematic review demonstrates the need for the development of a core outcome set for fistulising pCD to encompass clinical, radiological and patient-reported outcomes, and represents the first phase of this process.

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

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5.1 Abstract

Introduction:

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

Method:

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

Results:

In total, 187/238 (78.5%) of the recruited participants completed round one *(92 outcomes),* 176/187 (94.1%) completed round two (*80 outcomes, including five de-novo outcomes*) and 183/187 (97.9%) completed round three *(49 outcomes).*

The consensus meeting of 41 experts generated agreement on an eight domain COS. The COS comprised three patient-reported outcome domains (quality of life, incontinence and a combined score of patient priorities) and five clinician-reported outcome domains (perianal disease activity, development of new perianal abscess/sepsis, new/recurrent fistula, unplanned surgery and faecal diversion).

Conclusion:

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

5.2 Introduction

The management of fistulising perianal Crohn's disease (pCD) remains challenging. Fistulas are often complex in nature and recurrence after treatment is common. Perianal manifestations of Crohn's disease are recognised in the Montreal classification as a distinct phenotype[264] from luminal disease. Fistulising pCD is associated with significant morbidity and reduced quality of life.[265] The established treatment pathway is multidisciplinary[109] and involves management of proctitis and drainage of sepsis, prior to optimisation of medical treatment, usually with a combination of thiopurine and anti-TNF therapies[266]. Initial drainage of sepsis and placement of loose setons are the mainstay of surgical treatment, although reparative surgery aimed at fistula closure may be offered in selected patients, and defunctioning or ablative surgery may sometimes be required. Undrained ongoing perianal sepsis, injudicious surgery, and recurrent perianal sepsis may all result in poor functional outcome for the patient.

There has been significant recent innovation in managing fistulising pCD both in biological therapy with trials studying fistula healing as a primary outcome measure[184], and in the introduction of novel, sphincter preserving techniques[267,268,173] as well as modification of existing operations, such as the BioLIFT[269] or LIFT-Plug.[270] There are restrictions in the current literature that impair evidence synthesis and meta-analysis. One limitation is a lack of standardised outcome measurements, which hampers effective analysis and comparison of techniques, and leads to a high risk of reporting bias.[271] Most importantly, the currently used outcomes lack relevance to patients.[272]

Measuring success or failure should not be determined by researchers alone and the views of patients and other healthcare professionals involved in the care of patients with perianal Crohn's fistula must be considered. The COMET (core outcome measures in effectiveness trials; www.comet-initiative.org/initiative) initiative has improved understanding of outcome reporting, and standardised outcome reporting through the development of core outcome sets (COS). COS are the minimum outcomes which should be reported in every study of a given condition.[263] They have usually been informed by a systematic review and developed through a Delphi consensus process with key stakeholders.

COS are not restrictive, trialists may choose to investigate other outcomes, but should always as a minimum include the COS within their study design. New COS are increasingly being developed[273] and they are widely recognised in a number of specialties, such as rheumatology[274], paediatric surgery[275] and colorectal surgery.[276] Increasingly, funding bodies advocate the inclusion of COS within proposed trial methodology[276] and uptake amongst trialists is increasing.[277]

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

5.3 Methods

Protocol Registry

The development of this COS is based on the principles advised by the COMET initiative[278] and reported in accordance with the COS-STAR Statement.[279] This study has been registered with the COMET initiative (www.comet-initiative.org).

Scope

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

Overview

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

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

In Phase 3, a consensus meeting with all stakeholders was used to finalise and ratify the core outcome set.

Participants

Stakeholder representation was chosen to correlate with the clinical scenario since patients with perianal Crohn's fistulas are managed by multi-disciplinary teams, including surgeons, gastroenterologists, radiologists and inflammatory bowel disease

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

All stakeholders were recruited through national organisations (and their sub-committees) and the study management group agreed that this should be limited to the UK to facilitate the process of ensuring equal though broad representation. The stakeholders were divided into three panels. Patients were given a panel to themselves as they were considered essential stakeholders **Box 5-1.**

PANEL SuRa

Colorectal Surgeons (Su)

ACPBGI (Association of Coloproctology of Great Britain and Ireland) with a declared specialist interest in managing IBD

Radiologists (Ra)

BSGAR (British Society of Gastrointestinal and Abdominal Radiology)

PANEL GaNu

Gastroenterologists (Ga)

BSG (British Society of Gastroenterology) IBD section

IBD specialist nurses (Nu)

RCN (Royal College of Nursing) regional and national network group of IBD nurses

PANEL Pa

Patients (Pa)

CCUK (Crohn's and Colitis United Kingdom), ForCrohn's, 'St Mark's Patient panel', and IA (The ileostomy and internal pouch Support Group)

Box 5-1. Stakeholder groups demonstrating the 3 panels

A participant information sheet was available on the webpage of the organisations and charities. Upon registration participants were again provided with information about the survey and invited to complete an initial registration survey to capture demographic

data. One reminder was sent if no response was received after two weeks. Non-probabilistic purposive sampling was conducted to ensure variation based upon geographical regions.

There are limited data to inform severity stratification or prognostic classification of patients' with Crohn's fistula, an 'unmet need' recognised internationally.[280] After discussion by the study management group, it was decided that 'health states' would be a more useful way of categorising patients.

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

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

Previous Delphi studies have calculated the minimum response rate to a Delphi online questionnaire is approximately 40%[281,282] We used 40% to guide recruitment and thus aimed to invite at least 180 experts to enter into round one to ensure at least 70 experts per round. To maximise on-going commitment to the process, we offered acknowledgement of participants completing all three rounds on publication of the study and sent newsletters after each of the Delphi rounds.

Information sources

A list of candidate outcomes was generated from three sources; i) systematic review of the literature[272], ii) interviews with patients and a dedicated patient and public involvement (PPI) meeting [283], and iii) the study management group.

Three members of the study team, 2 researchers (KS, PJT) and a patient representative (AV), categorised similar outcomes identified from the systematic review into domains by consensus. Four members of the study team (KS, PJT, SOA, AV) assessed and categorised the transcripts from the patient interviews and from the PPI meeting to supplement the list generated from the systematic review. All the included outcomes were categorised into themes and presented as such throughout the rest of the process.

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

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

Consensus process

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

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

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

Each round was open for 4 weeks. A reminder email was sent to participants who had not completed the round after 2 weeks, and then again at 3 weeks. The final reminder asked if participants were experiencing difficulties in completing the questionnaire, or if they

had decided not to participate further in the study. Participants, who completed round one, were invited to complete both round two and round three. A newsletter was sent to all participants in between all rounds to update the participants of progress and modifications.

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

Outcome Scoring and Consensus Definition

Outcomes were carried forward between rounds if more than >70% of all participants scored them as 'really important' (7-9). Each outcome was assessed for heterogeneity between the panels using a histogram depicting median scores. In addition, during each round, participants were given the opportunity to comment on the clarity and appropriateness of each outcome. All comments were reviewed by the study management group, and outcomes modified to improve clarity if necessary.

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

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

Ethical considerations

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

5.4 Results

Protocol Modifications

Following the analysis of the round two of the Delphi process, it was identified that Panel SuRa was the most discriminatory and the patient panel the least. Using the pre-specified criteria, only 6/79 (7.6%) outcomes were voted below the threshold for inclusion by the patient panel, compared with 45/79 (57.0%) by the surgeons and radiologists **Appendix E.**

The criteria for retention in the second round of the Delphi process were therefore modified, so that inclusion of outcomes was deemed on two aspects (i) outcomes where >70% participants overall scored them 7-9 and also (ii) the outcomes where >90% of the patient panel had scored as 7-9 were carried forward to phase three. A further 4 outcomes (**Appendix E**) were retained by the study management group, as they were felt to be of key importance, and analysis of the voting overall and review of the outcome descriptions suggested ambiguity or misunderstanding, such that they would benefit from further evaluation and discussion.

High patient scoring and a change to the protocol in round two meant the study management group decided that no outcomes were to be excluded in round three. Analysis of round three confirmed the decision as again the 70% cut-off was deemed to be insufficiently discriminatory (**Appendix F**). This allowed the participants in the consensus meeting to be given the opportunity to vote on all the remaining outcomes at the end of round 2.

Participants

A total of 238 participants registered their interest. Of these, 187/238 participants (78.5%) registered their demographics and completed round one of the Delphi survey. Some 176/187 participants (94.1%) completed round two and 183/187 participants (97.9%) completed round three. In total, 47 participants attended the face-to-face meeting across the panels (16 from *panel SuRa*, 17 *panel GaNu*; and 14 *panel Pa).* Demographic details for each stakeholder group are summarised in **Table 5-1** and **Table 5-2**.

1

Participants characteristics									
	Registered Participants (n=238)						**Consensus meeting (n=47)**		
	Clinicians		**Patients**		***Total***		**Clinicians**	**Patients**	***Total***
Gender									
Male	108		18		**126**		23	2	**25**
Female	45		65		**110**		10	12	**22**
Did not answer	2		0		**2**		0	0	**0**
Region									
Northern England	37		18		**55**		8	2	**10**
Midland	22		8		**30**		5	1	**6**
Southeast England	58		33		**91**		13	9	**22**
Southwest England	20		8		**28**		3	2	**5**
Wales	6		6		**12**		1	0	**1**
Scotland	7		6		**13**		1	0	**1**
Northern Ireland	2		3		**5**		2	0	**2**
Did not answer	3		1		**4**		0	0	**0**
Type of hospital									
DGH	56		64		**120**		10	7	**17**
Tertiary unit	97		17		**114**		23	7	**30**
Private			1		**1**		0	0	**0**
Other			1		**1**		0	0	**0**
Did not answer	2		0		**0**		0	0	**0**
Other Clinicians characteristics									
Length of consultant appointment		0-5 years	46				8		
		6-10 years	34				4		
		11-20 years	53				16		
		>20 years	20				5		
Other Patient characteristics									
Age		20-29	32					3	

		30-39	27					4	
		40-49	17					5	
		50-59	5					2	
Years with Crohn's disease		0-5 years	25					4	
		6-10 years	19					2	
		11-20 years	24					6	
		>20 years	15					2	
Years with anal fistula		0-5 years	52					2	
		6-10 years	18					8	
		11-20 years	11					2	
		>20 years	1					0	
		Did not answer						2	
Fistula status		First anal fistula	24					2	
		Previously healed anal fistula, now new fistula	12					2	
		Recurrent anal fistula	32					4	
		Fistula healed following intervention	12					1	
		Did not answer	0					5	

Table 5-1 - Demographics of Stakeholders

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

Table 5-2 - Voting across rounds

Outcome prioritisation

The systematic review generated 89 unique outcomes[272]. Eleven further outcomes were generated through a combination of patient interviews and the PPI day. The study management group added a further six. The resultant 106 outcomes were reviewed by the study management group and fourteen were excluded as they were felt to be applicable only to luminal disease, resulting in 92 unique outcomes that entered round one of the Delphi process. A summary of outcomes used in the online Delphi process with their lay definitions, organised according to themes, is presented in **Table 5-3.**

1

THEMES	OUTCOME	LAY DEFINITIONS
Fistula response to treatment (symptoms)	**≥50% tracts not draining on clinical examination**	More than half the openings on the bottom are dry and not oozing anything
	Closure of internal opening	The hole inside the bottom (as opposed to on the buttock skin surface) closes. This must be assessed by a doctor
	Rectal mucosal healing	An assessment of the last part of your intestine in clinic, assessed by inserting a small probe into your bottom
	Complete fistula healing assessed clinically	An assessment of the bottom in clinic, whereby all the opening/holes on the skin have closed on ≥ 2 consecutive clinic appointments (i.e. assessed more than once)
	Partial fistula healing assessed clinically	An assessment of the bottom in clinic, where there is a decrease in the size/number of fistula and a reduction in drainage
	Closure of all the external openings on clinical examination	An assessment of the bottom in clinic, whereby all the opening/holes on the skin have closed on a single examination (i.e. assessed once)
	Clinical assessment of drainage either spontaneously or on gentle finger pressure	An assessment of the bottom in clinic, where the doctor presses around the openings on the bottom to look for discharge and also asks the patient about the drainage from their fistulas
	Local perianal inflammation/induration assessed clinically	An assessment of the bottom, looking for acute inflammation around the fistula (swelling, redness) and chronic inflammation (scarring, shrinking of the anal opening)
	A validated score to assess perianal disease activity e.g. Perianal disease activity index (PDAI)	A scoring system used to assess whether the perianal disease is active & flaring up or stable
	Development of perianal features of Crohn's (other than fistula)	Developing, skin tags, anal stenosis (narrowing), anal fissures, ulcers OR cancer
	Patient-reported reduction in fistula drainage	The patient saying there has been a decrease in the oozing/draining from the openings on the bottom
Direct impact of fistula on the patient	**Incontinence to wind**	Unable to stop wind/flatulence/gas escaping from your bottom
	Mucus leakage	Unable to stop mucus coming out from your bottom
	Recurrence of fistula	The same fistula hole that closed opens up again (the hole inside the bottom or the hole on the buttock skin surface)
	Development of a new fistula	A new perianal fistula develops in another place i.e. a new hole forms on the buttock skin surface or deeper inside the bottom after the intervention

	Perianal abscess on clinical assessment after intervention	An abscess (collection of pus/infection) or lumps in the bottom area which forms after treatment
	Wound infection	Increasing pain, redness, swelling in the wound requiring antibiotics (without an abscess)
	An incontinence score	A scoring system used over time to assess change in continence/bowel motion (consistency/frequency)
	Incontinence to liquid stool	Unable to stop liquid stool escaping from your bottom
	Incontinence to solid stool	Unable to stop stool/faeces escaping from your bottom
	Pads for continence/leakage	Needing to use pads inside underwear to soak up liquid discharge/oozing from the fistula
	Plug for continence/leakage	Needing to use anal plugs to soak up liquid discharge/oozing from the fistula
	#Discrimination between passing stool and gas	Unable to know whether you have passed wind/flatulence/gas or whether you have passed faeces/stool
	Tenesmus or incomplete evacuation	Feeling like you need to go to the toilet all the time (even if just been)
	Anal bleeding	Blood coming out of the bottom area (either from the fistula or the bowel)
	Anal pain	Pain around the bottom
	Increased frequency of loose stool	Runnier bowel motion and having to empty bowels more often than before
	Perianal related hospitalisation	Being admitted to hospital because of your perianal Crohn's disease, such as an abscess
	Surgical re-intervention	Another operation is needed after the first treatment
	Faecal diversion or proctectomy	Operation to remove the rectum (last part of the bowel) and/or having a stoma bag fitted
	Faecal urgency	Inability to delay going to the toilet/defaecation for 15 minutes
Impact on the patient as a person	**Lifestyle alterations (pain/restriction of activities)**	Change in lifestyle because of the fistula.
	Limitation to moderate activities	Difficulty performing tasks such as light housework
	Limitation to vigorous activities (e.g. running, lifting heavy objects, participating in strenuous sports)	Unable to run, lift heavy objects, participate in strenuous sports
	Change in general health - physical	Change in physical ability to do things
	#A quality of life scores e.g. Short form survey 36 (SF-36)	A scoring system which patients fill in themselves to assess the various aspects of a person's life.

	Change in general health - psychological	Change in thought and feelings
	Lethargy and fatigue	Exhausted, tired because of the fistula
	Social interaction avoidance	Stop leaving the house unless you have to (going to work & medical appointments but not going to see friends or going to parties/celebrations)
	Anxiety & worries	Anxious or worried about impact of the fistula
	Feeling depressed & down and hopelessness	Feeling depressed & down and hopelessness
	Irritable, frustrated and angry	Feeling irritable, frustrated and angry
	Concern over further intervention	Concerns over needing more treatment (having just had one type of treatment)
	Sleep disturbance	Having to get up at night due to toileting needs, soling sheets, underwear change etc.
	***Modifying how you walk, sit or stand because of your fistula**	Sitting on one buttock rather than both, standing as sitting is too painful, or having to walking with your legs wider apart
	***Modifying travel**	Choosing modes of transport depending on access to the toilet (e.g. train) or planning car journeys around toilet stop-offs
	***Body detachment**	Feeling 'medicalised' and that rather than yourself you are a 'body' upon which medical treatment is performed
	***A feeling of being unhygienic**	Feeling unclean, dirty and unhygienic (rather than actual being unclean, dirty and unhygienic)
	***Concerns about and impact on fertility, birth, parenthood and family**	Worried about getting pregnant in the first place, about actually going through labour, keeping up with busy children and inability to give them everything because of limitation of the disease (e.g. not being able to go for long walks etc.)
	Restriction of sexual activity	Unable to have sex or be physically close to someone
	Physically restricted in self care	Unable to wash, get dressed, or look after yourself without help from someone else because of the fistula
	Patient perception of continence compared to others OR baseline	A difference/change in continence compared to other people or how you used to before the fistula
	Tolerability of treatment	An overall assessment of how 'acceptable' a treatment is e.g. does it have so many side effects that you want to stop it
	Decisional regret of treatment choice	A measure of regret of choosing a specific treatment option whether (medical or surgical)
	***Avoidance of intimacy**	Avoiding getting too close with another person (hugging, sitting next to each other etc.) due to fears that you smell, or they might know that you have a fistula. This includes getting into new relationships
	Unable attend school/work	Can't go to school/college/university or do your usual job because of perianal fistula due to need to be off at short notice

	Change in lifestyle based on toileting needs	Go out less or only go to places where you know there's a clean toilet and washing facilities because of perianal fistula. Or take spare clean underwear and wipes with you when you go out.
	***Restricted in what you wear**	Being unable to wear tight clothing and wearing baggy clothes to reduce pain, conceal bulging pads or bulky gauze inside underwear. Also wearing dark clothing to conceal stains
	***Embarrassment & feeling isolated**	Feeling conscious of the fistula, which subsequently affects the way I walk/behave/interact with the world, which is obvious to others and leaves me embarrassed so that I alter what I do
Assessment with imaging techniques (scans)	**#MRI assessment of fistula volume**	Calculating the size of fistula on an MRI scan to generate a number, and then comparing the size/number over time
	Fistula response on endoanal ultrasound (USS)	A rectal probe is inserted into the bottom to look for and assess the fistula using an ultrasound machine to see if the fistula is better/worse/the same
	Abscess on MRI following treatment	A collection of pus on MRI scan
	T1 enhancement on MRI	A specific way to assess inflammation within a fistula on an MRI (it adds time to a normal MRI but allows doctors to better decide what is fistula and what is blood vessel)
	Hyperintensity on T2 weighted MRI	A specific way to assess inflammation within a fistula on an MRI - this is standard care
	MRI assessment of rectum (proctitis)	Looking for inflammation of the rectum (last part of the intestine/bowel) on MRI
	Fistula response on MRI imaging	The fistula looks 'better' or 'about the same' or 'worse' on MRI imaging
	#An activity based MRI score e.g. Van Assche Score	A scoring system used by radiologists (MRI doctors) to assess whether a fistula is 'active' i.e. acute inflammation or nearer to the other end of the scale of healing
Fistula response to treatment (tests)	**Time to loss of response to medical treatments**	The length of time taken before you develop resistance to a medication (biologics/anti-TNF)
	Objective blood markers of inflammation	Blood tests looking for inflammation
	C-reactive protein (CRP)	A specific blood test looking for inflammation
	Non-inflammatory blood markers *(related biologics)*	Blood tests looking for other things, such as anaemia, B12 levels, etc.

	Instability of weight (assessed by BMI)	Putting on weight or losing weight, assessed using BMI (a score based on weight and height)
	Fever	Feeling 'hot' and feverish/getting 'the chills' with a high temperature
Safety implications related to treatment	**Nausea or vomiting**	Feeling sick or vomiting after treatment
	Death	Death as a result of a treatment
	Rash or other skin/hair problems	Changes in the skin (rash, dryness, acne etc.), hair thinning or hair loss
	Allergic reaction	A reaction to a treatment (ranging from a rash to swelling of the throat)
	Cardio-respiratory complications	Complications of treatment related to cardio-vascular system - heart attacks, abnormal heart rhythms
	Neurological complications	Complications of treatment related to nervous system - visual symptoms, headaches, nerve damage
	Urinary complications	Complications of treatment related to urinary system - waterworks infections, damage to the any of the anatomical structures during surgery
	Grading system for surgical complications e.g. Clavien-Dindo	A generic validated grading system of all complications related to surgery (covers all systems - cardiovascular, neurological, etc.)
	Safety (adverse events) and toxicity	Measuring how safe and tolerable a given treatment is
	Surgical complications specific to the surgical procedure (e.g. plug extrusion)	Specific surgical complications e.g. such as plug extrusion (following anal plug insertion)
	#Medical complications specific to the immunosuppression (e.g. opportunistic infections, cancers)	Increased risk of cancer (e.g. lymphoma) and an increased risk of any infection as a result of being on an immunosuppressive medication (anti-TNF/biologics/thiopurines)
Impact on the patient over time	**Duration of healing/improvement**	How long the treatment helped you to feel better for
	Biologic free remission	Period of time not needing to take biologics/anti-TNFs (e.g. Infliximab/Remicade, Humira/Adalimumab)
	Cost effectiveness	A measure of how effective the treatment has been but also factoring in the cost of this treatment
	***Increasing analgesia**	Needing more painkillers to get through the day
	***Antibiotic free remission**	Period of time not needing to take antibiotics
	Use anti-diarrhoeal drugs	Taking medication to make the stool less runny (e.g. loperamide)

	Recovery time after intervention	Length of time off work/study after treatment intervention
	***Financial implications**	Financial hardship including loss of income, career stagnation, extra expenses e.g. buying pads, clean underwear etc.
ORIGIN	**From SR (n= 76)**	
	***Added from patients (n=11)**	
	#Added from SMG (n=5)	
Excluded by the SMG (n=14)	**Faecal calprotectin**	*Not specific to perianal Crohn's and more to luminal disease*
	Steroid free remission	*Not specific to perianal Crohn's and more to luminal disease*
	Abdominal discomfort	*Not specific to perianal Crohn's and more to luminal disease*
	Dietary supplements as oral intake low	*Not specific to perianal Crohn's and more to luminal disease*
	A validated Crohn's disease activity score	*Not specific to perianal Crohn's and more to luminal disease*
	Remission of Crohn's disease	*Not specific to perianal Crohn's and more to luminal disease*
	Identification of endoscopic signs suggestive of failure of treatment (relating to systemic/overall Crohn's)	*This relates to luminal relapse and we have included assessment of the rectal mucosa separately*
	MRI features (luminal)	*Not specific to perianal Crohn's and more to luminal disease*
	Abdominal mass	*Not specific to perianal Crohn's and more to luminal disease*
	Extraintestinal manifestations of Crohn's disease	*Not specific to perianal Crohn's and more to luminal disease*
	Comparison with other individuals (luminal)	*Not specific to perianal Crohn's and more to luminal disease*
	Haemorrhage	*Not specific to perianal Crohn's and more to luminal disease*
	Feasibility of technique	*Not specific to perianal Crohn's and more to luminal disease*
	Decrease in size of fistula	*Definition unclear and not defined within the study. Likely to have covered through other forms of clinical assessment (consensus to remove)*

1

Table 5-3. Outcome domains identified through Phase one with lay definition

In round one, 92 outcomes were reviewed by the participants, which generated 201 individual comments. The study management group retained nine outcomes and the name (or lay description) was changed due to polarising views/heterogeneity or comments by participants **Appendix D.** Five de novo outcomes were added following comments by participants, and 18 outcomes were excluded according to the pre-set criteria. At the end of round one, interim analysis demonstrated that the top ten outcomes rated by the panels were similar and are seen in **Table 5-4.**

1

Item	Outcomes	Panel SuRa high	Panel SuRa low
30	**Faecal diversion or proctectomy**	97	0
75	**Death**	97	3
15	**Development of a new fistula**	89	0
20	**Incontinence to solid stool**	89	0
28	**Perianal related hospitalisation**	89	0
29	**Surgical re-intervention**	89	2
14	**Recurrence of fistula**	86	0
16	**Perianal abscess on clinical assessment after intervention**	86	2
56	**Unable attend school/work**	84	0
19	**Incontinence to liquid stool**	83	0

		Panel GaNu high	Panel GaNu low
75	**Death**	100	0
30	**Faecal diversion or proctectomy**	98	0
15	**Development of a new fistula**	97	0
84	**Medical complications specific to the immunosuppression (e.g. opportunistic infections, cancers)**	97	0
14	**Recurrence of fistula**	94	0
20	**Incontinence to solid stool**	94	0
28	**Perianal related hospitalisation**	94	0
19	**Incontinence to liquid stool**	92	0
56	**Unable attend school/work**	92	0
21	**Pads for continence/leakage**	91	0

		Panel Pa high	Panel Pa low
19	**Incontinence to liquid stool**	96	0
30	**Faecal diversion or proctectomy**	96	0
20	**Incontinence to solid stool**	93	1
16	**Perianal abscess on clinical assessment after intervention**	92	6
15	**Development of a new fistula**	92	0
28	**Perianal related hospitalisation**	91	3

75	**Death**	91	5
17	**Wound infection**	90	0
39	**Social interaction avoidance**	89	6
29	**Surgical re-intervention**	86	5

Table 5-4. Top 10 outcomes voted after Phase 1

Of the 79 outcomes that entered round two, 41 were below the pre-set threshold for exclusion. After a modification to the protocol, 12 of these were retained (eight due to high patient scoring and four by the study management group), which resulted in 29 (36.7%) being dropped from round two **Appendix E**. The resultant 49 outcomes entered into the third round and all were taken forward to the face-to-face consensus meeting **Table 5-5**. The process is described in **Figure 5-1** and individual scores for each round are in **Appendix D, Appendix E** & **Appendix F.**

		% in					
	Question	Panel SuRa	Panel GaNu	Panel Pa	Overall	Patient vote alone	FINAL CONSENSUS
1	Patient reported reduction in fistula drainage	57.1%	53.3%	30.0%	46.8%		
2	Development of other perianal features	53.8%	73.3%	70.0%	65.7%		
3	Complete fistula healing assessed clinically	53.3%	40.0%	44.4%	45.9%		
4	Validated score to assess perianal disease activity	100.0%	93.8%	77.8%	90.5%		IN
5	Development of a new fistula	69.2%	83.3%	87.5%	80.0%		IN
6	Incontinence to solid stool	26.7%	33.3%	40.0%	33.3%		
7	Pads for continence/leakage	26.7%	40.0%	40.0%	35.6%		
8	Recurrence of fistula	85.7%	68.8%	80.0%	78.2%		
9	Perianal abscess on clinical assessment after intervention	86.7%	100.0%	90.0%	92.2%		IN
10	Incontinence to liquid stool	71.4%	93.3%	100.0%	88.3%		^Combined
11	Perianal related hospitalisation	35.7%	50.0%	10.0%	31.9%		
12	Faecal diversion or proctectomy	100.0%	100.0%	100.0%	100.0%		IN
13	Wound infection	0.0%	0.0%	30.0%	10.0%		
14	Anal pain	66.7%	87.5%	90.0%	81.4%		
15	Discrimination between passing stool and gas	6.7%	33.3%	12.5%	17.5%		
16	Surgical re-intervention	93.3%	93.8%	80.0%	89.0%		IN
17	Anal bleeding	0.0%	14.3%	60.0%	24.8%		
18	Reversal of defunctioning stoma	33.3%	37.5%	22.2%	31.0%		
19	A global assessment of incontinence that covers all aspects of leakage	92.9%	100.0%	100.0%	97.6%		IN
20	Fistula response on MRI imaging	85.7%	86.7%	80.0%	84.1%		IN
21	Hyperintensity on T2 weighted MRI	46.7%	38.5%	62.5%	49.2%		
22	MRI assessment of fistula volume	35.7%	53.8%	55.6%	48.4%		
23	Fistula T1 enhancement on MRI	13.3%	45.5%	60.0%	39.6%		
24	Abscess on MRI following treatment	66.7%	87.5%	60.0%	71.4%		
25	An activity based MRI score	86.7%	93.3%	88.9%	89.6%		IN

26	A Global quality of life score	100.0%	93.8%	100.0%	97.9%	n/a	IN
27	Physically restricted in caring for oneself	15.4%	26.7%	70.0%	37.4%	70.0%	
28	Change in lifestyle based on toileting needs	23.1%	53.3%	87.5%	54.6%	90.0%	IN
29	Embarrassment and feeling bloated	25.0%	42.9%	60.0%	42.6%	60.0%	
30	Unable to attend school/work	36.4%	86.7%	100.0%	74.3%	100.0%	IN
31	Restriction of sexual activity	58.3%	80.0%	90.0%	76.1%	100.0%	IN
32	Lethargy and fatigue	0.0%	20.0%	66.7%	28.9%	60.0%	
33	Limitation to moderate activities	8.3%	12.5%	30.0%	16.9%	40.0%	
34	Change in general health	16.7%	64.3%	80.0%	53.7%	80.0%	
35	Avoidance of intimacy	36.4%	60.0%	88.9%	61.8%	88.9%	§ Combined
36	Anxiety and worries	8.3%	25.0%	55.6%	29.6%	75.0%	
37	Change in physical ability to do things	0.0%	12.5%	77.8%	30.1%	80%	
38	Feeling depressed, down, hopeless, unable to cope	7.7%	42.9%	90.0%	46.8%	90%	IN
39	Modifying how you sit, walk, stand because of your fistula	33.3%	57.1%	70.0%	53.5%	80%	
40	Life style alterations (pain/restriction)	25.0%	53.8%	80.0%	52.9%	100%	IN
41	Social interaction avoidance	50.0%	46.2%	70.0%	55.4%	80%	
42	Duration of improvement	53.8%	80.0%	88.9%	74.2%		
43	Death	46.2%	42.9%	55.6%	48.2%		
44	Allergic reaction	7.7%	6.7%	37.5%	17.3%		
45	Safety (adverse events) and toxicity	7.7%	7.1%	50.0%	21.6%		
46	Urinary complications	38.5%	76.9%	77.8%	64.4%		
47	Cardio-respiratory complications	7.7%	0.0%	44.4%	17.4%		
48	Neurological complications	0.0%	8.3%	60.0%	22.8%		
49	Medical complications specific to immunosuppression	0.0%	15.4%	44.4%	19.9%		

Table 5-5. Outcomes to be included in the COS at the consensus meeting

** "Patient Priorities" Following a discussion and consensus agreement it was decided that these outcomes should be voted on by patients alone*

^Combined with "A global assessment of incontinence that covers all aspects of leakage"

§ Combined with "Restriction of sexual activity"

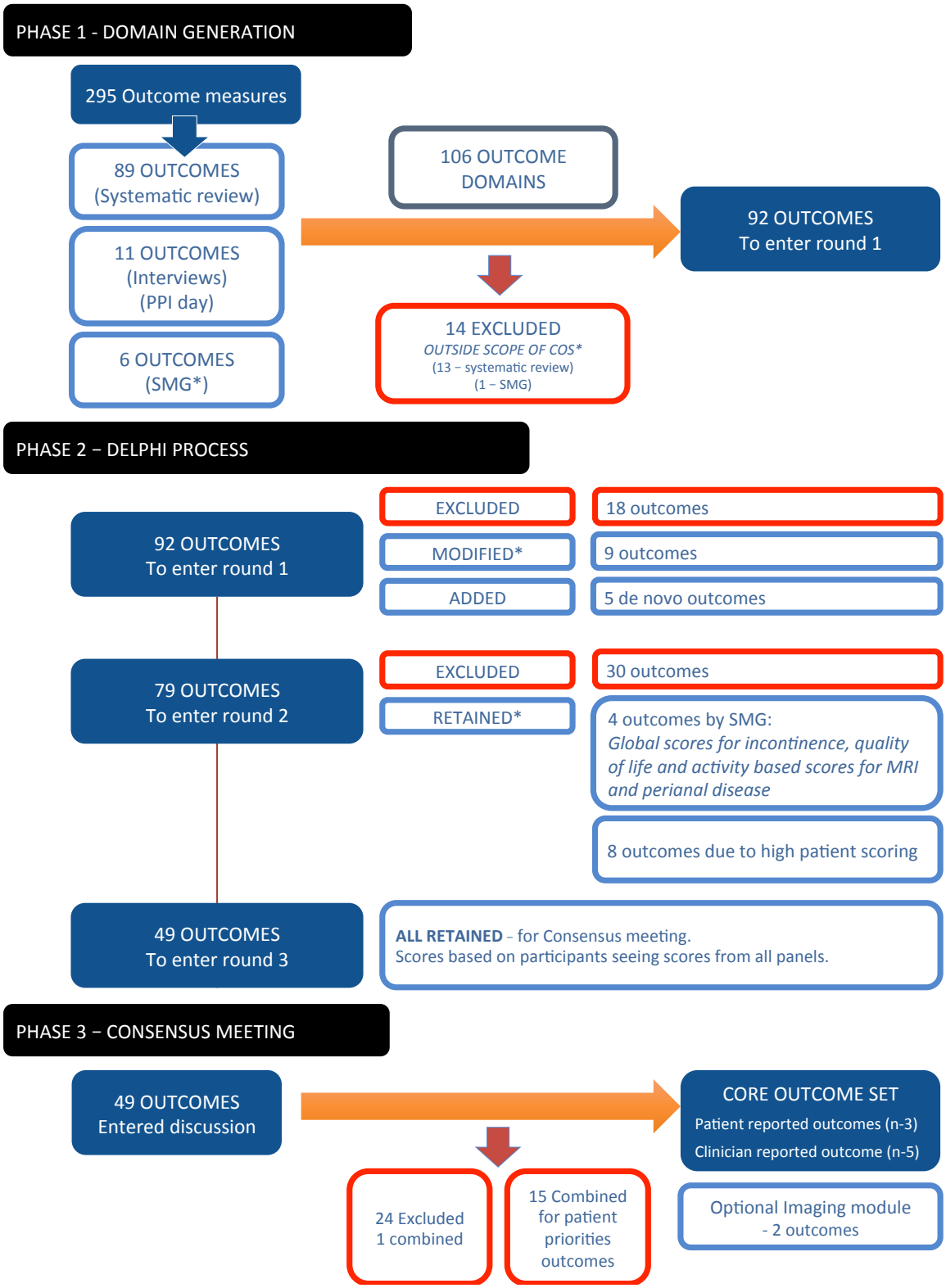


Figure 5-1. Outcome flow diagram

Consensus meeting

Following scoring at the consensus meeting, eight outcomes were retained in the COS. This constituted three patient-reported and five clinician-reported outcome domains **Box** 5-2. The outcome *radiological outcome* was felt to be important by the attendees at the consensus meeting but did not meet criteria for retention in the core outcome set. Attendees' main reasons for excluding the outcome were that the cost associated with Magnetic Resonance Imaging was likely to prohibit its use in the majority of fistulising pCD research, and that it was therefore not appropriate for inclusion in a COS. The meeting attendees did however note that it should be recommended for use as an outcome in all studies where it was feasible to do so.

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

Patient Reported outcomes

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

Clinician Reported outcomes

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

Imaging (optional module)

- *Fistula response on MRI imaging*
- *An activity-based MRI score responsive to change*

Box 5-2 Core outcome set for fistulising perianal Crohn's disease

5.5 Discussion

This is the first study aiming to standardise outcome reporting in fistulising pCD. An exhaustive list of candidate outcome measures was generated through a systematic review of contemporary outcomes, together with patients' views. Using an online tool, a large number of stakeholders were able to participate in a pragmatic Delphi consensus process that ensured emphasis on patient perspective and clinical relevance. Consensus

voting, and discussion generated a COS that all stakeholders supported with applicability to all study designs. The aim is not only to improve research but also to use this COS as an impetus to also drive improvement in the clinical management within the field. The COS allows measurement of outcomes for all cohorts of adult pCD patients, regardless of disease state, the intervention under assessment or the presence of luminal disease. In this study, we established an eight-domain core outcome set (COS) for use in studies evaluating interventions in fistulising pCD.

Fistulising perianal Crohn's disease denotes a severe and disabling disease course characterised by the need for multiple hospitalisations and operations. It also has a high economic cost, particularly with the use of biologic agents as the mainstay of treatment.[284,285,286,287] The James Lind Alliance, a national Priority Setting Partnership group of patients and clinicians, identified perianal Crohn's disease (pCD) and specifically the individual factors that influence various treatment strategies and outcomes, as one of the 'Top 10 unanswered questions' in the field of IBD.[288] However, the means by which success is measured, in the management of Crohn's perianal fistula has hitherto been a consistent challenge to researchers.[289] Most studies have used a measure of the degree of clinical healing as their primary outcome, however deep tissue healing has been shown to lag behind simple closure of the external openings[290] and, crucially, success measured this way has generally been disappointingly poor. Moreover, if control of symptoms is the primary objective of treatment, these measures are wholly inappropriate and will fail to demonstrate a benefit, even if patients perceive one. The multimodal treatment of perianal fistulas in Crohn's disease: seton versus anti-TNF versus advancement plasty (PISA) trial group have proposed a set of primary outcomes, which aim to address this deficit.[168] Of note, the primary outcome is based in clinical reality and measures re-

interventions following treatment. The secondary endpoints include quality of life, disease activity and importantly use an MRI based evaluation to determine fistula closure as a long-term measure at 18 months. Recently the largest randomised controlled trial of stem cell therapy in fistulising pCD was published.[262] The authors used a new composite primary endpoint, comprising clinical and radiological healing, further revealing the lack of agreement on which fistula outcomes to use, but also recognising the inadequacy of a single (particularly a single clinic) outcome measure to define success.

An ICHOM (International Consortium for Health Outcome Measurement) for IBD has recently been published which emphasises the importance of patient reported outcome measures but it has been designed for IBD in general and has limited information collected on fistulas.[291] This COS aims to address an unmet need in pCD where standardising outcome measures is particularly difficult due to the patient's goals of treatment changing over time, the refractory nature of perianal disease compared to luminal disease and the specific symptoms associated with the condition.[1,292]

A strength of this study is that every stage of the process, including amalgamation, and addition and exclusion of outcomes, was performed by consensus and always included patient representation. Examples include the intervention specific complications and morbidity, which featured in the outcomes presented on the consensus day but were excluded from the final COS, as the participants felt these would be reported as a minimum in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) harms checklist.[293] A similar discussion excluded "death" as an outcome. The initial design of this study followed the guide set by the OMERACT[255] group but at the consensus meeting it was felt that "death" was less suitable for this COS and a more

relevant hard endpoint would be "faecal diversion." Another consensus decision was that of an optional imaging module, since as MRI is not universally accessible it did not reach the threshold for general inclusion. Another strength was the diversity in the study management group, with stakeholder leads and methodologists from a number of different institutions and geographical locations, and the crucial stakeholders (patients) were always prioritised. For example, we found that patients tended to rank most outcomes highly, gastroenterologists slightly less so and surgeons least of all. This meant that the outcomes that fell below the inclusion bar tended to do so as a result of the views of the clinicians, rather than the patients, potentially deviating from the aim of a patient centred COS. There is currently no guidance on how to discuss outcomes with patients and carers in qualitative research[294] but in efforts to ameliorate this effect, the study management group used separate thresholds for clinicians and patients, to allow for prioritisation for outcomes scored particularly highly by the patients. In addition, some outcomes seemed to score poorly despite very similar outcomes scoring highly. This was taken as evidence of poorly worded descriptions or concepts difficult to explain in pithy prose. For example, the concept of a global assessment of quality of life reached the threshold for exclusion in the online Delphi but was discussed at the consensus meeting for the reasons above and was selected as part of the final COS once it was adequately explained to the patients, by whom it was then championed.

Given the poor rates of fistula closure experienced by most patients, the range of new medical and surgical treatments emerging and the high cost of many of them, determining their relative efficacy and cost effectiveness is important. Comparison of different techniques from different studies mandates standardised outcome reporting, which this COS will provide. Outcomes specific to a given study as a result of the

technique used or population studied, such as the rate of plug extrusion, or complications relating to immunosuppression, remain important to measure and are not excluded by a COS. Innovation, progress and pragmatism will require researchers to measure other outcomes but in order to appraise interventions completely and ensure relevance to patients, this COS should also be used. Although MRI is crucial to determine deep tissue healing, its value in the assessment of symptom palliation is less clear and it is not readily available to all studies or institutions, so could not be considered a core outcome but is a strongly advocated addition where appropriate.

The ENiGMA (Evaluating goal-directed management of fistulising perianal Crohn's disease) research group is building a portfolio of foundational research, of which this core outcome set is a central part. This COS requires international validation if it is to be used outside the UK. It is also necessary to develop a core measurement set, a collection of measurement tools and standards by which these outcomes can be assessed in a given study. For example, there is no validated, disease specific, patient derived quality of life measurement tool for Crohn's anal fistula. This is another 'unmet need' described by the European Crohn's and Colitis Organisation's consensus group.[280] Creation of such a measurement tool is underway and development of a core measurement set to complement this COS is also underway.

5.6 Limitations

As per other core outcome sets a protocol was decided a priori with respect to determining the inclusion/exclusion of the outcome measures. The decision to change the protocol in the second round was difficult as elucidated in the results section and the cut off values were chosen with reference to the previously published literature. A key

concern was to balance scientific rigor with critique about inappropriate influence from the SMG. One of the methodologists was concurrently co-authoring the COMET handbook and escalated the discussion to then COMET team. Other COS developers had encountered the same problem with the least discrimination occurring in the patient panel and as such the COMET team where conscious of this phenomenon. To the effect, the COMET handbook now has a section dedicated to 'changes to protocol' on the premise this is acknowledged in a separate section and clearly explained.

Other limitations of this study are that all the participants were based in the UK, which could affect generalisability to other populations, especially in low-income countries. There was an active decision by the study management group to minimise attrition through the rounds and to achieve maximum recruitment. One missing stakeholder was industry; this was discussed and specifically excluded due to concern about potential bias. An online survey was chosen due to its ease of use, increasing the feasibility of national sampling, as well as removing interview bias.[295] To date, this study has one of the largest numbers of participants and one of the lowest attrition rates.

5.7 Conclusion

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

Section C – Developing an objective outcome measure

Despite the creation of a core outcome set the field of perianal Crohn's disease is still missing an objective measure of success. Arguably, patient reported outcome measures are the most appropriate method of clinical observation and our group is working to develop such a tool for patients with pCD. However, for the proportion of patients necessitating radiological evaluation, the current standard is subjective and carries within is substantial heterogeneity.

This section describes our pilot study in developing a novel objective radiological outcome measure using volume assessment of the fistula tract. In this section we compare our outcome measure against the current standard as well as intra- and inter-observer variability.

6 Volume assessment MRI technique for monitoring perianal Crohn's fistulas

This chapter has been published in Therapeutic Advances in Gastroenterology. I am joint first author with Dr Phillip Lung. As a SAGE journal author, I have permission for reuse of this material for this thesis.

6.1 Abstract

Background

Perianal Crohn's fistula and their response to anti-TNF therapies are best assessed with MRI, but radiologist reporting is subjective and variable. This study investigates whether segmentation software could provide precise and reproducible objective measurements of fistula volume.

Methods

We undertook a retrospective analysis of patients with perianal Crohn's fistula at our institution between 2007 and 2013. Pre- and post-biologic MRI scans were used with varying time intervals. Two expert GI radiologists recorded fistula volumes, mean signal intensity and time taken to measure fistula volumes using validated open-source segmentation software. Three expert GI radiologists assessed fistula response to treatment (improved, worse or unchanged) by comparing MRI scans.

Results

Eighteen cases were reviewed for this pilot study. Inter-observer variability was very good for volume and mean signal intensity; ICC 0.95 (95%CI 0.91-0.98) and 0.95 (95%CI 0.90-0.97) respectively. Intra-observer variability was very good for volume and mean signal intensity; ICC 0.99 (95%CI 0.97-0.99) and 0.98 (95%CI 0.95-0.99) respectively. Average time taken to measure fistula volume was 202s and 250s for readers 1 and 2.

Agreement between 3 specialist gastrointestinal (GI) radiologists was good (kappa 0.69 [95%CI 0.49-0.90]) for the subjective assessment of fistula response. Significant association was found between objective percentage volume change and subjective consensus agreement of response (p=0.001). Median volume change for improved, stable or worsening fistula response was -67% (IQR:-78,-47), 0% (IQR:-16,+17), and +487% (IQR:+217,+559) respectively.

Conclusion

Quantification of fistula volumes and signal intensities is feasible and reliable, providing an objective measure of perianal Crohn's fistula and response to treatment.

6.2 Introduction

One third of all Crohn's disease patients develop perianal fistula[85], representing a distinct and aggressive phenotype[296], causing pain and discharge that results in reduced quality of life.[265] The disease course is often severe and disabling, involving multiple medical and surgical interventions.[85,292,66] Established treatment principles involve a multi-disciplinary approach[109], aggressively managing proctitis, judicious use of surgery to drain sepsis, and optimising medical Crohn's treatment through a combination of antibiotics, immunosuppressants and anti-TNF therapies.

Response to treatment can be assessed in a variety of ways. The most common scoring tools and techniques used include: FDA (Fistula drainage assessment, described below); PDAI (perianal disease activity index)[297]; CDAI (Crohn's disease activity index)[298]; IBDQ (Inflammatory bowel disease questionnaire)[299] and MR imaging[298]. The current standard of clinical response to treatment is the FDA as used in the ACCENT II trial, which defines remission as complete cessation of drainage from all fistula openings present at baseline despite gentle finger pressure, on at least two occasions over at least a 4 week period, and improvement as a 50% reduction in the number of external openings present or draining.[160] CD is a chronic relapsing and remitting disease as are its fistulising complications,[260] so clinical remission cannot be determined at individual time points, as the very nature of the discharge is sporadic. Furthermore, closure of an external opening does not necessarily equate to deep healing of the tracts,[261] or indeed improved quality of life.[298]

Pelvic MRI has been shown to be the most accurate method for classification of the primary tract and secondary extensions[300]; the recognition and treatment of the latter

being essential to ensure satisfactory healing.[301] MRI scans inform clinicians about fistula complexity, for example, the number of tracts, presence of undrained sepsis and the patients' response to treatment interventions. Importantly, MRI can evaluate deep tissue healing, which cannot be clinically assessed.[298]

Assessment of radiological improvement is subjective and wide variation exists between radiologists. Previous attempts to standardise radiological response, such as the Van Assche system, have been criticised due to insensitivity to change,[261,298] and represent descriptive scores rather than monitoring tools. Currently, there is no universally accepted or reliable method of monitoring long-term radiological response to treatment. However, it is our view that clinical monitoring alone is inadequate. Proper evaluation of interventions for perianal Crohn's fistula requires accurate monitoring of response, as does the development of tools that will enable prediction of successful treatment. Future research and development needs therefore to focus on accurate forms of imaging to provide standardised, responsive and accurate tools to assess radiological response to treatment.

The imaging module of the recently published fistulising Crohn's disease core outcome set comprises two outcomes, 'Fistula response on imaging' and 'an activity-based MRI score responsive to change'.[302] At present, perianal fistula complexity on MRI is judged based on fistula configuration, involvement of adjacent pelvic spaces, presence of undrained sepsis and volume.[298,261,303,304] Whilst the first three components are based on anatomical assessment, there is currently no method to calculate fistula volume and it is not performed in routine practice. We hypothesise that volume change is an important measure of fistula response that may be incorporated as part of a core measurement set.

This pilot study aims to confirm the feasibility of objectively calculating perianal fistula volume using segmentation software through evaluation of repeatability, reproducibility and comparison with the current standard of subjective assessment of MRI fistula response.

6.3 Methods

Ethical Approval

All patients were treated on the basis of clinical need according to standard clinical care at our institution, on an open-label basis and according to licensed or published regimens. After consultation with the local Research and Development (R&D) department (London North West Healthcare NHS Trust), it was advised that approval by an NHS research ethics committee or the R&D department was deemed unnecessary owing to the non-patient identifiable retrospective nature of this feasibility study. The study received departmental approval by the research lead of St Mark's Hospital, London, United Kingdom. The study was registered as a service evaluation and all patients were treated only after full and informed clinical consent as part of routine care.

Patients & Setting

We performed a retrospective analysis of patients with perianal Crohn's fistula selected using a random number generator from a cohort treated at St. Mark's Hospital between 2007 and 2013. Adult patients were selected if they met the following inclusion criteria: perianal Crohn's fistula; current anti-TNFα treatment (Infliximab or Adalimumab); and had two MRI studies more than one year apart. MRI scans were initially performed twice a year following biological therapy and then annually as part of the St Mark's fistula

algorithm. A cohort of eighteen patients were selected using a random number generator by one of the authors (NY) for this pilot study as a previous paper was able to assess inter-observer variability on assessment of fistula scoring in a group of this size. Patient demographic data were retrieved.

MRI technique

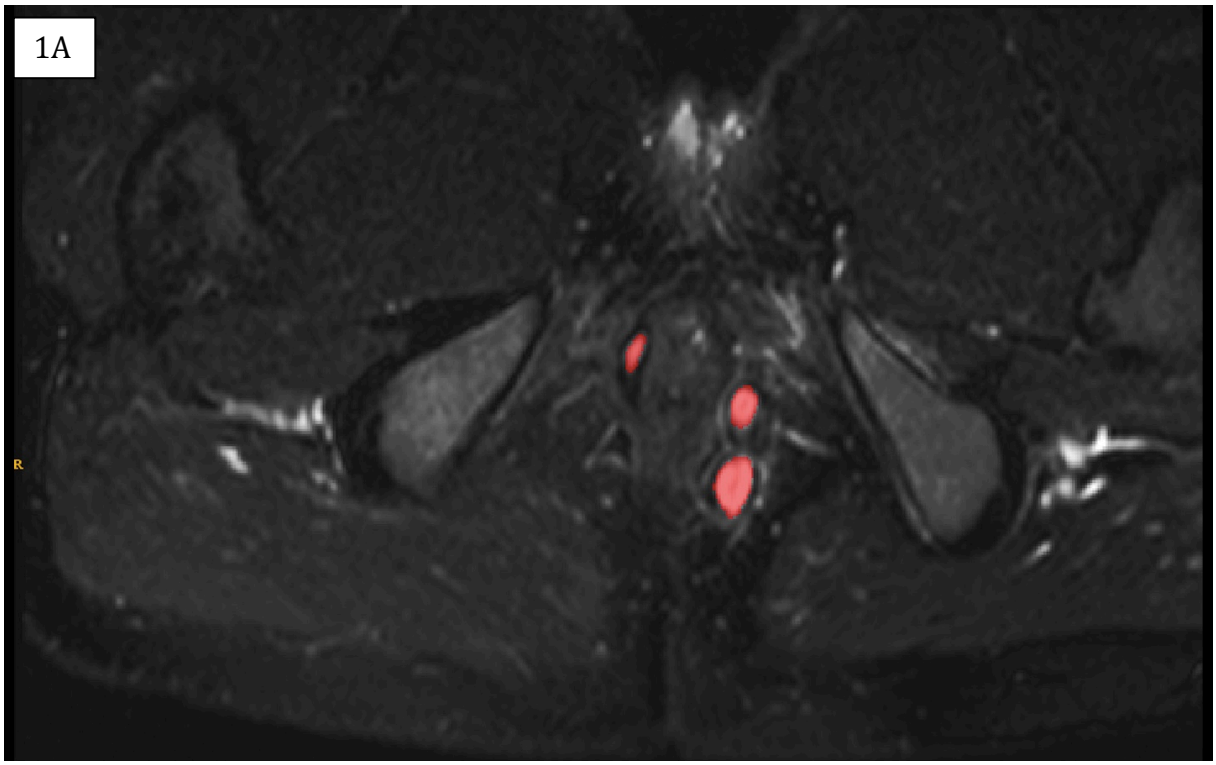
Standard axial T2-weighted Spectral Attenuated Inversion Recovery (SPAIR) MRI sequences were acquired (TR 8000; TE96; thickness 4 mm; gap 0.2 mm; FOV 240 mm; averages 4, flip angle 150, bandwidth 130Hz/PX). Digital imaging and communications in medicine (DICOM) images of the MRI sequences were retrieved from the picture archiving and communication system (PACS) and anonymised.

MRI Evaluation

Perianal fistulas were defined as tubular structures that abnormally connected the enteric lumen to the skin and the borders defined as the transition between T2 high signal and low signal fibrosis/fat on fat suppressed sequences. Each fistula tract at baseline and follow up was assessed and characteristics documented by reader PL. Fistula characteristics included: fistula type based on Park's classification; simple or branched fistula configuration; supralevator or ischioanal fossa involvement; presence of horseshoe configuration; presence of interstitial high signal surrounding the fistula tract; and presence of proctitis.

Two specialist gastrointestinal radiologists (PL and JB with 7 and 3 years' experience) measured fistula volumes, signal intensity and time taken to measure fistula volumes on baseline and follow up MRI scans using ITK-SNAP (version 2.2.0), a validated open-source segmentation software[305] **Figure 6-1**. All contents within the borders of the fistula were

considered part of the fistula volume. Reader PL repeated the readings for MRI studies after 2 months.



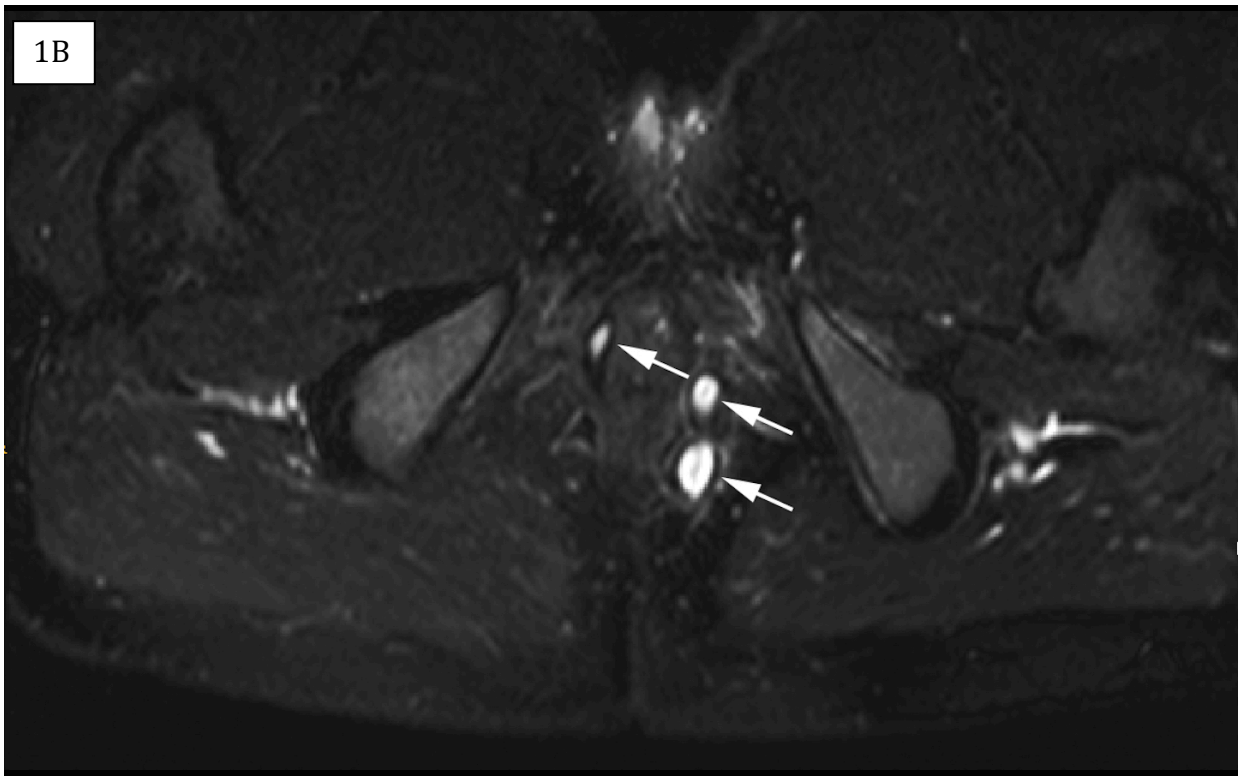


Figure 6-1. Segmentation of a perianal fistula. Image A shows an axial fat saturated T2 weighted image showing a complex high signal fistula (arrows). Image B shows the same image with the fistula having been manually segmented (now highlighted in red).

To minimise bias, three experienced, specialist gastrointestinal radiologists (PL, AG, DB with 7, 12- and 15-years' experience) also assessed fistula response to treatment (improved, worse or unchanged) by comparing baseline and follow up MRI scans for each patient.

Statistics

Inter and intra-observer correlation for measurement of fistula volumes were assessed using intra-class correlation (ICC). Subsequent analysis of fistula volume was performed using data from reader PL. Agreement between specialist gastrointestinal (GI) radiologists for fistula response to treatment was assessed using the kappa statistic. Consensus agreement was taken if 2 or more radiologists agreed. Differences in percentage volume change and overall fistula assessment were also deemed for the radiologists and assessed using the Kruskal-Wallis test.

The Mann-Whitney test was used to compare percentage volume change with fistula characteristics with only two categories, whilst the Kruskal-Wallis test was used where there were more than two categories.

6.4 Results

Eighteen patients (12 men, 6 women) with Crohn's perianal fistula were recruited with median age of 29 yrs (range 19-52yrs). At baseline, they had a total of 23 fistula tracts; 13 with single tracts only and 5 with two fistula tracts. 15 of 23 (65%) tracts were transsphincteric, 5 (22%) were intersphincteric and 3 (13%) were extrasphincteric. Five patients had proctitis. Fistula characteristics during the course of this study are detailed in Error! Reference source not found..

Variable	N	Median % volume change (IQR)	P-value
Fistula Tract Type			
Intersphincteric	3	514 (-78, 559)	0.63
Transsphincteric	12	-5 (-61, 301)	
Extrasphincteric	3	-55 (-67, 217)	
Configuration			
Solitary	4	337 (54, 523)	0.34
Branched	14	-30 (-67, 217)	
Supralevator/Ischioanal Involvement			
No	3	515 (-78, 559)	0.37
Yes	15	-17 (-67, 217)	
Horseshoe Sepsis			
No	9	186 (-47, 487)	0.20
Yes	9	-42 (-74, 17)	
Peri-fistula Interstitial High Signal			
No	6	-47 (-74, 416)	0.88
Yes	12	6 (-17, 217)	
Proctitis			
No	13	6 (-55, 416)	0.59
Yes	5	-42 (-82, 217)	

Table 6-1. Patient fistula characteristics and their association with percentage volume change.

Average time taken to calculate volume measurements was 3 minutes 22 seconds and 4 minutes 10 seconds for readers 1 and 2 respectively with moderate agreement (ICC 0.73) in time taken between readers.

Inter-observer variability between readers was very good for volume and mean signal intensity with ICC of 0.95 (95% CI 0.91-0.98) and 0.95 (95% CI 0.90-0.97) respectively. Intra-observer variability was also very good for volume and mean signal intensity with ICC of 0.99 (95% CI 0.97-0.99) and 0.98 (95% CI 0.95-0.99) respectively.

There was good agreement for assessment of subjective fistula response between all three radiologists (kappa 0.69; 95% CI: 0.49-0.90), with all (100%) cases agreed by at least two radiologists and most (13/18; 72%) agreed by all three radiologists.

Manual segmentation measuring percentage change in fistula volume was significantly associated with subjective assessment of radiological response to treatment by all three radiologists (p=0.001). The calculated median volume change was -67% (IQR -78, -47), 0% (IQR -16, +17), and +487% (IQR +217, +559) for fistulas assessed by radiologists as improved, stable or worsening respectively.

Percentage volume change measured by manual segmentation was not associated with any of the fistula characteristics assessed by radiology **Table 6-1**.

The observed difference in median percentage change in fistula volume between Infliximab and Adalimumab, -45% (IQR -70%, +216%) and +201% (IQR +6%, +559%) did not reach significance (p=0.16).

No significant association was found between the categorical (**Table 6-2)** and continuous (**Table 6-3)** variables relating to participants' Crohn's disease and percentage volume change.

Variable	Category	N	Mean Fistula % Volume Percentage Change (SD)	P-value
Gender				
	Male	12	-5 (-66, 337)	0.71
	Female	6	85 (-67, 416)	
Site affected at presentation				
	Perianal disease only	7	-47 (-67, 217)	0.62
	Perianal + Luminal disease	11	6 (-74, 487)	
Biologic Therapy				
	Infliximab	12	-45 (-70, 216)	0.16
	Adalimumab	6	201 (6, 559)	
Thiopurines				
	No	5	-47 (-78, 6)	0.30
	Yes	13	17 (-55, 416)	

Table 6-2. Categorical patient and disease factors, and their association with fistula volume change

Variable	Correlation coefficient	P-value
Age	-0.02	0.95
Duration of Crohn's disease	0.11	0.65
Time between Crohn's diagnosis & scan	-0.08	0.74
Duration of fistula	0.08	0.75
Time between fistula diagnosis & scan	-0.08	0.74
Length of time between scans	-0.17	0.51

Table 6-3. Continuous patient and disease factors, and their association with fistula volume measurement.

6.5 Discussion

MRI is the gold standard test for assessment of perianal Crohn's fistula and subjective assessment of change in fistula volume is frequently reported to help determine response to treatment, particularly for Gastroenterologists assessing the impact of drug treatment.[298,261] However, there has been no objective method for quantification of fistula volume and this has therefore not been included in MRI scoring systems to date.[298,261,304,306] Studies of surgical treatment have also struggled to identify a robust, objective measure of radiological improvement.[262] The present study has shown that volume of perianal fistula in patients with Crohn's disease can be reliably measured by MRI with very good inter- and intra-observer agreement. Objective measurement of volume is facilitated by the sharp boundary between high intensity fistula and the surrounding low intensity fat or scar tissue (fibrosis), which can be perceived easily by the human observer.

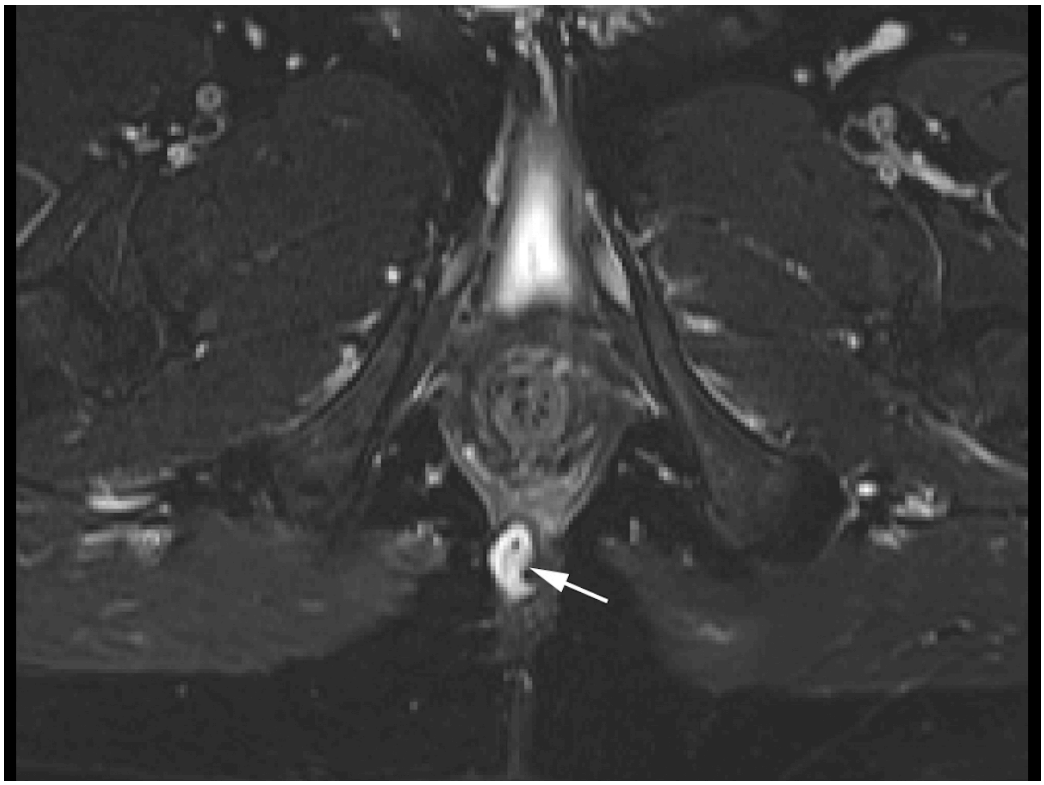
Manual measurement of fistula volume took a relatively short time to perform (up to 4 minutes 10 seconds) with the difference between readers likely related to experience. The authors acknowledge that any significant delay in reporting times limits generalizability and warrants scrutiny, and therefore determination of the additional clinical benefit of precise volume measurement over subjective assessment will be required. That said, objective fistula volume measurement can be applied to very complex disease that involves multiple tracts and collections, which are usually more difficult to assess subjectively. Furthermore, it will be possible to automate measurement of fistula volume in the future, negating any impact on reporting times and enabling less experienced observers to assess fistula volume more accurately.

We found good inter-observer agreement for the subjective assessment of fistula response on MRI indicating that it potentially represents a good standard against which to assess volume as an objective measure. We also demonstrated minimal inter and intra-observer variability in volume measurement indicating this represents a consistent and repeatable measure. We investigated the association between change in fistula volume and subjective assessment of fistula response by experienced gastrointestinal (GI) radiologists at St. Mark's. We found strong agreement between this objective measure and the subjective assessment.

Having determined that volume demonstrates good inter- and intra-observer variability, is quick to perform and correlates well with the current standard of subjective assessment of improvement when performed by experienced GI radiologists, we are now able to investigate the relationship of these radiological measures of change with clinical outcomes in larger longitudinal and prospective studies. Such studies will require larger

groups of consecutive patients so that correlation between clinical and radiological change can be assessed. Furthermore, whilst not within the scope of this pilot study, new drugs and surgical techniques may also be evaluated using objective fistula volume measurement, such as the increasing array of biologic treatments, surgical repairs such as the LIFT procedure, or local injection of stem cells, as in the ADMIRE-CD study[184].

Despite good agreement overall, disagreement between readers for individual patient assessments are noteworthy. One fistula with an objective 17% increase in volume was reported as 'no change' by two readers and 'worse' by one reader. When reviewed retrospectively, all readers agreed there was a mixed response where different component of the fistula increased and decreased in volume over time **Figure 6-2.**



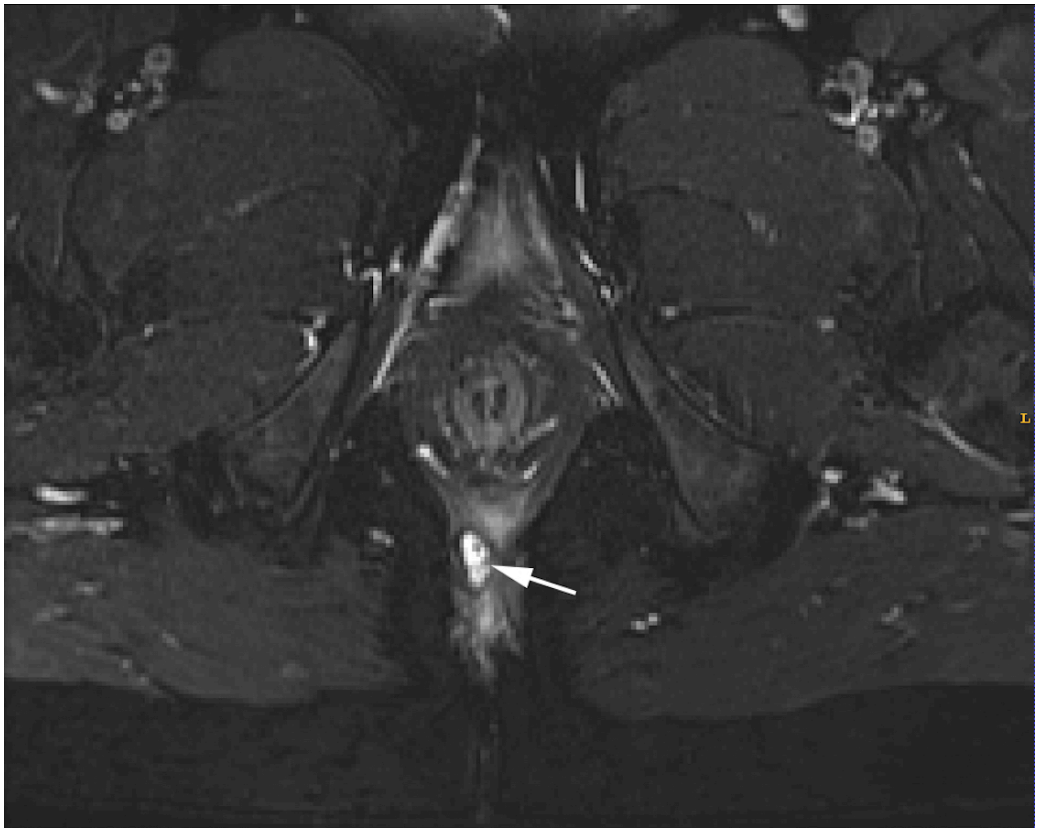


Figure 6-2. This perianal fistula (arrows) at similar levels shows a subjective improvement between baseline (2A) and follow up (2B). Manual segmentation is able to quantify this difference with a -42% percentage change in fistula volume.

Similarly, another fistula had nearly healed bar a subcutaneous fluid focus, which had increased in size leading to an overall 6% increase in fistula volume. These cases reinforce the need to assess additional fistula characteristics, beyond volume alone, when judging response to treatment. Notably, our study also found that these additional characteristics (**Table 6-1**) are independent of percentage volume change (implying that scoring systems based on description of these characteristics may remain insensitive to change, and that specific fistula configurations do not appear to obviate the utility of this technique, although larger studies are required to confirm these concepts).

We believe that accurate assessment of reduction in inflammation and volume is key to the clinical utility of this technique. One hypothesis is that the rate and/or extent of

volume reduction in a given period following treatment (at 3 months from induction, for example), will predict the rate and completeness of fistula closure, the duration of remission or the risk of fistula recurrence. This would be beneficial in stratifying patients undergoing expensive treatment with significant adverse effects.

6.6 Limitations

Although we did not find significant correlation between fistula volume and clinical findings, we suspect this is related to the small sample size and heterogeneous cohort. This pilot work was designed to develop the volume measurement technique and not to detect such a correlation with clinical findings.

The present study has several limitations, including a small sample size and its retrospective design. However, it confirms the feasibility of our technique to measure perianal fistula volumes. Additionally, the standard with which we compared our objective measurement is subjective and complete agreement between all three assessors (from a single institution) was not observed. Nevertheless, agreement between them was strong and as experienced, specialist GI radiologists their subjective assessment represents the best currently available standard with which to compare volume assessments.

6.7 Conclusion

Quantification of fistula volumes is feasible and reliable, with the potential to provide objective measurement of perianal Crohn's fistula and response to treatment. This is the first step towards developing an objective and responsive MRI based volume score.

Section D – Novel imaging strategies to better understand complex perianal disease

Anatomy of perianal fistulas dictates treatment strategy, but 3D visualization of complex fistula by the surgeon, based on 2D MRI images, can be difficult to achieve. Often surgeons rely on a combination of their own view of the MRI scans and reports (and often only the latter) but these can still be challenging to interpret. Novel innovative strategies can easily be employed to better improve the understanding of these complex fistulas to improve operative decision making, educating trainees and better informing patients.

In this section, segmentation strategies have been employed to create 3D reconstructions of complex perianal fistulas. Proof of concept studies looking at various media of 3D communication are described in the following chapters.

7 Improving the understanding of perianal Crohn's fistula through 3D modelling

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7.1 Abstract

Introduction

Perianal Crohn's fistulas are often complex, translating to difficult surgery and poor outcomes. MRI is the reference standard for assessment of perianal fistula, defining anatomy and guiding surgery. However, communication of findings between radiologist and surgeon remains challenging. The aim of this chapter is to demonstrate different platforms to aid communication and understanding of complex perianal fistula through 3D imaging.

Methods

Standard axial T2-weighted Spectral Attenuated Inversion Recovery (SPAIR) MRI sequences were acquired. Digital imaging and communications in medicine (DICOM) images of the MRI sequences were retrieved from the picture archiving and communication system (PACS) system and anonymized. DICOM images were imported on validated open-source segmentation software. A specialist consultant gastrointestinal

radiologist performed segmentation of the fistula tract, and the internal and the external sphincter.

Results

3D models of the fistula tract and sphincter complex were created from several patients with complex perianal Crohn's fistula. A combination of static images and short animations were created. In addition, the reconstructions were uploaded onto an app to allow for manipulation of the images and also removal of the surrounding structures.

Conclusion

Accurate 3D reconstruction of complex perianal fistula is feasible and has the potential to improve surgical understanding and decision-making but also to augment training and aid patient comprehension for informed consent.

7.2 Introduction

Anal fistulas occur in a third of all Crohn's disease patients[85] and form a distinct and aggressive phenotype,[1,2] with higher risk of severe and disabling disease course, relapse and need for repeated operations. They cause pain and discharge, resulting in reduced quality of life.[87] In a population study Schwartz et al. found the cumulative risk of patients with Crohn's disease having at least 1 perianal fistula after 1 year was 12%; after 10 years 21%; and after 20 years 26%.[230]

Conventional 2-dimensional MRI is the gold standard for imaging fistula and has been shown to be superior to examination under anesthesia[95] and endoanal ultrasound[98]. It has been shown to be the most accurate method for classification of the primary tract and any secondary extensions;[300] the recognition and treatment of the latter being essential to ensure satisfactory healing.[301] A technical review by the American Gastrointestinal Association[54] found the diagnostic accuracy to be 76-100% in complex Crohn's fistula[99,100,77,101,102,103,104]. MRI scans are used to inform clinicians about fistula complexity, number of tracts, presence of sepsis and relation to the anal sphincter, as well as the patients' response to treatment interventions. Comprehensive understanding of perianal fistula anatomy is dependent on radiologist communication of MRI findings to the surgeon, and surgical understanding of MRI images, both of which can be variable.

3D imaging provides a more realistic image based on cross-sectional data that has been shown to be a useful aid for patient education, clinical communication[307] and surgical planning.[308] Magnetic resonance cholangiopancreatography highlights the benefits of 3D imaging and, since it's advent in 1991, it is now standard in biliary tract imaging.[309]

Segmentation of the relevant anatomy and then re-assembling these segments to form a 3D model may aid understanding of the complex relationship between sphincter anatomy and fistula, guiding surgical decisions and improving outcomes. Studies have shown that accurate 3D MRI reconstruction of complex pelvic anatomy can be achieved, but this has yet to be demonstrated in perianal fistula.[310]

This study describes our experience of 3D modelling of the anorectum and perianal fistulas.

7.3 Methods

Ethical Approval

After consultation with the local Research and Development (R&D) department (London North West NHS Trust), it was advised that approval by an NHS research ethics committee or the R&D department was not required. The study received departmental approval by the research lead of St Mark's Hospital.

MRI technique

Standard T2-weighted Spectral Attenuated Inversion Recovery (SPAIR) MRI sequences were acquired in axial (TR 8000; TE 96; thickness 4 mm; gap 0.2 mm; FOV 240 mm; averages 4, flip angle 150, bandwidth 130Hz/PX) and coronal (TR 8860; TE 89; thickness 4 mm; gap 0.2 mm; FOV 250 mm; averages 4; flip angle 150, bandwidth 130Hz/PX) planes, with a sagittal T2-weighted BLADE sequence (TR 5400; TE 100; thickness 3 mm; gap 0.9 mm; FOV 290 mm; averages 1; flip angle 150, bandwidth 362Hz/PX; BLADE coverage 200%). Digital imaging and communications in medicine (DICOM) images of the

MRI sequences were retrieved from the picture archiving and communication system (PACS) system and anonymized.

Segmentation

DICOM images were imported into validated open-source segmentation software.[305] Perianal fistulas were defined as tubular structures that connected the enteric lumen to the skin and the borders defined as the transition between T2 high signal and low signal fibrosis/fat on fat suppressed sequences. All contents within the borders of the fistula were considered part of the fistula. Segmentation was performed on the axial T2-weighted SPAIR sequence with coronal and sagittal sequences used for cross-reference. A specialist consultant gastrointestinal radiologist manually segmented the following structures: fistula tract; internal and external sphincters; rectum; levator plate; and skin. Individual labels were applied to each anatomical structure.

Each mesh was imported into MeshLab V1.3.3.1 as a Stereolithography (STL) file for surface smoothing to be applied. Animations were created in collaboration with Touch Surgery™.

7.4 Results

Static images

Static images were reconstructed for two complex perianal fistulas **Figure 7-1**, an intersphincteric fistula tract **Figure 7-2, Figure 7-3** and a trans-sphincteric fistula tract **Figure 7-4, Figure 7-5, Figure 7-6.** In each of the examples the various parts of the sphincter complex and the fistula were segmented and displayed in a different colour

(Red: Fistula Tract; Green: External Anal Sphincter (EAS) and Levator Plate; Blue: Internal Anal Sphincter (IAS) and Rectum). The overlying structures were made transparent to further explain the exact morphology of the tract.

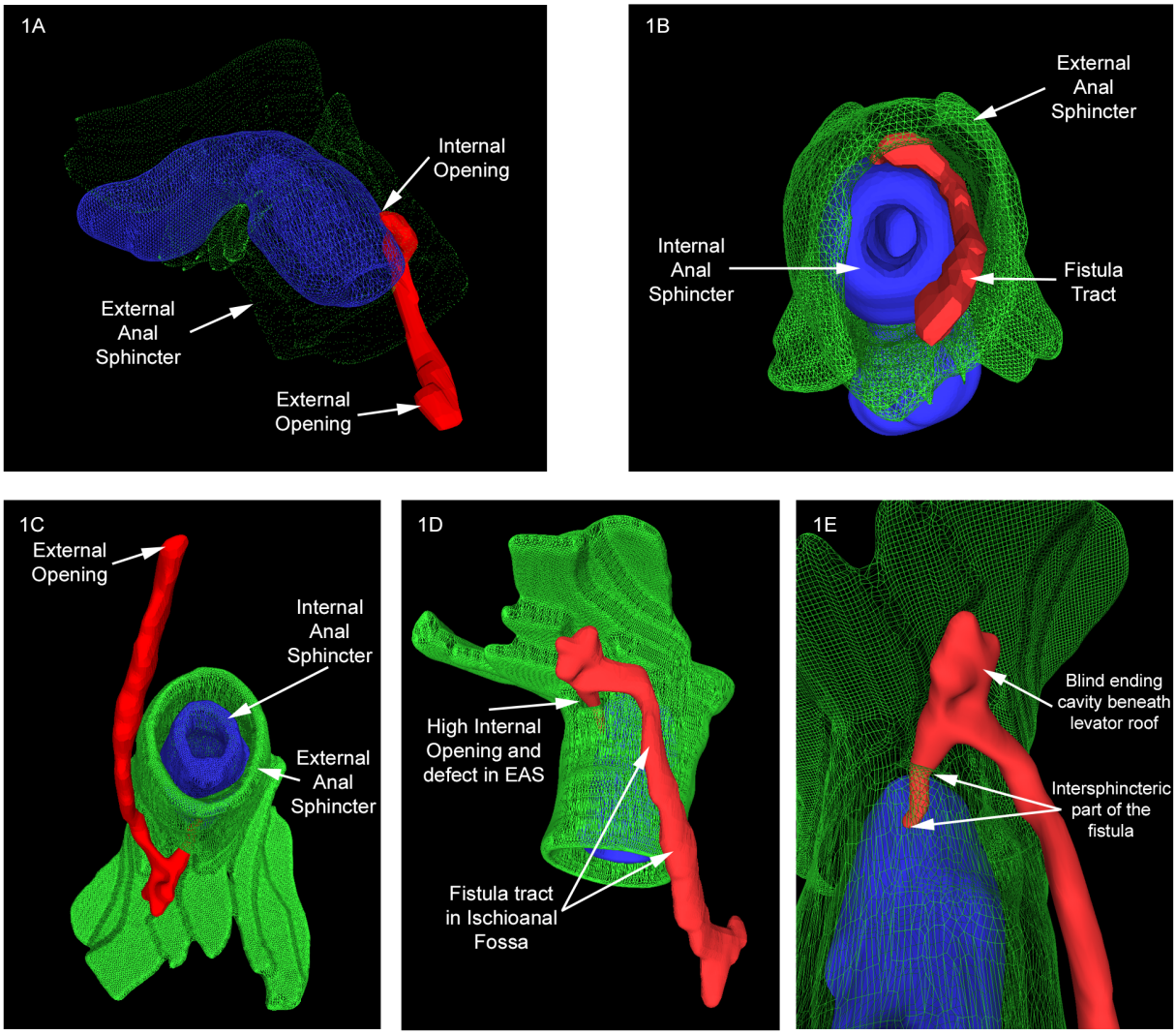


Figure 7-1. 3D reconstructions of intersphincteric (1a-b) and transsphincteric (1c-e) fistulas.

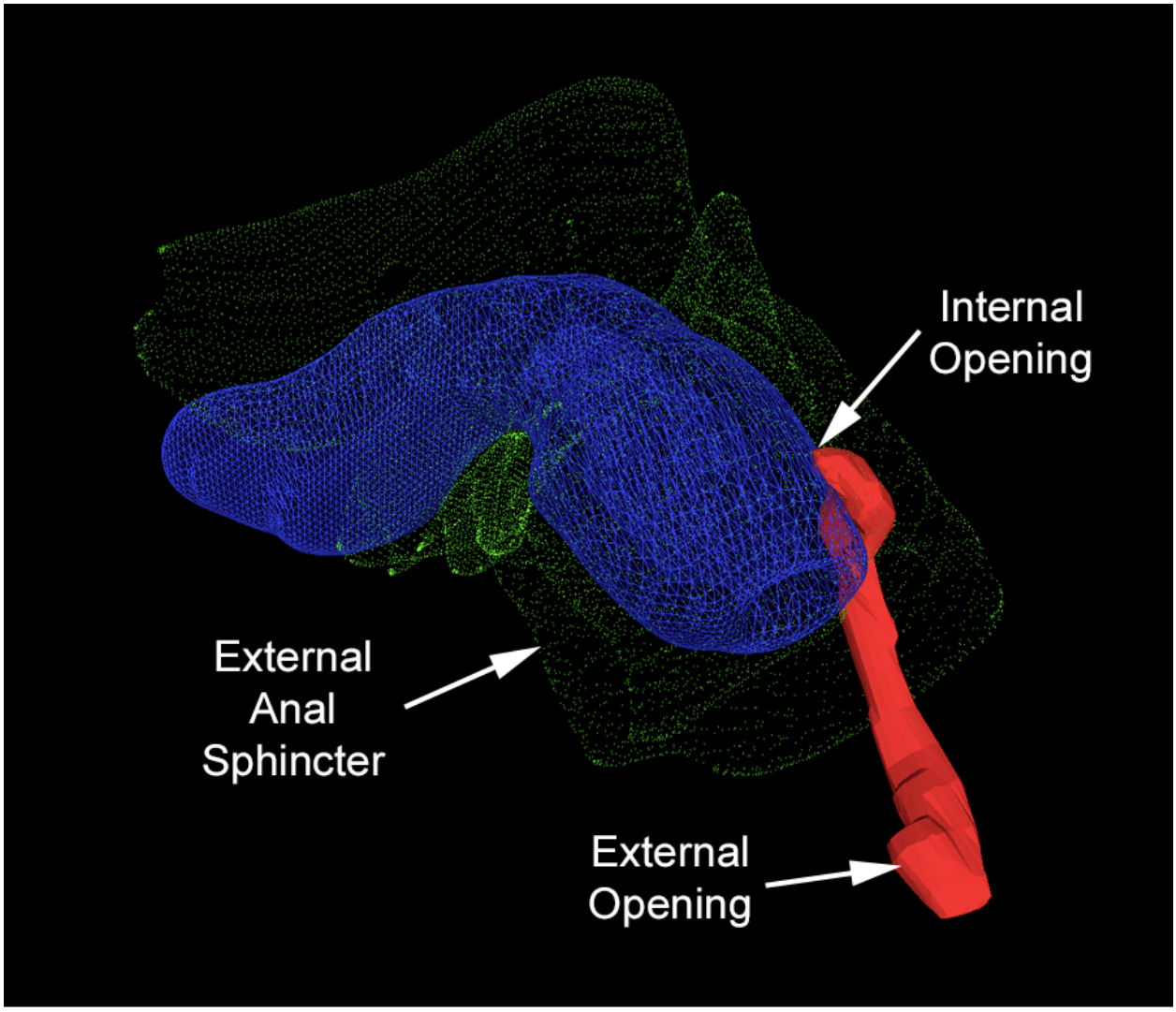


Figure 7-2. Angled view of the fistula from the right with a translucent EAS visualizing the intersphincteric fistula and internal opening

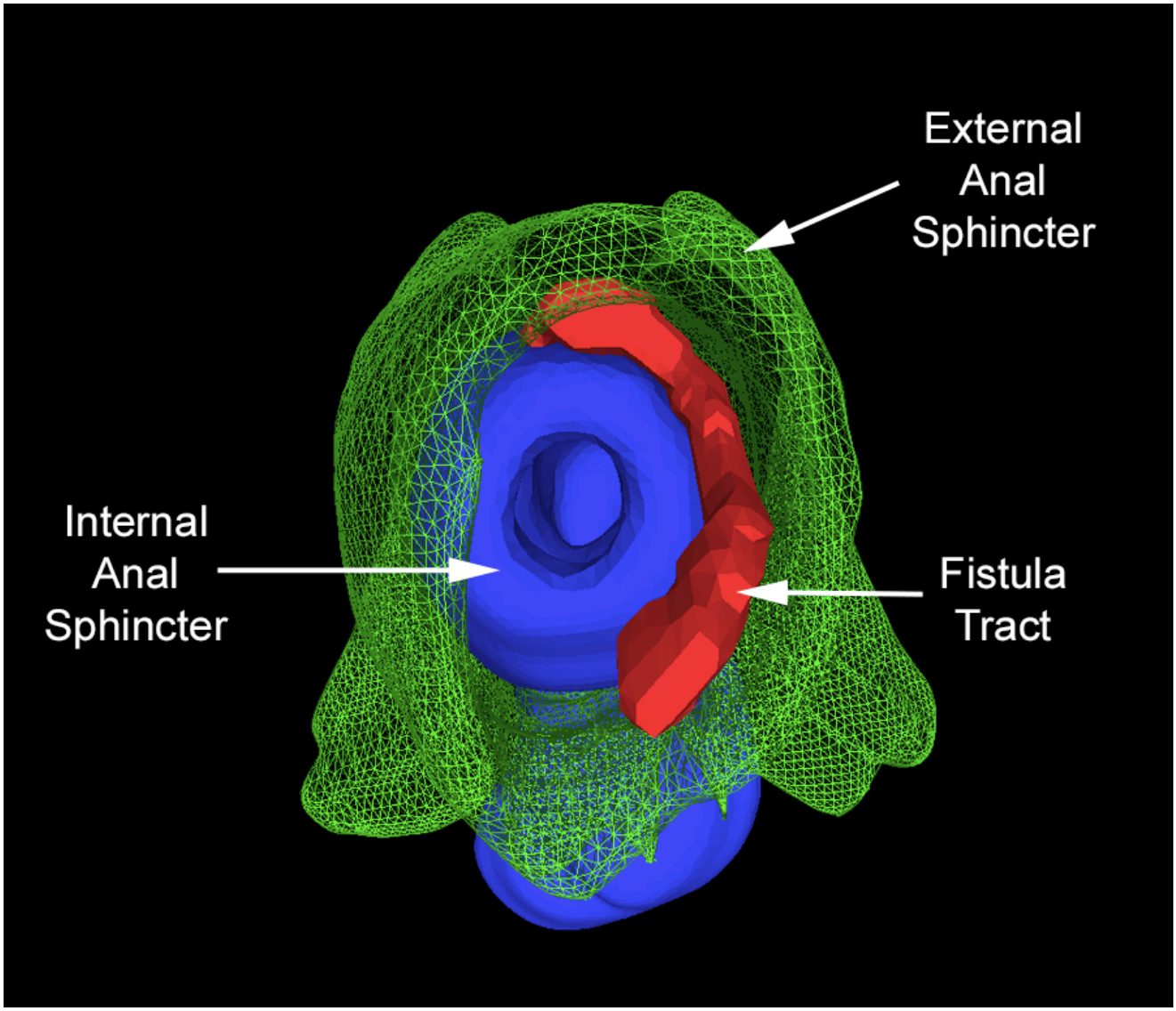


Figure 7-3. View of the sphincter complex with patient in lithotomy position showing the intersphincteric fistula.

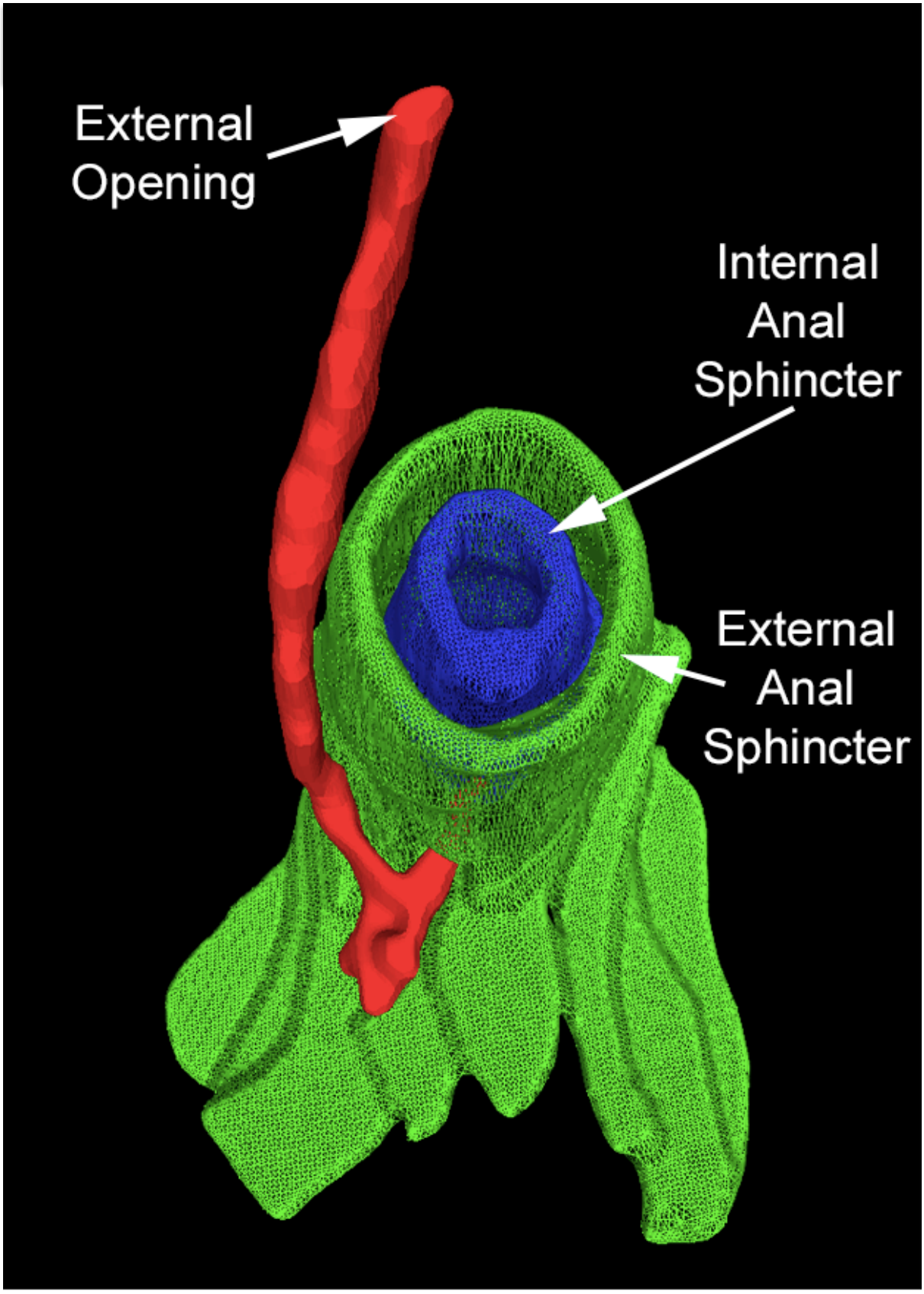


Figure 7-4. View of the sphincter complex with patient in lithotomy position and anal canal angled anteriorly showing the trans-sphincteric fistula.

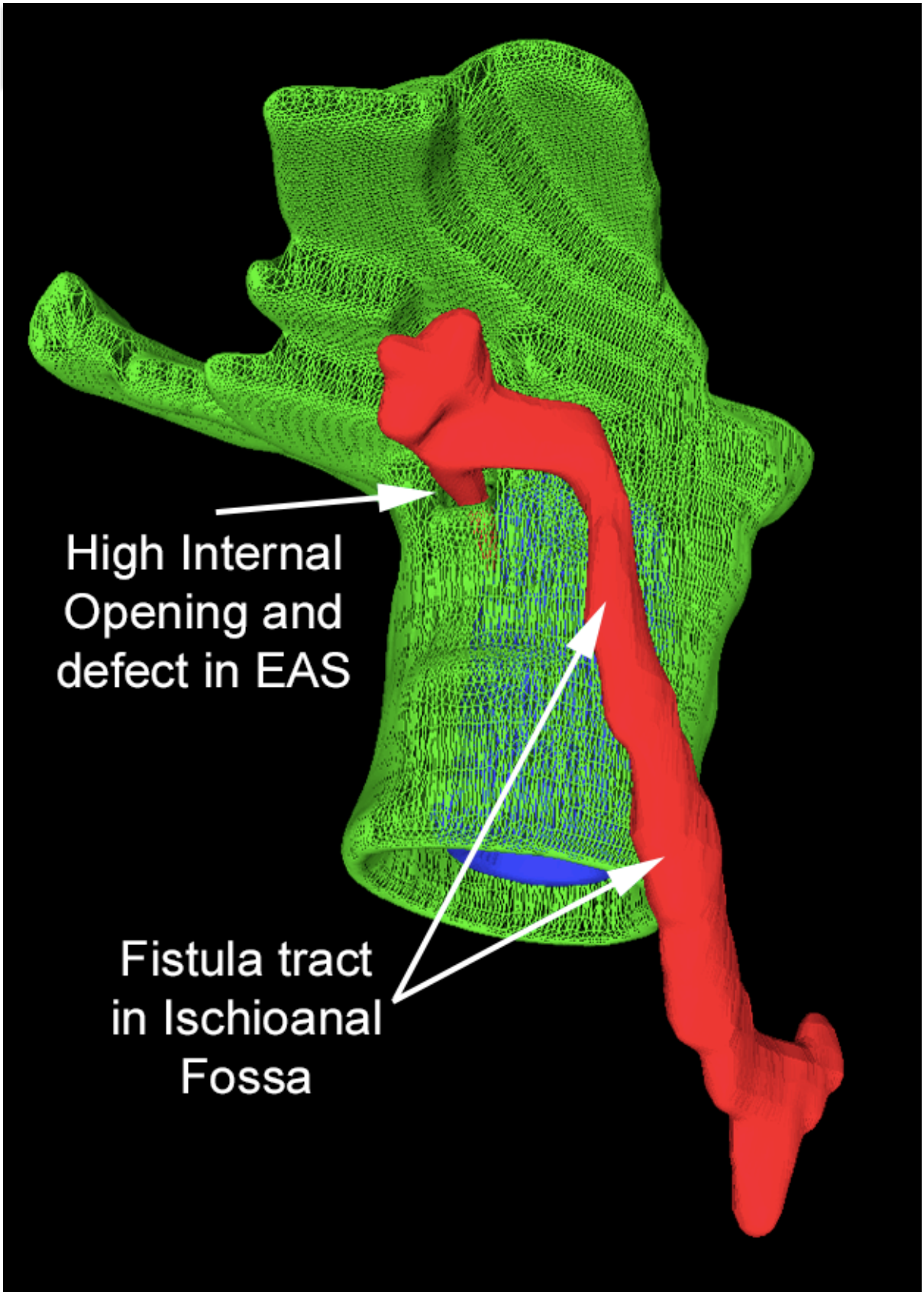


Figure 7-5. Angled view of the fistula from the right visualizing the ischioanal portion of the fistula, the defect in the external sphincter (mesh view) and the external opening.

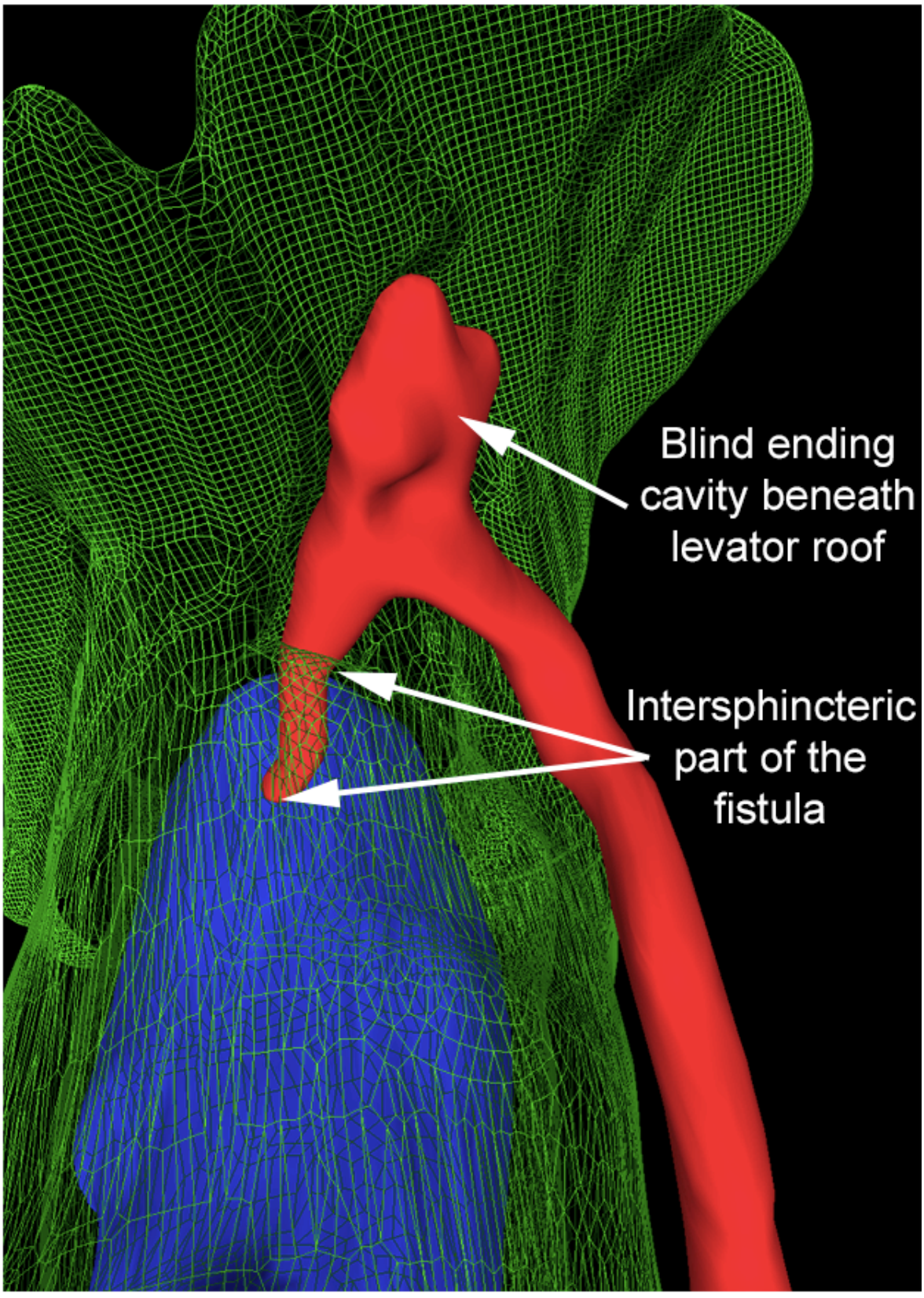


Figure 7-6. Close up view from the right visualizing the proximal fistula and defect in the external sphincter.

3D Images in animation

A more complex fistula is demonstrated in **Figure 7-7** with large supralevator and infralevator components. To further aid comprehension and allow for appreciation for the degree of sepsis, the sphincter complex has been reconstructed from a number of angles. In addition, **Figure 7-8, Figure 7-9, Figure 7-10** demonstrate comparison of the reconstruction with conventional 2D MRI scans.

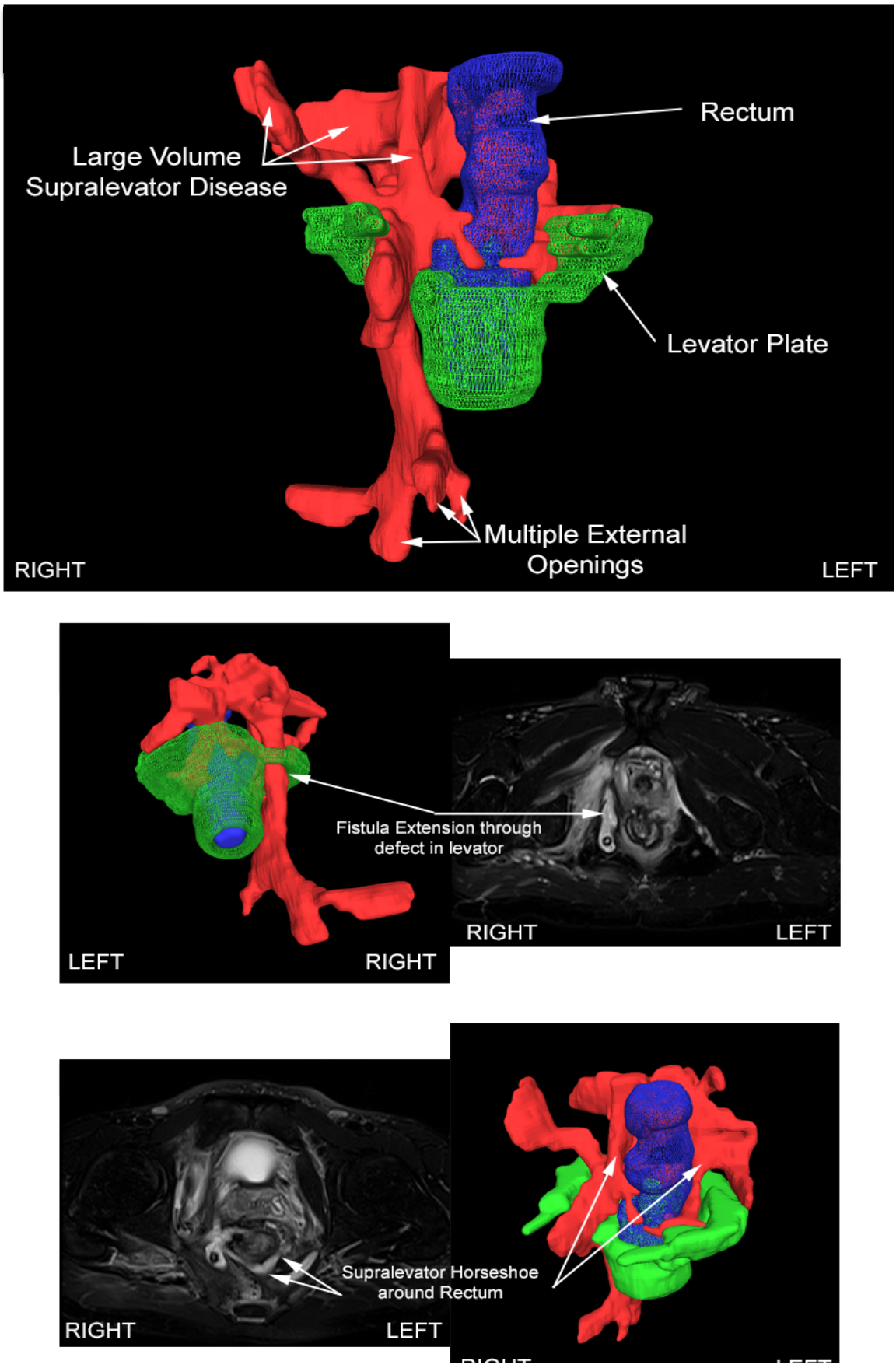


Figure 7-7. 3D reconstruction of a complex perianal Crohn's fistula with large supralevator and infralevator components.

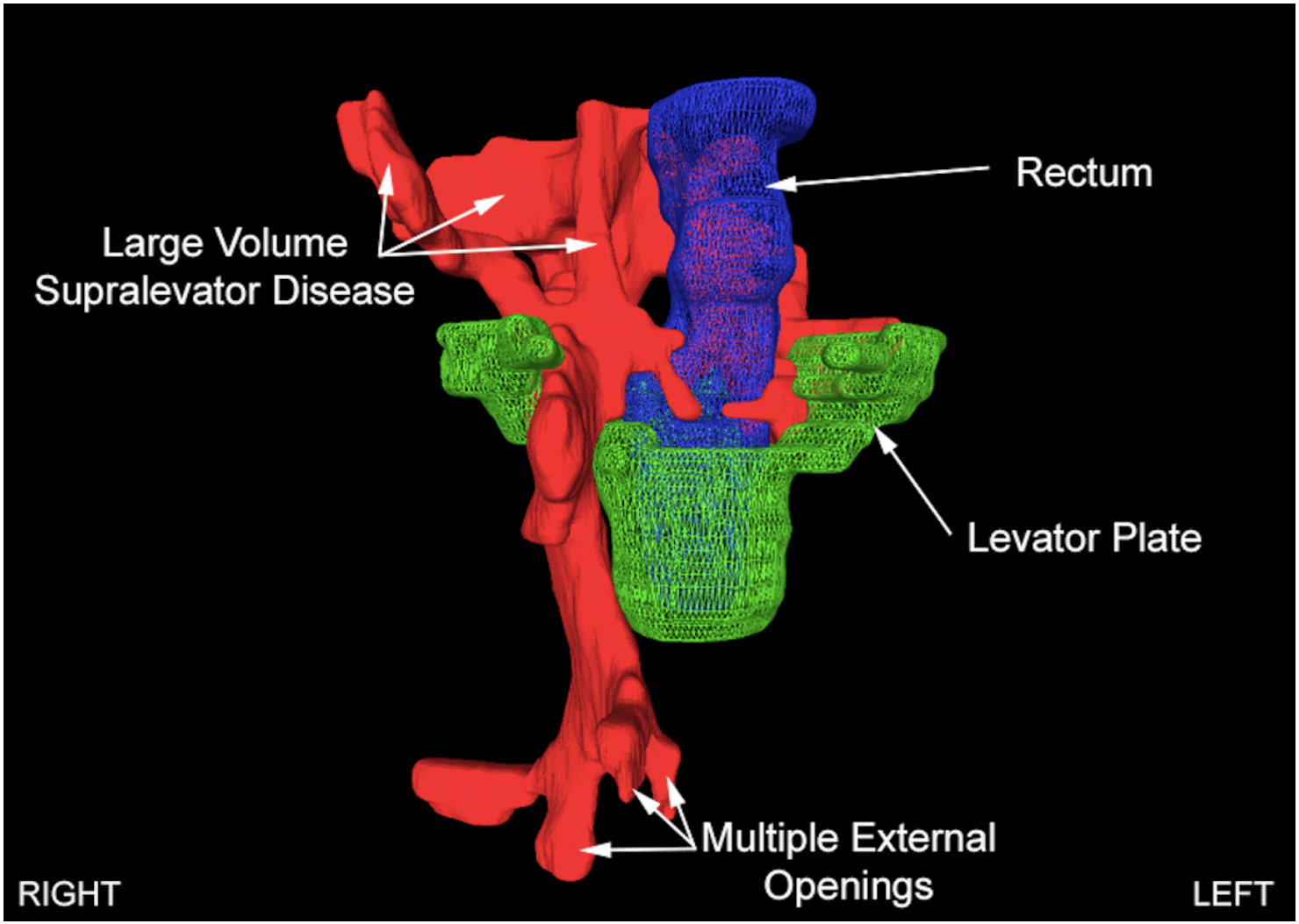


Figure 7-8. Anteroposterior view of the sphincter complex and levator plate with extensive fistulising disease.

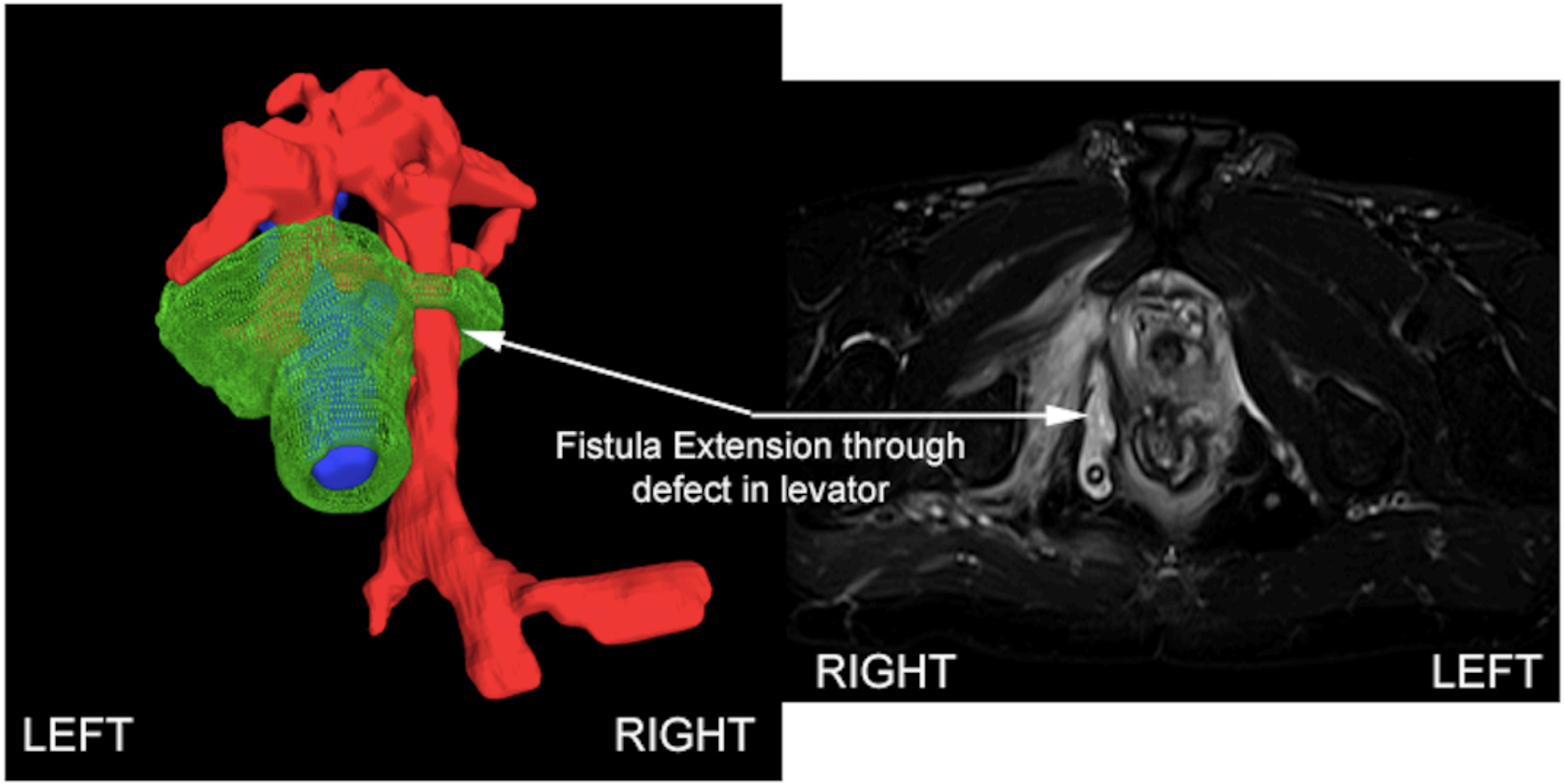


Figure 7-9. Angled view from the right of posterior sphincter complex showing fistula tract traversing through a defect in the levator plate on the right.

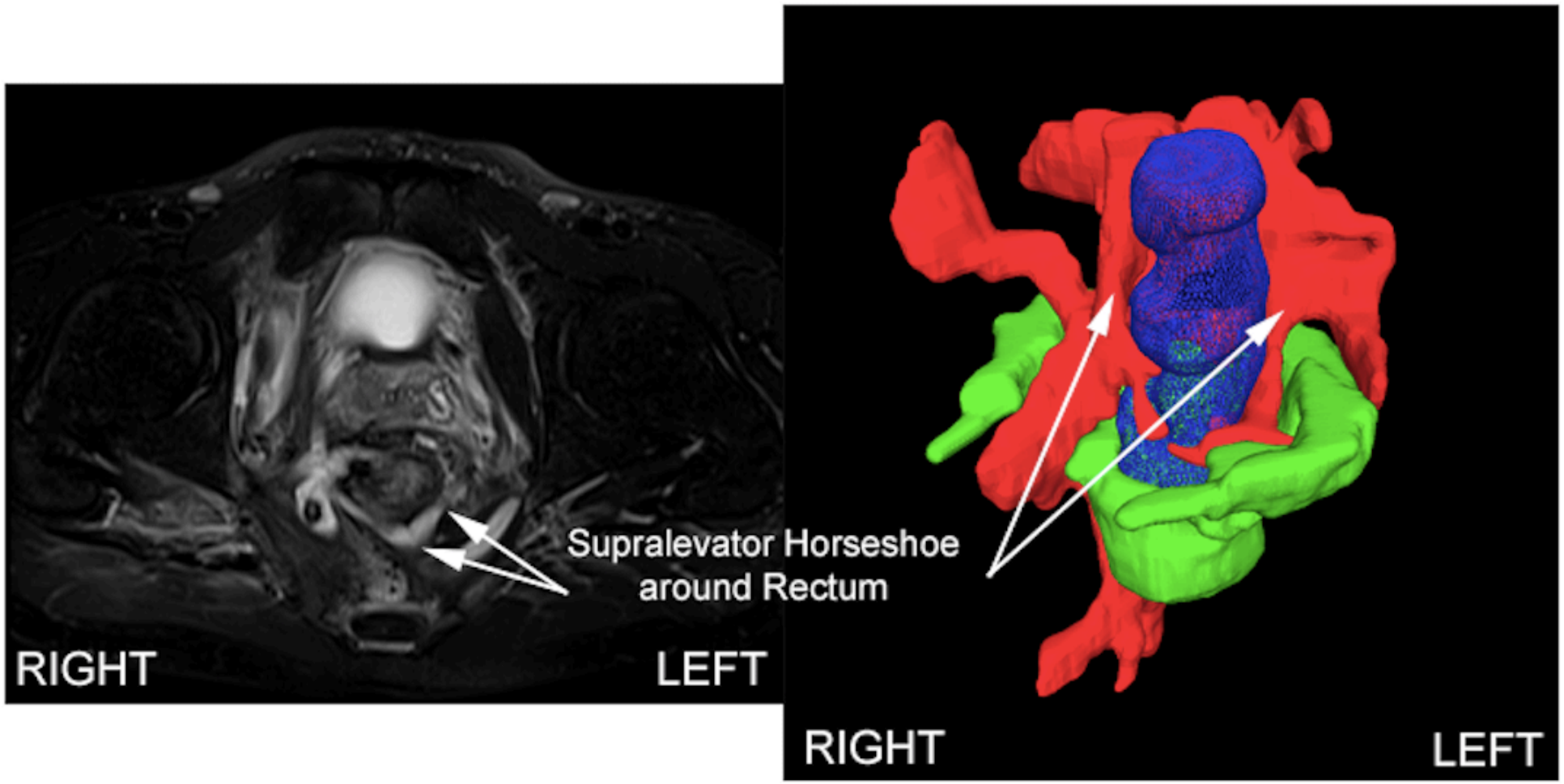


Figure 7-10. Angled view from the left of the anterior sphincter complex showing large volume supralevator extension around the rectum.

3D images on an app-based technology

In order to further improve understanding an animation was created. With the operating surgeon in mind, demonstrates the patient in the lithotomy position with the fistula complex shown in context, **Figure 7-11**. Various parameters are displayed towards the end of the animation, including fistula tract measurements (volume, surface area and length) and a distance between the anus and the internal opening.

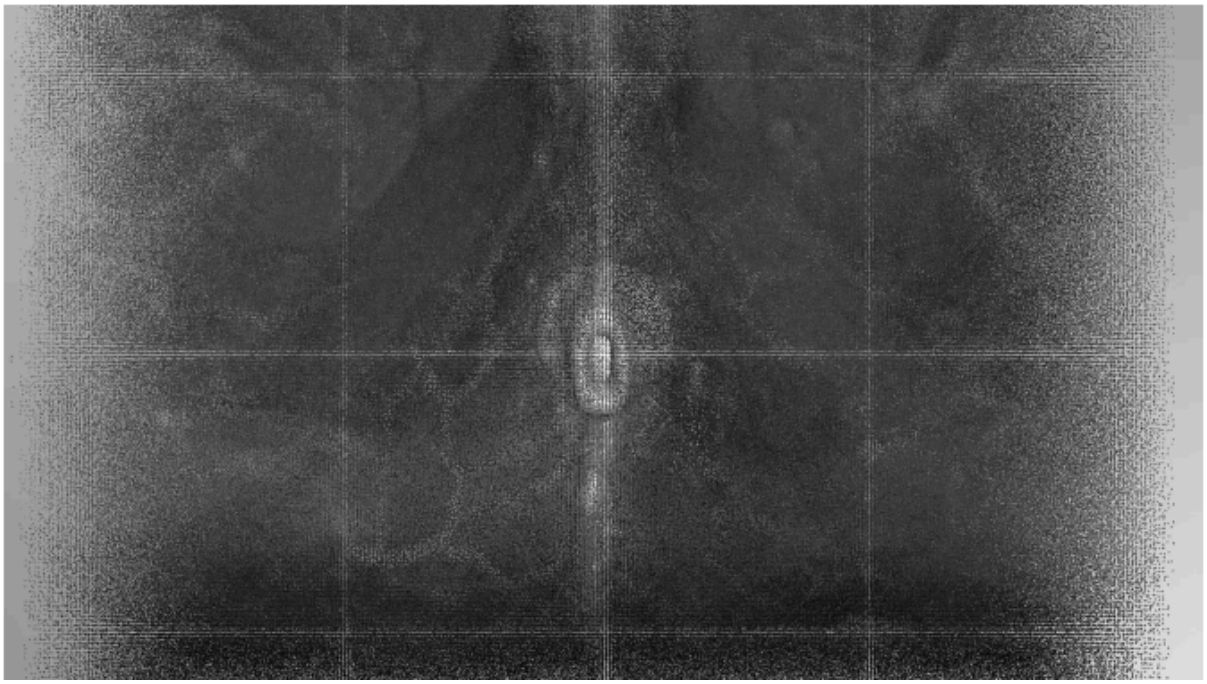


Figure 7-11 - Digital subtraction MRI from the surgeon's view of the patient in the lithotomy position

App-based manipulatable 3D images

The segmented fistula complex was then uploaded upon an app, in order to improve further the interface of learning **Figure 7-12**. Here the operator has the ability to manipulate the images in orientation and also to remove the surrounding structures (sphincter muscle and anal canal), allowing a detailed review of all aspects of the fistula anatomy from all angles.

1

2

3

4

5

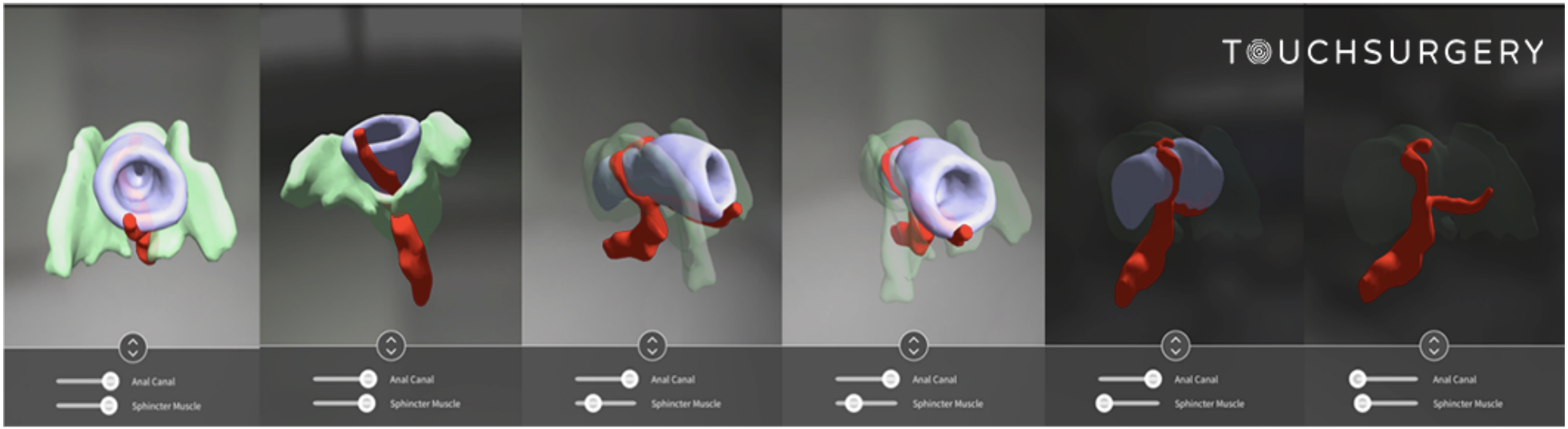


Figure 7-12. Screenshots of a segmented trans-sphincteric tract. The images denote the ability of manipulate the image on the screen and to also "ghost" the surrounding structure as the operator choses.

7.5 Discussion

Conventional 2D pelvic MRI is the imaging modality of choice to demonstrate fistula anatomy in perianal Crohn's disease. Surgeons acquire comprehensive understanding of fistula anatomy through a combination of radiology reports, discussion with radiologists and personal review of MRI images. However, shortcomings in any of these factors can limit surgical understanding to the detriment of surgical planning and outcomes. Perianal Crohn's fistulas are frequently complex, and it is important to reduce recurrence rates as each surgical intervention on the background of undrained sepsis leads to further tissue destruction and anatomical distortion, making subsequent procedures more challenging. Furthermore, appreciation of fistula anatomy in relation to the sphincter complex can help avoid complications such as incontinence. Techniques to improve understanding of the fistula and its relations based on MRI are likely to improve the chance of successful treatment. 3D MRI represents our attempt to improve a surgeon's acquisition of information for the MRI and we have demonstrated the accessibility of this technique in a number of platforms.

Whilst the underlying disease process can be unforgiving and result in treatment failure, one of the keys to avoid recurrence is to identify correctly and treat all secondary extensions, and drain any collections/abscess.[109] It may in some cases prove useful to undertake MDT discussion of complex cases, and for 'surgical rehearsal.' The surgeon could review the images via an app-based technology prior to operating and one might hypothesize that this may reduce the overall operating time.[311,312] It may also help the surgeon in choosing the type of operation best suited to the patient[312] for example by demonstrating the intersphincteric complexity which may preclude a LIFT procedure, or

by elucidating secondary extensions which would doom a fistula plug to failure.

There is an international appetite for the use of 3D modelling of complex perianal Crohn's fistula.[313] As well as surgical planning[314,315], other benefits to 3D modelling include (i) communication with patients to aid informed consent; and (ii) medical education.

The patient-clinician relationship is undoubtedly unique and a variety of factors, such as choice of language, prior understanding and interpersonal skills, govern success. Communication to the non-expert through 3D visuals is not a new area of research and as well as influencing clinical interactions, has a role in medico-legal cases and public education. A recent study on congenital heart defects quantified the benefit of 3D models in facilitating communication with patients.[316] The study also demonstrated patients' enthusiasm for the technique with over three-quarters of the study participants asking to keep the models. Patients with perianal Crohn's fistula are often young and have considerable knowledge through their own research on the Internet and through peer-to-peer discussions in online forums. They are often well versed in repeated procedures and are understandably anxious about post-operative incontinence and pain. 3D visualization in this patient cohort may be a hugely beneficial adjunct to aid communication and assist in establishing understanding and informed consent.

There has been considerable innovation within the field of medical education. Teaching through simulation, virtual reality and artificial reality are still in their infancy but are likely to be mainstays of education in the next decade.[317] Due to the complexity of tracts and their intimacy with the anal sphincter, perianal fistulas are an example of a topic that is not only hard to understand but also hard to teach. Such topics lend themselves to 3D

modelling very well. Much of the key to understanding the treatment options and the likely success is by deciphering the exact morphology of the tract(s), their relation to surrounding structures and the amount of sphincter involved in them. Having the option to rotate an animation around and remove layers from the nodal to better understand this is therefore particularly exciting.

MRI is the gold standard in fistula imaging and has been shown to reduce recurrence by up to 75% in patients with recurrent fistula-in-ano[318] and guide surgery.[319] T2 weighted images with fat suppression provide good quality scans and reconstructions. However, MRI has limitations, for example that the location of the internal opening can be difficult to ascertain[105]. Previous MRI innovations include reducing scan times by utilizing higher field strengths and greater signal-to-noise ratio,[320] breath hold image capture,[321] fat suppression[322] and the use of oral/intravenous contrast agents, such as gadolinium.[323,324]

3D printing and imaging have already shown huge benefits in other surgical specialties such as orthopaedics, with proven feasibility and accessibility.[325] Many of these reconstructions use CT rather than MRI, and it must be recognized that fistulas and the anorectum are harder to segment. However, the technique to create segmentations is reproducible and hence generalizable, although the accuracy is dependent on the expertise of the radiologist. As such, as the technology is advancing, this might be most appropriate for use in high-volume centres with specialist gastrointestinal radiologists. An alternative would be to have external expert sites performing the reconstructions remotely and interact in a virtual MDT format. Automated segmentation techniques have been described in other specialties[326,327,328] including abdominal MRI of Crohn's patients[329] and could be readily applied here.

7.6 Limitations

3D modelling is derived from conventional 2D MRI and image quality is essential during the modelling process. Our MRI parameters are standard when compared to other authors[330,331] enabling any centre to perform our techniques. A slice thickness of 4 mm allows satisfactory contrast between different components of the anal canal and fistula with good signal to noise ratio. Additionally, there are fewer slices through the anal canal, reducing time taken to segment the fistula and anal canal. However, segmentation using thicker slices result in blocky 3D images, which we found hard to interpret. Judicious use of smoothing algorithms was necessary to deliver a smooth structure. Smoothing may be reduced where thinner slices are used, but is still necessary, and this is associated with a significant time cost. We found the oblique transverse plane orthogonal to the anal canal is the simplest plane in which to perform segmentation; other planes suffer from partial volume artefact where the structure is parallel to the plane. Whilst the benefit is somewhat intuitive, a randomised controlled trial of learning could show a demonstrable effect.[332]

7.7 Conclusion

In conclusion, this proof of concept study on 3D reconstruction has demonstrated how the technique has the potential to improve surgical understanding, improve surgical decision-making, augment training and aid patient comprehension for informed consent. It represents a readily accessible innovation in the field and is translatable to other pathologies.

8 Innovation in the imaging of perianal fistula using 3D printing and MRI fistulography: a step towards personalised medicine and the application to training.

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8.1 Abstract

Introduction

Perianal fistula is a topic both hard to understand and to teach. The key to understanding the treatment options and likely success, is deciphering the exact morphology of the tract(s) and the amount of sphincter involved.

Our aim was to explore alternative platforms better to understand complex perianal fistulas through 3D imaging and reconstruction, using 3D printing and a new technique – MRI fistulography. With a focus on bringing together our previous work in the previous chapter to illustrate the specific benefit to surgical training.

Methods

Digital imaging and communications in medicine (DICOM) images of Spectral Attenuated Inversion Recovery (SPAIR) MRI sequences were imported into validated open-source segmentation software. A specialist consultant gastrointestinal radiologist performed segmentation of the fistula, internal and external sphincter.

Segmented files were exported as STereoLithography (STL) files and Cura (Ultimaker Cura 3.0.4) was used to prepare the files for printing on an Ultimaker 3 Extended 3D printer.

Animations were created in collaboration with Touch Surgery™. A 3D camera was used to create immersive reality footage.

Results

Three examples of 3D printed models demonstrating complex perianal fistula were created. The anatomical components are displayed in different colours: Red: Fistula Tract; Green: External Anal Sphincter and Levator Plate; Blue: Internal Anal Sphincter and Rectum. One of the models was created to be split in half, to display the internal opening and allow complexity in the intersphincteric space to better evaluated.

An animation of MRI fistulography of a trans-sphincteric fistula tract with a cephalad extension in the intersphincteric space was also created.

Following this, three complex cases were chosen, and the trainee used an immersive reality platform to view the 3D images whilst the surgeon was described each case. The

3D reconstructions were added post-production to illustrate the concept of an augmented reality platform.

Conclusion

MRI is the reference standard for assessment of perianal fistula, defining anatomy and guiding surgery. However, communication of findings between radiologist and surgeon remains challenging. 3D reconstructions of complex perianal fistula are feasible with the potential to improve surgical planning, communication with patients and augment training.

The next phase is to create a true immersive reality-learning environment, and to apply it to wider audiences. 3D reconstructions of complex fistula are feasible with the potential to improve surgical education and augment training.

8.2 Introduction

Crohn's perianal fistulas are frequently complex, with patients suffering from reduced quality of life[87]. MRI is the gold standard[77] for fistula imaging with scans informing clinicians about fistula complexity: the morphology of the tracts; presence of extensions/sepsis and the relation to the anal sphincter. Longitudinally, it is used to assess a patient's response to treatment. The disease process itself is frequently refractory, with high recurrence and reoperation rates.[85,292,66] A vicious cycle often ensues due to the combination of a recurrent inflammatory process and distortion of the anorectum from scar tissue following each operative procedure.

Despite improvements in fistula imaging and increasing use of additional scan techniques and contrast, conceptualisation of the fistula can be difficult. Understanding of complex fistula anatomy by surgeons is sometimes mediated through interactions with radiologists either informally or through multidisciplinary meetings but may still prove challenging. Also, not all surgeons review imaging with radiologists; it is not always possible in environments such as busy clinics or in theatre, where better methods than written reports are needed to convey satisfactory understanding for surgery. Explaining fistula anatomy and options for surgery to patients amplifies these challenges further, which impact their ability to make management decisions.

There has been an influx of novel techniques to treat perianal fistulas[129] of which Video Assisted Anal Fistula Treatment (VAAFT) is one. A recent meta-analysis found that mean operative time was 42+/-14.2 min, that the internal opening was identified in 85.7% of patients, and that recurrence occurred in 112 (14.2%) patients after a median follow-up

of 9 months.[333] However, this underestimated the complexity encountered in Crohn's fistulas as only 13 of the 788 patients included in the meta-analysis had Crohn's disease, and these findings need to be interpreted with caution. It is the first of the novel procedures that combines a diagnostic phase with intervention and highlights the surgeon's desire for the operator to obtain a peri-operative mechanism to understand tract morphology. The technique uses a rigid endoscope of fixed diameter, which makes visualisation difficult in some cases and impossible in others, particularly in complex Crohn's fistula and/or curved tracts. Whilst the technique is not used worldwide, the authors of this paper have found the technique particularly useful in complex Crohn's perianal fistula.[334]

3D reconstructions offer no new information to the 2D image but aims to improve conceptualisation, whereby a multitude of 2D pictures/slices, separated by a predetermined slice thickness, are "stacked" upon each to create a 3D representation.[335] 3D imaging provides a more realistic representation of anatomy, based on cross-sectional data that been shown to be a useful aid for patient education, clinical communication[307] and surgical planning.[308] The optimum medium of 3D reconstruction with reference to improving communication and understanding, may vary according to the target audience which may be expert (consultant surgeon), intermediate (trainee or medical student) or novice (lay public/patient). The St Mark's IBD patient panel, when shown previous 3D reconstructions by our institution,[336,337] suggested 3D printing as a viable alternative. All media require further evaluation not only for acceptability and efficacy, but also resource use (availability of the necessary technology, cost and time).

We postulate that a physical representation of the fistula will further improve patient and

surgeon understanding (or at least facilitate acquisition of understanding), and also that a 'virtual VAAFT' or MRI fistulography, may help surgeons approaching the fistula in theatre with a probe or VAAFT scope.

We have therefore developed these two further innovations for subsequent assessment. We describe the feasibility of creating 3D printed fistula models and MRI fistulography. In addition, we illustrate the benefit of the reconstructions in a video vignette highlighting the benefit of 3D reconstructions for surgical training.

8.3 Methods

Ethical approval

After consultation with the local Research and Development (R&D) department (London North West NHS Trust), it was advised that approval by a National Health Service (NHS) research ethics committee or the R&D department was deemed unnecessary owing to the non-patient identifiable retrospective nature of this feasibility study. The study received departmental approval by the research lead of St Mark's Hospital, London, United Kingdom.

MRI technique

Standard T2-weighted Spectral Attenuated Inversion Recovery (SPAIR) MRI sequences were acquired in axial (TR 8000; TE 96; thickness 4 mm; gap 0.2 mm; FOV 240 mm; averages 4, flip angle 150, bandwidth 130Hz/PX) and coronal (TR 8860; TE 89; thickness 4 mm; gap 0.2 mm; FOV 250 mm; averages 4; flip angle 150, bandwidth 130Hz/PX) planes, with a sagittal T2-weighted BLADE sequence (TR 5400; TE 100; thickness 3 mm;

gap 0.9 mm; FOV 290 mm; averages 1; flip angle 150, bandwidth 362Hz/PX; BLADE coverage 200%).

Segmentation

Digital imaging and communications in medicine (DICOM) files of the MRI sequences were generated from picture archiving and communication system (PACS) and these were segmented and smoothed using validated open-source software.[305,338] A specialist consultant gastrointestinal radiologist manually segmented the following structures using axial sequences: fistula tract; internal sphincter; external sphincters/levator plate; and rectum.

The segmented files were exported as STereoLithography (STL) files. We used Cura (Ultimaker Cura 3.0.4) to prepare the files for printing on an Ultimaker 3 Extended 3D printer. The animation, titled MR fistulography was created in collaboration with Touch Surgery™ from the STL files.

In order to conceptualise the proposed benefit to trainees a video vignette was created to illustrate the peri-operative management of three complex fistula cases (https://www.youtube.com/watch?v=SGrHjfH55vI). A 3D camera was used to create immersive reality footage. Separate 3D reconstructions were added post-production to illustrate the concept of an augmented reality platform.

8.4 Results

3D printing

2D axial MRI scans were segmented for three patients detailing the fistula complex, are shown in **Figure 8-1**. The various anatomical components are displayed in different colours (Red: Fistula Tract; Green: External Anal Sphincter (EAS) and Levator Plate; Blue: Internal Anal Sphincter (IAS) and Rectum). Segmentation of patient images took approximately 15 minutes per case. A further 10 minutes was required for smoothing and uploading the images to the 3D printer. Each of the models took approximately 60 minutes to make.

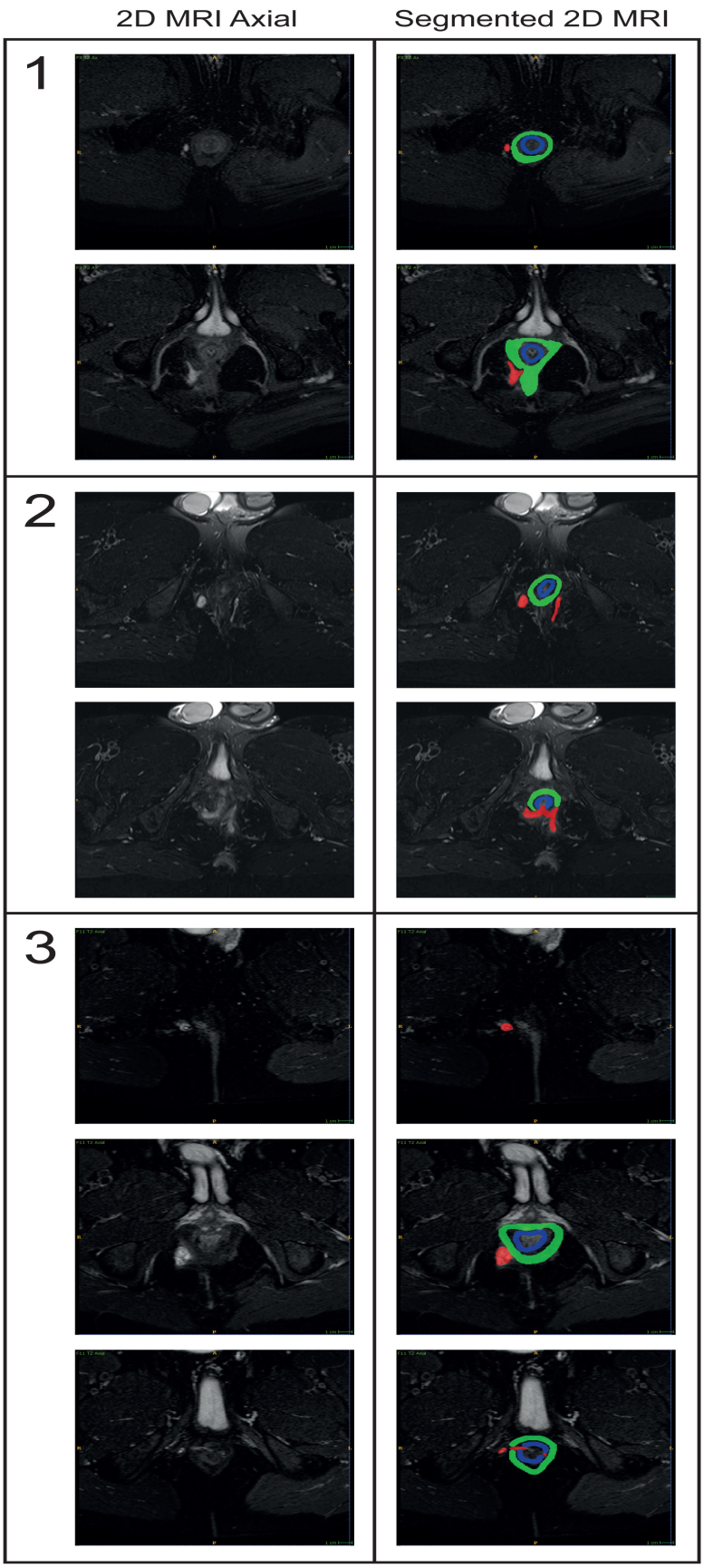
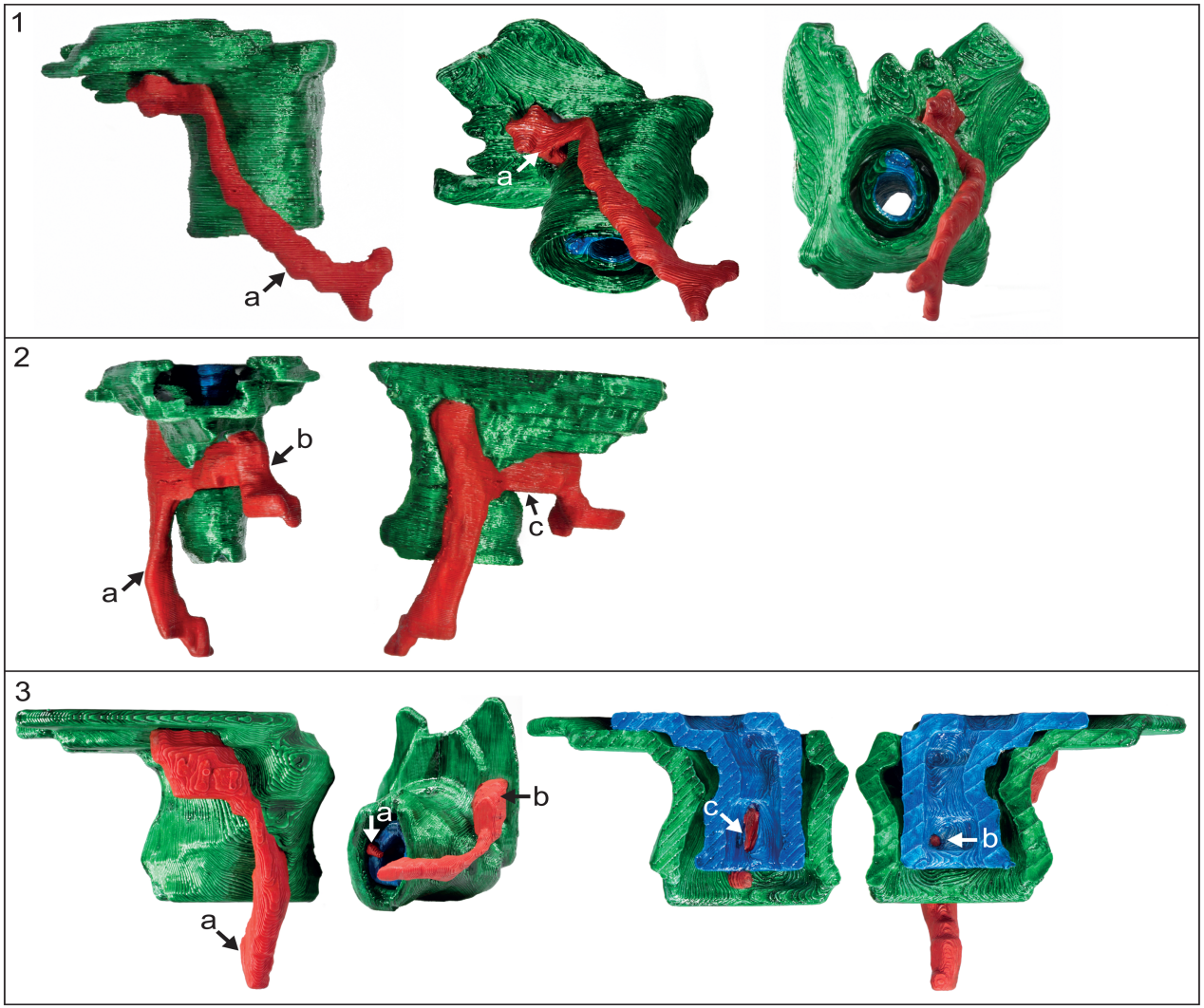


Figure 8-1. 2D axial scans with fistula complex segmented. The various anatomical components are displayed in different colours (Red: Fistula Tract; Green: External Anal Sphincter (EAS) and Levator Plate; Blue: Internal Anal Sphincter (IAS) and Rectum).

Figure 8-2 shows various orientations of the 3D models for the same patients. 1) is a transsphincteric fistula (black arrow) with a small blind-ending cavity (white arrow) beneath the levator plate. 2) is a transsphincteric fistula with the right tract (black arrow) passing through the ischioanal fossa and the left tract (double black arrow) being blind ended, connecting via a posterior horseshoe (triple black arrow). 3) shows a right-sided transsphincteric fistula (black arrow) with a blind-ending cranial extension below the levator (double black arrow), and a short left-sided intersphincteric fistula (white arrow). Internal openings of the right transsphincteric fistula (double white arrow) and left intersphincteric fistula (triple white arrow) are shown on the internal views of the composite model. Of note, the final 3D model has been created so it can come apart to demonstrate the internal opening and complexity in the intersphincteric space.



1

2 **Figure 8-2. 3D perianal anal fistula models; 1. Trans-sphincteric fistula with an infra levator extension 2. Trans-sphincteric fistula with a horseshoe 3. Complex trans-**
3 **sphincteric and intersphincteric fistula.**

MRI Fistulography

An animation demonstrating a trans-sphincteric fistula with a cephalad extension in the intersphincteric space is shown in *Error! Reference source not found.* (fistula-red, internal sphincter-blue, external sphincter/levator plate- green). In the animation clip, which is in the form of a 'fly through' akin to virtual colonoscopy, the video demonstrates when the tract passes through the sphincters with a colour change.

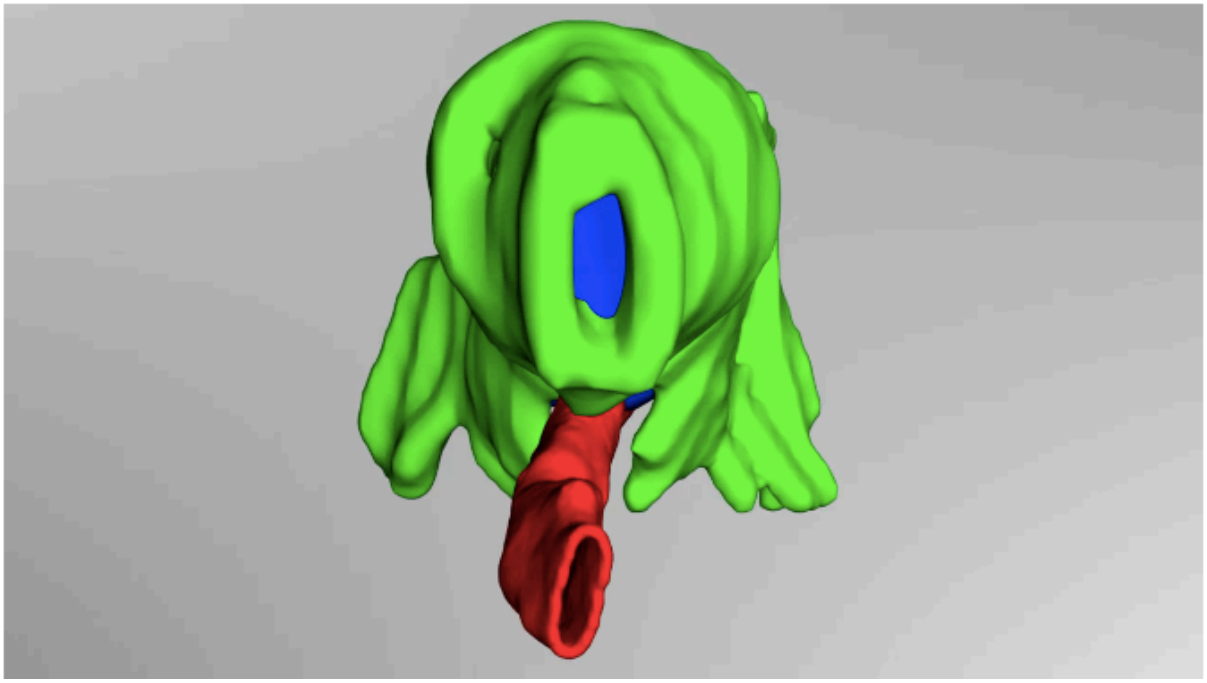


Figure 8-3 - MRI fistulography

Video Vignette

Three potential stakeholders have been described in reference to the utility of 3D reconstructions; trainees, the operating surgeon and patients. The video vignette, (https://www.youtube.com/watch?v=SGrHjfH55vI),[339] describes the peri-operative decision making for three complex perianal fistula cases with the consultant surgeon explaining the morphology and treatment options to a surgical trainee. The trainee uses

an immersive platform to view pre-segmented reconstructions on the headset that the consultant has chosen to guide the trainee through the difficult case.

8.5 Discussion

Conventional 2D pelvic MRI is the imaging modality of choice to demonstrate fistula anatomy in fistula-in-ano[340] and has been shown to reduce recurrence by up to 75%[318] when used to guide surgery.[319] The innovations described in this paper are derived from conventional MRI and do not provide any additional anatomical information or require additional sequences, but they do change the medium by which this information is communicated to surgeons, and beyond. 3D printing and MRI fistulography represent further attempts to improve a surgeon's understanding of information from the MRI but could also have similar benefits in the explanation to patients and trainees.

Our MRI parameters are standard compared to other institutions[330,331], allowing for ease of adoption of the technique to other centres. A slice thickness of 4 mm provides satisfactory contrast between different components of the anal canal and the fistula with good signal to noise ratio. Additionally, there are fewer slices through the anal canal, reducing time taken to segment the fistula and anal canal. With technology advancing rapidly, these innovations represent the first step to automated segmentation techniques that have been described in other specialties[326,327,328], including abdominal MRI of Crohn's patients[329], and could become the standard of care for perianal fistulas.

In Crohn's perianal fistula, the underlying disease process can be unforgiving and sustained remission can only be achieved in 26–50%.[81] One of the key objectives to reduce recurrence is to identify correctly and treat all secondary extensions and drain any collections/abscess.[109]

VAAFT is a recent innovation which aims to address both aims[267]. Criticisms of the technique are that the rigid scope limits manoeuvrability and as with any technique, it carries an associated new expense and a learning curve. MR fistulography may facilitate novices in the 'diagnostic' phase to climb the learning curve faster, helping them to identify/negotiate tracts with the potential to limit overall operative time, whilst providing a 'road-map' for more challenging fistulas, aiding identification of secondary extensions which might otherwise be missed and lead to inevitable recurrence. And of course, the same benefit would apply to other reparative techniques performed with a clearer understanding of the tract anatomy.

For surgeons, a 3D model can potentially aid understanding of the complex relationship between sphincter anatomy and fistula, guiding surgical decisions and improving outcomes. Our initial experience was of "whole" printed models, which allowed for an overall appreciation of the anatomy, but had similar benefits to 3D images. As our experience grew, we sought to deliver visualisation of intersphincteric complexity and identification of key anatomical landmarks such as the internal opening, through the creation of composite fistula models that can be separated to highlight internal structures. 3D printed models represent a 'concrete' step toward personalised medicine[341]. Whilst the technique offers an intuitive benefit, clinical utility maybe difficult to ascertain. Any effect is likely to be harder to demonstrate amongst 'experts' but may

have benefit to those surgeons with less experience and as such we envisage the junior trainee may benefit the most. It was for this reason that the video vignette was created to specifically illustrate the benefit to the trainee. One could extrapolate further from this and in the future see an audience wearing a similar headset whilst watching an expert in a live operating session.

As illustrated in the video there are huge potential benefit in medical education. Due to the complexity of tracts and their relationship with the anal sphincter, perianal fistulas are an example of a topic that is not only hard to understand but also hard to teach. Such topics lend themselves to 3D reconstructions very well. Much of the key to understanding the treatment options, difficulties and likely success of surgery is in deciphering the exact morphology of the tract(s) and the amount of sphincter involved. If the trainee does not understand the fistula, they cannot plan surgery, consent patients or understand how their consultant does so. We have previously demonstrated an international appetite for 3D reconstructions at an international conference at which 85% of respondents expect 3D modelling to be useful for perianal fistula surgery and 88% would use 3D modelling if available.[342]

The patient-clinician relationship centres around shared decision making, with the clinician offering options with their associated risks and benefits, and patients deciding which options are most appropriate to their own balance of symptoms and goals. A variety of factors including the patient's prior understanding and the clinician's interpersonal skills, as well as the complexity of the decision and a balance of the patient's ability to understand and the clinician's ability to explain, govern the success of this decision-making process. Some of these factors are not modifiable but clinicians can

improve their delivery of information, including by using adjuncts. When the complexity is related to anatomical understanding, 3D models provide a theoretical advantage. An example of this benefit was demonstrated in a recent study on congenital heart defects, which quantified the benefit of 3D models in facilitating communication with patients.[316] The study also demonstrated patients' enthusiasm for the technique with over three-quarters of the study participants asking to keep the models. Further work is needed to confirm this in patients with perianal Crohn's fistula, particularly in facilitating informed consent.

The precise metric needed to demonstrate clinical utility is part of future work. We postulate that the metric will be stakeholder (surgeon – generalist vs. specialist, trainee, patient) and time specific (pre-, peri-, post-operatively – such as in describing the nature of a case to a lay audience as part of a medico-legal proceeding). Future improvements in clinical applicability in terms of raw materials to print with, speed of printing and reduced costs are likely to make 3D printing more widespread.[343] Ultimately, the benefit of these techniques in patient understanding, training of junior surgeons and communication between radiologist and surgeon, need to be demonstrated in further work, underway at our institution.

8.6 Limitations

There are several limitations of this proof of concept study. Firstly, expertise is required to create the 3D models and fistulography. The accuracy of the segmentation of the fistula and the sphincter complex is dependent on the radiologist but the technique is generalizable and uses open-source software. The use of 3D printing is increasingly widespread, and institutions in which a need exists for such models are often affiliated

with universities who might grant access to 3D printers. An additional resource consideration is cost (printer and materials) and as such, one may choose to limit such techniques to complex and/or refractory cases. Separate 3D reconstructions were added post-production to illustrate the concept of an augmented reality platform. This was chosen to serve as method to appreciate the feasibility as and not to deceive the audience. Indeed, the next phase is to create a true immersive reality-learning environment, and to apply it to wider audiences. 3D reconstructions of complex fistula are feasible with the potential to improve surgical education and augment training.

Ultimately, applicability of this technique beyond the experimental, will depend on a quick, cheap easy process to produce the 3D models, and a clear demonstrable benefit found in outcomes relevant to the group studied. These goals are beyond the scope of this feasibility study and represent future work, currently underway at our institution.

8.7 Conclusion

3D printed models and MRI fistulography have been developed with specific functions in mind. We suggest that 3D printed models will offer a medium which will enhance the education of trainees and provide a useful adjunct for communication with patients. It will be difficult to demonstrate improvement in surgical outcomes. MRI fistulography is a concept that has been derived from the success of virtual colonoscopy and offers the operating surgeon a realistic road map to follow. Both of these innovative techniques offer intuitive advantages to surgeons, trainees and patients which need testing in future objective assessments.

Thesis Discussion

8.8 Main Findings of the Thesis

During this thesis, several aspects of the necessary background information to perform a clinical trial on perianal Crohn's disease have been established. In addition, various forms of 3D imaging modalities have been created to aid with communication of this complex disease between different health care professional and with patients.

When considering the PICO criteria for clinical trial design, Section A, has provided the necessary epidemiological data for the population, not only of perianal Crohn's disease but also of the comparator group, idiopathic fistulas. Section B has used a Delphi process to establish and inform a core outcome set for trials on perianal Crohn's disease. Section C has demonstrated the subjectivity of our current radiological standard and proposed a viable objective outcome tool. Finally, Section D, contains a variety of different media of 3D presentations considering the views of patients and genuine co-creation.

Section A

This section discusses the role of an anorectal abscess as a precursor lesion to a fistula and identifies an overall rate of progression and in addition a similar rate for idiopathic, ulcerative colitis and Crohn's disease presentations. An incidence (Age Standardised Rate) of *first-time* admissions with an abscess as 20.2 per 100,000 in England. Has been derived. Approximately a sixth of all patients develop a fistula following an abscess, surprisingly women have the greatest risk, although both abscess and fistula are more common in men. Independent predictors of fistulation following abscess drainage were

found to be female gender, age 41-60yrs and location of the initial abscess as ischiorectal or intersphincteric. Nearly half of all patients with Crohn's abscesses develop a fistula with the majority occurring within the first 12 months and 2.8% of patients with an anorectal abscess but without a diagnosis of Crohn's disease will be found to have the disease after a median of 14 months.

This study is the largest to date with the longest follow up investigating demographic and diagnostic predictive markers of fistula formation. We report a large number of observations, over fifteen years with almost complete data capture, which makes these findings reflective of the population. A representative incidence of new abscess admissions has been derived. Independent predictors of fistula development from preceding abscesses have similarly been described and the role of inflammatory bowel disease has been explored.

The findings from the subsequent chapter aimed to validate these findings. Patients presenting with anorectal abscess to a district general hospital over an 11-year period were studied. Whilst men were more likely to present with an abscess overall and regardless of the presence of Crohn's disease, women were more likely to develop a persistent fistula following anorectal abscess drainage. One in seven patients developed a fistula following anorectal abscess drainage overall, rising to just under a third of patients with CD. Crohn's disease increased the risk of persistent fistula after anorectal abscess drainage more than twofold. Patients with diabetes developed persistent fistula after abscess drainage less commonly than those without diabetes. Location of the anorectal abscess, comorbidity and patient age were not associated with an altered risk of fistula. The strength of this study is that the rate of, and risk factors associated with,

fistula formation are in line with our previous administrative dataset study in England, corroborating the findings from the Hospital Episode Statistics (HES) database for perianal sepsis. In addition, it confirms our previous finding that female gender is a risk factor for developing a fistula following abscess drainage, contrary to the findings of other studies, and surgical dogma.

It is our view that the findings in diabetic patients and in terms of the association between gender and fistula following abscess drainage, support the idea of the separation of aetiology and persistence. In short, that some patients are predisposed to fistula formation/persistence, and that these factors might be different to those which drive abscess formation. For example, diabetic patients might be expected to develop more superficial infections, or indeed cryptoglandular infections, but by a mechanism of reduced immune competence rather than the factors which are likely to drive fistula persistence, which we have discussed separately.[344] By the same token, men seem more likely to develop abscesses than women – in women, when an abscess appears it is more likely to be via the mechanism which will drive fistulation or fistula persistence, rather than alternative mechanisms such as lifestyle factors, or a relationship to hair or sweating, which might influence superficial infections. These hypotheses are untested but the gender differences seen in both national and local data warrant further investigation.

Section B

There are currently a number of different treatment regimes, both medical and surgical, for perianal Crohn's disease. Often such a variety of options suggests that there is no

single good way to treat the condition and a nuanced management strategy is needed. Despite this fact, identification of the current gold standard of treatment is challenging to ascertain. A lack of standardised outcome measures hampers effective analysis and comparison of data when comparing treatments in fistulising pCD. To this end a core outcome set for fistulising pCD was developed.

The process commenced with a systematic review of the contemporary literature and demonstrated the degree of heterogeneity in the outcome measures used in fistulising pCD studies. The individual outcomes were categorised into analogous concepts resulting in eighty-nine unique outcomes across 49 studies being identified. Of note, no outcome was reported universally. Reporting of and defining secondary outcomes were less robust than for primary outcomes and only a third of authors explained the rationale behind their choice of outcomes. Heterogeneity in the definition of healing was particularly marked and only one in four studies used at least two time points to measure success, despite the relapsing remitting nature of Crohn's disease including anal fistula. Our review has demonstrated that the most common scoring tools used are: ≥50% tracts not draining on clinical examination[160] (part of the fistula drainage assessment), PDAI[259] and CDAI[152]. All are subjectively assessed and there remains no universally accepted objective measure of success in this field.

The extensive list of candidate outcome measures generated through systematic review was combined with additional outcome measures suggested by patients. Using an online tool, a large number of stakeholders were able to participate in a pragmatic Delphi consensus process that ensured emphasis on patient perspectives and clinical relevance. Consensus voting, and discussion generated a COS that all stakeholders supported with

applicability to all study designs. The COS allows measurement of outcomes for all cohorts of adult pCD patients, regardless of disease state, the intervention under assessment or the presence of luminal disease. Through this study, and using rigorous methodology and representative stakeholder engagement, we established an eight-domain core outcome set (COS) for use in studies evaluating interventions in fistulising pCD.

Our core outcome set has one the largest number of participants and the lowest attrition rates to date. Groups assessing treatment in fistulising perianal Crohn's disease should be strongly encouraged to adopt and use this core outcome set, to reduce the heterogeneity of outcome reporting and improve the quality and comparability of future research. Application of the COS will reduce heterogeneity in outcome reporting, thereby facilitating more meaningful comparisons between treatments, data synthesis and ultimately benefit patient care. With the aim not only to improve research but also to use this COS as an impetus to drive improvement in clinical management within the field.
Having identified the important outcomes, the next phase is to consider measures which can be used to identify improvement in those outcomes.

Section C

Despite the creation of a core outcome set, the field of perianal Crohn's disease is still missing an objective measure of success. Arguably, patient reported outcome measures are the most appropriate method to measure successful treatment, certainly from a qualitative point of view, and our group is working to develop such a tool for patients with pCD. However, for patients and techniques necessitating radiological evaluation, for

example techniques or medications which claim healing of anal fistula, the current standard is subjective and contains substantial heterogeneity within and between studies.

This pilot study has shown that volume of perianal fistula tracts in patients with Crohn's disease can be reliably measured by MRI with very good inter- and intra-observer agreement. Manual measurement of fistula volume took a relatively short time (up to 4 minutes 10 seconds) with the difference between readers likely related to experience. Objective fistula volume measurement can be applied to very complex disease that involves multiple tracts and collections, which are usually more difficult to assess subjectively. Good inter-observer agreement for the subjective assessment of fistula response on MRI was demonstrated and used as a gold standard against which to assess volume as an objective measure. We also demonstrated minimal inter- and intra-observer variability in volume measurement, suggesting it is a consistent and repeatable measure. We investigated the association between change in fistula volume and subjective assessment of fistula response by experienced gastrointestinal (GI) radiologists at St. Mark's. We found strong agreement between this objective measure and the subjective assessment.

Quantification of fistula volumes is feasible and reliable, with the potential to provide objective measurement of perianal Crohn's fistula and response to treatment. This is the first step towards developing an objective and responsive MRI based volume score, and also perhaps towards developing a prognostic score, based on volume change or rate of change after initiation of treatment.

Section D

We believe there is a significant gap between the accurate representation of a fistula on 2D MRI, and the final understanding of that fistula by the surgeon, other health care professionals and by patients. 3D MRI represents our attempt to close this gap and improve a surgeon's acquisition of information from the MRI, and we have demonstrated the accessibility of this technique in a number of platforms. As perianal Crohn's disease fistulas are frequently complex, it is important to reduce recurrence rates as each surgical intervention on the background of undrained sepsis leads to further tissue destruction and anatomical distortion, making subsequent procedures more challenging. Furthermore, appreciation of fistula anatomy in relation to the sphincter complex can help avoid complications such as incontinence. 2D MRI has been shown to improve surgical outcomes, and it follows that an improved understanding of the fistula, beyond that which 2D MRI can offer, may improve them further.

Much of the key to understanding the treatment options, difficulties and likely success of surgery is in deciphering the exact morphology of the tract(s), the amount of sphincter involved and the impact of previous surgeries.

The advantages from clinicians can be further dissected into the novice (trainee) and the expert (consultant). If the trainee does not understand the fistula, they cannot plan surgery, consent patients or understand how their consultant does so. For surgeons, a 3D model can potentially aid understanding of the complex relationship between sphincter anatomy and fistula, guiding surgical decisions and improving outcomes. This can be more important in those surgeons who may not see complex fistulas regularly, and a

better appreciation of the imaging may allow them to better decide whether they are best suited to operate or to refer the case on to a specialist.

The final stakeholder to benefit is the patient and displaying their imaging in a more accessible medium would the aim to augment shared decision making. The clinician offering options with their associated risks and benefits, and patients deciding which options are most appropriate to their own symptoms and goals, can only do so if they understand the anatomy of the fistula and the implications of that anatomy. A variety of factors including the patient's prior understanding and the clinician's interpersonal skills, as well as the complexity of the decision and a balance of the patient's ability to understand and the clinician's ability to explain, govern the success of this decision-making process. Some of these factors are not modifiable but clinicians can improve their delivery of information, including by using adjuncts. When the complexity is related to anatomical understanding, 3D models provide a theoretical advantage.

8.9 Limitations of this Thesis

The limitations of each individual chapter have been described in detail at the end of the thesis. Below is a general summary of limitations, discussed by section.

The main limitation of the epidemiological work within Section A is that the dataset is retrospective, so causation is only implied. Also, the datasets were designed for administrative purposes and not for medical research. The datasets do not carry the same richness of data fields as a registry would. There are a number of factors that have not been evaluated such as the role of smoking, use of antibiotics, use of immunodulators,

obesity and post-operative packing, any of which may play a role in subsequent fistula development. Another issue with retrospective dataset analyses is determining cohorts, such as patients with Crohn's disease. Patients were labelled as having Crohn's if they were identified with a diagnosis of Crohn's at any time point. It is therefore possible that certain patients (particularly those with short follow up) have been labelled as having a Crohn's abscess/fistula even though at that point in time they had not developed Crohn's yet. However, it is known that diagnosis in Crohn's disease often occurs sometime after symptoms have begun and also that Crohn's perianal fistula can predate the diagnosis of luminal Crohn's.

Whilst the coding accuracy within HES has been validated[243] it is nevertheless a limitation. The coding data is as good as the individual entering the diagnosis on the system and it is important to note that coders do not have medical backgrounds. For example, the coding of abscess location is particularly suspect. The phrase 'perianal abscess' is used as a catch-all term by junior surgeons who are unfamiliar with the more nuanced classification of anorectal abscess used by experienced proctologists and as such may mis-label an ischiorectal or intersphincteric abscess. There could also be more than one abscess location and the surgeon may only code one of them. In addition, an unquantifiable element of human error exists with coding. For example, whether the surgeon chooses to code the EUA as well as the definitive procedure. Also, codes do not give any degree of extent, for example a fistulotomy may be for a high or low fistula and the difference in morbidity between these two may be vast. Another concern is interpretation and individuals may code the same procedure differently.

The issue of complete data is also a limitation. This dataset only looks at hospital admissions but does not account for diagnosis in a primary care setting. This of course is more of a concern when looking at benign conditions such as perianal sepsis as compared with colonic resectional surgery where the treatment can only be carried out in a hospital setting. Certain variables with the dataset are coded better than others and are therefore more reliable (e.g. only 35% of the population have an ethnicity code). The other concern is that granularity within certain variables is not possible, for example severity of Crohn's disease or height of fistula, and as such surrogate markers need to be employed or this level of detail simply discarded.

With respect to establishing co-morbidity, diagnosis codes were derived from the dataset to allow the Charlson Comorbidity Index to be used, which predicts 10-year survival. This scoring system can be described as outdated (1987) and doesn't account for the improved survival seen in the data period we studied in particular diseases, for example with HIV/AIDS. In addition, not all co-morbidities are encompassed within the Charlson Comorbidity Index. In an effort to mitigate bias using analysis from the HES dataset, the question asked needs to be unambiguous and carefully considered, which I believe is the case with this project.

In generating candidate outcomes for the COS from the systematic review, retrospective designs were excluded, which may raise the limitation of the list of outcomes not being exhaustive, although this represented only one source of outcomes for the long list. Studies with both curative and palliative intent as well as those containing patients with both simple and complex fistula were also included. This gives rise to another potential limitation in that the goals of treatment may therefore be different across different

patient groups. Patients were recruited from a variety of sources but are essentially self-selecting so the particular issues identified might be more relevant to patients with severe and long-lasting disease than a cohort with new diagnoses.

The main limitation of the core outcome set is that the stakeholders were all from the U.K. which limits the international generalisability of the COS, especially to less economically developed countries. This is mitigated somewhat by the optional inclusion of the imaging module but the principle of having an optional module to a core outcome set to some may seem somewhat contradictory. A further limitation is that some of the items in the COS are aspirational, such as the quality of life outcome, and are currently being developed i.e. the Crohn's Anal Fistula Quality of Life score (CAF-QoL), though there is ambiguity such that researchers may interpret this as advice to use the best currently available outcome measure, such as SF-36 or IBDQ.

One missing stakeholder was industry; this was discussed, and we decided on exclusion due to concerns about potential bias. A further critique is that the Delphi consensus was performed exclusively online which may have excluded those without easy access to a computer, although we took the view that this would represent a very small proportion of IBD patients in the UK, and that online completion rates would be likely to be higher than a paper based alternative. The final critique of the Delphi process was the fact that some of the healthcare professionals may have found it difficult or uncomfortable to argue against the patient stakeholder group during the face-to-face consensus meeting. Whilst this was not felt to be a significant concern at the time of study design. it is a potential, if unquantifiable, source of bias. These potential limitations of the consensus process apply to all core outcome sets and other studies relying on this design. However,

it probably represents the best way to develop a consensus with patient views central to the outcome despite these limitations, especially when they are discussed openly as part of the process.

MRI fistula volumes need to be appreciated in the context of the overall morphology of the tract and one needs to assess additional fistula characteristics, beyond volume alone, when judging response to treatment. In addition, a small sample size and heterogeneous cohort were likely contributors to the lack of significant correlation between fistula volume and clinical findings. In addition, the study design can be criticised for its retrospective nature.

3D modelling is derived from conventional 2D MRI and image quality is essential during the modelling process. Importantly, there is no new information that a 3D model can provide that the 2D scan cannot; the model's aim is purely to display the information in a more understandable, accessible medium. A slice thickness of 4 mm allows satisfactory contrast between different components of the anal canal and fistula with good signal to noise ratio, although after initial segmentation, 'blocky' 3D images are created which necessitate judicious use of smoothing algorithms to deliver a smooth structure. The need for smoothing would be reduced if thinner slices are used, but is still necessary, and more smoothing would carry a significant time cost. Smoothing also represents an interpretation of the MRI data. This probably represents a very modest impact on the accuracy of the models but must be acknowledged.

There are a number of limitations or considerations from the proof of concept 3D work. Firstly, expertise is required to create the 3D images, models and fistulography. The

accuracy of the segmentation of the fistula and the sphincter complex is dependent on the radiologist. In addition, there is a resource cost both in terms of hardware (printer, materials) and also personnel. In time this will be reduced as artificial intelligence algorithms are employed but currently the resource use is not insignificant. Finally, assessment of the impact of these innovations is beyond the scope of this thesis but represents ongoing work within our unit. Their impact and generalisability remain unknown. We expect the impact to be greatest where a significant understanding gap already exists, for example for newly diagnosed patients, or for junior trainees in radiology or surgery. Generalisability will ultimately depend on a balance of ease of use of the segmentation process and the added value the technique produces.

9 – Future Work

This thesis has answered a number of questions but, as ever, many more questions that need answering have been identified. Below, I have listed some potential avenues for future research.

9.1 Section A. Epidemiology of perianal sepsis

In order to mitigate some of the limitations described above one could again look retrospectively but using linked datasets – for example combining HES with the community practice data (Clinical Practice Research Datalink – CPRD) and endoscopic data (National Endoscopy Database – NED) would be a more robust method of (i) data capture of IBD patients (ii) capturing episodes of treatment in primary care and (iii) defining medications of patients with IBD as medications such as antibiotics, steroids,

5ASA's and 6-MP are not captured in the HES database. Alternatively, one could try to answer such questions from prospective registries. The difficulty is identifying one with enough registered participants and with a long enough follow-up period. One may also consider future studies into the microbiological, immunological, molecular and wound healing factors that predispose to fistula formation, which may yield biomarkers that would help predict which patients will develop a persistent fistula following abscess presentation.

Our HES dataset suggested nearly 3 in 100 patients eventually present with Crohn's disease. Perianal sepsis is common within surgical departments, but it is unclear how many of these patients also have Crohn's disease and how best to identify this cohort. The presence of perianal Crohn's disease, predicts those who are more likely to develop more extensive (ileo-colonic) and more complicated (stricturing and penetrating) disease behaviour which occurs more rapidly.[345,89] Such patients have more complex fistulas, recurrences and associated morbidity. With repeated surgery and episodes of sepsis, perianal disease becomes harder to assess both clinically and radiologically due to an increase in scar tissue and distortion of the surrounding anatomy.[346] The effect of a delayed diagnosis on outcome remains unknown, however. Early identification of patients with perianal Crohn's disease is important in order to try to avoid complications and may lead to improved outcomes. One prospective avenue would be to ensure thorough clinical history/examinations and selective use of faecal calprotectin assays.

To truly understand the extent to which perianal Crohn's disease is indeed a disease modifier, only a well thought out prospective registry will suffice. Eventually, these data

will be linked to biobanks to facilitate mechanistic studies, in order for causation and potential therapeutic targets to be developed.

9.2 Section B. Assessing outcomes for perianal Crohn's disease

The next step in this project would be to validate the COS in other countries. The considerations are not only resource utilisation (i.e. high vs. low income countries) but more importantly perceptions of living with an anal fistula in different countries, and in particular the relative importance of various quality of life factors, such as continence impairment, impact on sex and so on. The second stage would be to decide, through a consensus process, how best to assess each of the outcomes identified in the Core Outcome Set. This includes identifying which measurement tool should be used for each outcome and when they should measure.

This Core Measurement Set (CMS) would be created in a similar way to the COS, by reviewing the literature and creating a long list which would be supplemented by experts within the study management group and a PPI (patients and public consensus) exercise. This long list would then be used to inform a Delphi process across European stakeholders (colorectal surgeons, gastroenterologists, gastrointestinal radiologists, IBD nurses and patients with fistulising perianal Crohn's disease). In the first round the stakeholders would also be able to suggest additional measures not previously identified as per the methodology outline in this thesis.

These would be evaluated in the subsequent rounds and distilled down to a final number of outcome measures for discussion at a consensus meeting to inform the final core measurement set.

9.3 Section C. Developing an objective outcome measure

Our pilot data regarding MRI fistula volume are promising but may represent only a single facet of a wider scoring system. A number a facets, such as number of tracts, degree of sphincter involvement and others need to be evaluated in a longitudinal cohort with corresponding clinical data to identify those responsive to change. Factors which demonstrate this responsiveness would then be amalgamated together in a scoring system. This would need to be re-tested with both the current subjective standard but also other MRI scoring systems, such as the latest iteration of the Van Assche score.[331]

If one were to consider how to streamline the process of generating an MRI volume one would need to consider the use of machine learning and deep neural networks to recognise the fistula tract, the surrounding anatomy and the corresponding volume. This could be expanded to look at other factors such as signal intensity, for example determining how to distinguish between drainable fluid collections and granulation tissue, which would bring the advantage of being able to avoid unnecessary cessation of immunosuppression, and EUA. Artificial intelligence algorithms would be employed to determine factors predictive of undrained sepsis. The key once again is to have a granular, clinical registry to correlate with radiological features.

9.4 Section D. Novel imaging strategies to better understand and explain complex perianal disease

The next phase will be to evaluate the utility, effectiveness and generalisability of the innovations we have developed. This is not straightforward, particularly when trying to determine the benefit in terms of surgical planning, as it will be difficult to identify changes to clinical outcomes. A potential way would be for surgeons to review pre and post op MRI scans with 3D modelling, in cases of early recurrence, to see whether a 3D scan in retrospect would have altered their management. One difficulty is that not all surgeons have a complete operative repertoire and hence comparison will be difficult. Another option is a blinded vignette study for surgeons, radiologists and trainees for both specialities. Alterations in the surgical plan preoperatively, based on the addition of 3D modelling would provide some evidence of benefit, but again, demonstrating a change in clinical outcome would remain more difficult.

Changes in clinical outcome may not be the outcomes which are improved using this technique, but other, valuable outcomes may be improved and may vary between stakeholder groups. For example – (i) surgeons - consumer experience (ii) trainees - improved time to proficiency (radiology trainees in reading and reporting fistula scans accurately, surgical trainees in understanding fistula anatomy accurately) (iii) patients - patient satisfaction, understanding and informed consent. Some of these endpoints are not readily appraised in the medical literature and are more akin to commercial evaluation but represent a more useful and attainable set of outcomes to assess.

Assessing training, competence acquisition and trainee skill may be easier than determining the impact of 3D modelling on surgical planning. These are outcomes which are already assessed in the literature and existing methodology could be employed.

Easier still, and perhaps more valuable, may be assessment of the value of 3D modelling on patients' understanding of their disease, their options and therefore the impact on the quality of their informed consent process and patient satisfaction. Intuitively, the greater the understanding gap we are trying to bridge, the greater the potential impact of an intervention designed for this purpose. All of these approaches, but particularly enhancement of patient consultations and surgical training are the subject of ongoing study in our institution, as extensions of this work.

Another interesting area of work would be to expand on the app-based platform and identify how this might increase accessibility. For example, by facilitating a virtual MDT for discussion of complex perianal disease with surgeons regardless of their location.

Appendix

Appendix A. Search Strategy

Search Strategy:

Medline Search Strategy (Other search Strategies available on request)**:**

1 exp Crohn Disease/
2 crohn*.tw.
3 1 or 2
4 exp Fistula/ or exp Rectal Fistula/
5 fistul*.tw.
6 4 or 5
7 3 and 6
8 7 and 2010:2016.(sa_year).
9 randomized controlled trial.pt.
10 controlled clinical trial.pt.
11 randomized controlled trials.sh.
12 random allocation.sh.
13 double blind method.sh.
14 single-blind method.sh.
15 9 or 10 or 11 or 12 or 13 or 14
16 exp animals/ not human/
17 15 not 16
18 clinical trial.pt.
19 (clin$ adj25 trial$).ti,ab.
20 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
21 placebos.sh.
22 placebo$.ti,ab.
23 random$.ti,ab.
24 research design.sh.
25 or/18-24
26 25 not 16
27 26 not 17
28 comparative study.sh.
29 exp evaluation studies/
30 follow up studies.sh.
31 prospective studies.sh.
32 (control$ or prospective$ or volunteer$).ti,ab.
33 28 or 29 or 30 or 31 or 32
34 33 not 16
35 34 not (17 or 27)
36 17 or 27 or 35
37 7 and 36
38 37 and 2010:2016.(sa year).

1 Appendix B. Included studies

Author	Year	Title	Study design	Intervention	Total number of patients	Number of patients receiving treatment for fistula	Number of Outcome Measures	Core criteria for complete high quality reporting				
								Primary outcome clearly stated (73%)	*Primary outcome clearly defined (76%)*	*Secondary outcome clearly stated (57%)*	*Secondary outcome clearly defined (63%)*	*Use of outcomes explained (33%)*
Echarri	2010	Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure	Prospective cohort (multi-centre)	Combined	16	16	8			y	y	
Gligorijević	2010	The role of pelvic MRI in assessment of combined surgical and infliximab treatment for perianal Crohn's disease.	Prospective cohort	Combination	24	24	6		y		y	
Grimaud	2010	Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease.	Randomised clinical trial	Combination	77	77	2	y	y	y	y	y
Horsthuis	2010	Evaluation of an MRI-based score of disease activity in perianal fistulizing Crohn's disease.	Prospective cohort	Medical	19	19	7	y	y		y	y
Sciaudone	2010	Treatment of complex perianal fistulas in Crohn's disease: infliximab, surgery or combined approach.	Clinical controlled trial	Combined	35	35	7		y			
Soltani	2010	Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano.	Systematic review	Surgical	1243	91	3	y		y		
Alessandroni	2011	Local injection of infliximab in severe fistulating perianal Crohn's disease: an open uncontrolled study.	Prospective cohort	Medical	12	12	4	y				
Alvarez	2011	Surgical repair and biological therapy for faecal incontinence in Crohn's disease involving both sphincter defects and complex fistulas.	Prospective cohort	Combination	10	10	6	y	y			

Ciccocioppo	2011	Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease.	Prospective cohort	Surgical	12	12	8		y		y			
Khan	2011	Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis.	Systematic review and meta-analysis	Medical	2008	123	1	y						
Roumeguère	2011	Combined approach with infliximab, surgery, and methotrexate in severe fistulizing anoperineal Crohn's disease: results from a prospective study.	Prospective cohort (multi-centre)	Medical	34	NR	6	y	y	y	y			
Savoye-Collet	2011	Fistulizing perianal Crohn's disease: contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF-alpha therapy.	Prospective cohort	Medical	20	20	4		y		y			
Schreiber	2011	Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease - subgroup results from a placebo-controlled study.	Randomised clinical trial	Medical	58	58	6		y		y			
Sileri	2011	Surgery for fistula-in-ano in a specialist colorectal unit: a critical appraisal.	Prospective cohort	Surgical	247	26	7							
Panaccione	2011	Efficacy and safety of adalimumab in Canadian patients with moderate to severe Crohn's disease: Results of the Adalimumab in Canadian SubjeCts with ModErate to Severe Crohn's DiseaSe (ACCESS) trial	Phase III trial	Medical	304	NR	8	y	y	y	y	y		
Loftus	2011	Risk–benefit Analysis of Adalimumab Versus Traditional Non- Biologic Therapies for Patients with Crohn's Disease	Systematic review	Medical	3160	NR	7	y		y		y		
Dretze	2011	A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease	Systematic review	Medical	1783	NR	7	y	y	y	y	y		
Duff	2012	Infliximab and surgical treatment of complex anal Crohn's disease.	Retrospective analysis of prospective cohort	Medical	52	52	3	y						
O'Riordan	2012	A systematic review of the anal fistula plug for patients with Crohn's and non-Crohn's related fistula-in-ano.	Systematic review	Surgical	530	42	3	y	y		y			

Tozer	2012	Long-term MRI-guided combined anti-TNF-alpha and thiopurine therapy for Crohn's perianal fistulas	Prospective cohort	Medical	41	33	8	y	y	y	y	y
Antakia	2013	Combined modality treatment for complex fistulating perianal Crohn's disease.	Prospective cohort	Combination	48	48	3	y	y			
Cho	2013	Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: a phase I clinical study.	Phase 1 clinical study	Surgical	10	10	4	y		y		
delaPortilla	2013	Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial.	Clinical trial	Surgical	24	24	8	y	y	y	y	
Lee	2013	Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn's fistula.	Phase 2 clinical study (multi-centre)	Surgical	43	43	7	y	y	y	y	
Schwandner	2013	Video-assisted anal fistula treatment (VAAFT) combined with advancement flap repair in Crohn's disease.	Prospective cohort	Medical	11	10	4	y	y		y	
Da	2013	Adalimumab for Crohn’s disease after infliximab treatment failure: a systematic review	Systematic review	Medical	1009	NR	6	y	y	y	y	y
Steenholdt	2013	Individualised therapy is more cost-effective than dose intensification in patients with Crohn’s disease who lose response to anti-TNF treatment: a randomised, controlled trial	Randomised clinical trial	Medical	69	14	7	y	y	y	y	y
Panaccione	2013	Adalimumab maintains remission of Crohn’s disease after up to 4 years of treatment: data from CHARM and ADHERE	RCT *(long term follow up)*	Medical	329	70	5	y	y	y	y	y
Kawalec	2013	Tumour necrosis factor-α antibodies (infliximab, adalimumab and certolizumab) in Crohn's disease: systematic review and meta-analysis	SR and MA	Medical	4464	NR	6					
Chande	2013	Azathioprine or 6-mercaptopurine for induction of remission in Crohn’s disease (Review)	SR and MA	Medical	1211	18	7	y	y	y		y

Dewint	2014	Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI)	Randomised clinical trial	Surgical	76	76	7	y	y	y	y	y
Gingold	2014	A prospective evaluation of the ligation of the intersphincteric tract procedure for complex anal fistula in patients with Crohn's disease.	Prospective cohort	Surgical	15	15	4	y	y	y	y	
Hall	2014	Outcomes after operations for fistula-in-ano: Results of a prospective, multicenter, regional study	Retrospective analysis of prospective cohort (multicentre)	Surgical	158	29	2	y	y			
Reinisch	2014	AST-120 (spherical carbon adsorbent) in the treatment of perianal fistulas in mild-to-moderate Crohn's disease: FHAST-1, a phase 3, multicenter, placebo-controlled study	Randomised clinical trial	Surgical	249	249	4	y	y	y	y	y
Yassin	2014	Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease.	Systematic review and meta analysis	Combined	1139	NR	3	y	y			
Song	2014	Efficacy and safety of adalimumab for the Crohn's disease: a systematic review and meta-analysis of published randomized placebo-controlled trials	Randomised clinical trial	Medical	1676	NR	8		y	y	y	
Asma	2014	Stem cell transplantation as rescue therapy for refractory Crohn's disease: a systematic review	Systematic review	Surgical	115	65	15		y		y	
Göttgens	2015	Treatment of Crohn's disease-related high perianal fistulas combining the mucosa advancement flap with platelet-rich plasma: a pilot study.	Prospective cohort	Surgical	10	10	3		y		y	y
Molendijk	2015	Allogeneic Bone Marrow-Derived Mesenchymal Stromal Cells Promote Healing of Refractory Perianal Fistulas in Patients With Crohn's Disease.	Randomised clinical trial	Surgical	21	21	12	y	y	y	y	
Sirany	2015	The ligation of the intersphincteric fistula tract procedure for anal fistula: a mixed bag of results.	Systematic review	Surgical	683	15	4	y	y	y		

Su	2015	Use of antibiotics in patients with Crohn's disease: A systematic review and meta-analysis	Systematic review and meta-analysis	Surgical	1407	112	3	y	y			
Wiese	2015	Use of Endoscopic Ultrasound to Guide Adalimumab Treatment in Perianal Crohn's Disease Results in Faster Fistula Healing.	Prospective cohort (randomised)	Medical	20	20	4	y	y	y	y	y
Wu	2015	Meta-analysis of ciprofloxacin in treatment of Crohn's disease.	Meta-analysis	Medical	293	112	2	y		y		
Yang	2015	Long-term outcome of infliximab combined with surgery for perianal fistulizing Crohn's disease	Prospective cohort	Medical	28	28	8		y		y	
Inamdar	2015	Smoking and Early Infliximab Response in Crohn's Disease: a Meta-analysis	Meta-analysis	Medical	1658	NR	6			y	y	
Jones	2015	Effects of Concomitant Immunomodulator Therapy on Efficacy and Safety of Anti–Tumour Necrosis Factor Therapy for Crohn's Disease: A Meta-analysis of Placebo-controlled Trials	Systematic review and meta-analysis	Medical	1601	NR	5	y	y	y	y	y
deGroof	2016	Treatment of perianal fistulas in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-TNF treatment.	Systematic review and meta-analysis	Combination	1754	1754	3	y		y		y
Nasseri	2016	The anal fistula plug in Crohn's disease patients with fistula-in-ano: a systematic review.	Systematic review	Surgical	84	84	3	y	y	y	y	
Senéjoux	2016	Fistula Plug in Fistulising Ano-Perineal Crohn's Disease: a Randomised Controlled Trial.	Randomised clinical trial	Surgical	106	54	6	y	y	y	y	

Appendix C. Unique outcome measures following grouping

INDIVIDUAL OUTCOMES	GROUPED OUTCOMES*
Abdominal mass	**Abdominal mass**
Felt worried or anxious Limitation during last month - been a very nervous	**Anxiety & worries**
CDAI - effective (reduction of ≥70) CDAI - remission (≤150) CDAI remission ≤ 150 from baseline	**A validated Crohn's disease activity score**
PDAI	**A validated score to assess perianal disease activity e.g. PDAI**
Abdominal pain Cramps in abdomen How often during the past 2 weeks have you been troubled by pain in the abdomen? Abdominal bloating	**Abdominal pain/discomfort/bloating**
MRI - Collections (cavities >3mm) diameter MRI presence of infiltrate	**Abscess on MRI following treatment**

Abscesses Absence of abscess on MRI MRI - absence of collections (≥2cm)	
Allergic Early Adverse events - angioedema Early Adverse events - breathing difficulties	**Allergic reaction**
Anal bleeding Complications - bleeding Rectal bleeding in bowel motion	**Anal bleeding**
Anal pain Improvement in perianal pain	**Anal pain**
Pulmonary infection Cardiac rhythm Cardiac function Early Adverse events - hypotension Pericarditis	**Cardio-respiratory complications**
General Health (current) General Health (compared to one year ago) Excellent health	**Change in general health - physical**

Generally unwell General well being Embarrassed as a result of your bowel problem	**Change in general health - psychological**
Avoided attending events where there was no washroom close at hand Fear of not finding a washroom Change in lifestyle based on bowel motion	**Change in lifestyle based on toileting needs**
Closure of all fistulas that were draining at baseline to at least 2 other time points No drainage either spontaneously or on gentle finger pressure Disappearance of secretions >3 months Undefined drainage assessment	**Clinical assessment of drainage either spontaneously or on gentle finger pressure**
Closure of all the external openings on clinical examination Closure of all the external openings on clinical examination using a fistula probe	**Closure of all the external openings on clinical examination**
Closure of the internal opening	**Closure of the internal opening**
Get sick a little easier than other people Healthy as anybody I know	**Comparison with other individuals (luminal)**
Fistula remission	**Complete fistula healing assessed clinically**
Cost effectiveness	**Cost effectiveness**

Crohn's related hospitalisation	**Crohn's related hospitalisation**
CRP	**CRP**
Grade 5: Death related to AE.	**Death**
Decisional regret Whether would opt for same treatment again	**Decisional regret of treatment choice**
Decrease in size of fistula	**Decrease in size of fistula**
<3 fistulas ≥3 fistulas Number of perianal fistula Decrease in number of fistulas	**Development of new fistulas since intervention**
fissure Ulcer and Fissure Type of perianal disease None, skin tags Concomitant Disease Anal Stenosis	**Development of other forms of perianal features (other than fistula)**
Oral Alimentation	**Dietary supplements as oral intake low**
Difficulty getting a good night's sleep	**Difficulty getting a good night's sleep due episodes of getting up to toilet/wound care**

Fistula healing time Time to fistula re-opening for primary responders Maintenance of fistula closure for >26 weeks Length of follow up Time to relapse	**Duration of healing/improvement**
Extraintestinal manifestations of Crohn's disease	**Extraintestinal manifestations of Crohn's disease**
Faecal diversion and/or proctectomy	**Faecal diversion and/or proctectomy**
Inability to defer defaecation for 15 minutes	**Faecal urgency - Inability to defer defaecation for 15 minutes**
Feasibility of technique	**Feasibility of technique**
Limitation during last month - felt so down in the dumps that nothing could cheer you up Limitation during last month - felt calm and peaceful Relaxed or tension free Limitation during last month - downhearted and blue Felt a lack of understanding from others Unhappy with personal life Felt tearful or upset Felt depressed or discouraged	**Feeling Depressed & down and hopelessness**

How often during the past 2 weeks have you felt depressed or discouraged? How often during the past 2 weeks have you felt relaxed and free of tension? Limitation during last month - been a happy person Expect health to get worse	
Angry as a result of bowel problem How often during the past 2 weeks have you felt angry as a result of your bowel problem? Felt Irritable Felt frustrated	**Felt irritable, frustrated and angry**
Late Adverse events - fever Early Adverse events - fevers Early Adverse events - chills Fever	**Fever**
Width of the hypoechoic echotexture Amount of heterogeneity of in the area of inflammation Endoanal Ultrasound	**Fistula Response on Endoanal Ultrasound**
Fistulas on MRI	**Fistula response on MRI imaging**

MRI - Number of fistula tracks MRI - Location MRI - Extension Complete fibrosis of tract on MRI MRI fistula healing Partial tract closure MRI - Healed MRI - Improved MRI - Unchanged MRI - Worse	
Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated. Outcome of the adverse event	**Grading system for complications e.g. Clavien-Dindo**

Treatment causing adverse event Timing of adverse event Severity of the adverse event Frequency of adverse event Serious adverse events	
Haemorrhage	**Haemorrhage**
How often have you felt worried about further surgery	**How often have you felt worried about further intervention**
MRI - Hyperintensity on T2 weighted images Mural T2 signal on MRI Perimural T2 signal on MRI	**Hyperintensity on T2 weighted MRI**
No lesion in distal ileum on Endoscopy ≤ 5 aphthous lesions on endoscopy ≥ 5 aphthous lesions with normal mucosa between lesions, or lesions confined to the ileocolonic anastomosis on endoscopy Diffuse aphthous ileitis with diffusely inflamed mucosa on endoscopy Diffuse inflammation with already larger ulcer, nodules, and/or narrowing on endoscopy Endoscopy Deep ulceration on endoscopy	**Identification of endoscopic signs suggestive of failure of treatment (relating to systemic/overall Crohn's)**

Superficial ulceration on endoscopy Surface involved in disease on endoscopy Surface involved in ulceration on endoscopy Endoscopy - Luminal relapse	
Incontinence to liquid Stool Leakage of liquid stool % of motions that caused incontinence	**Incontinence to liquid stool**
Incontinence to solid stool Long term continence to solid stool	**Incontinence to solid stool**
Incontinence to gas Problems passing a large amount of gas Overall, in the past 2 weeks, how much of a problem have you had with passing large amounts of gas?	**Incontinence to wind**
Number of liquid stools Fluid bowel motion in past month Number of liquid or soft stools (yesterday) Frequency of bowel motion in last 2 weeks How many times during the last 2 weeks have your bowel movements been loose	**Increase frequency of loose stool**

Diarrhoea	
Body weight BMI Problems maintaining/getting to, a weight you would like to be at Overall, in the past 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be	**Instability of weight (assessed by BMI)**
Immunomodulator free remission	**Immunomodulator free remission**
Time to resume work	**Length of time off work/study after intervention**
Limitation of physical health - Cut down the amount of time you spent on work or other activities Limitation of physical health - Accomplished less than you would like Limitation of physical health - Had difficulty performing the work or other activities (for example, it took extra effort) Limitation of emotional health - Accomplished less than you would like Limitation of emotional health - Had difficulty performing the work or other activities (for example, it took extra effort) Limitation during last month - feel tired How much energy have you had in the last 2 weeks	**Lethargy and Fatigue**

As a result of your bowel problems, how much difficulty did you experience doing leisure or sports activities you would like to have done during the past 2 weeks? How often has the feeling of fatigue or being tired and worn out been a problem for you during the past 2 weeks? Limitation during last month - feel worn out Limitation during last month - energy levels Limitation during last month - full of pep Fatigue or tired Difficult getting a good night's sleep	
Limitation of physical health - Were limited in the kind of work or other activities Lifestyle impact Lifestyle alterations Pain/restriction of activities Pain and restriction on activities Limitation of emotional health - Were limited in the kind of work or other activities Difficult doing any sport of leisure activities	**Lifestyle alterations (Pain/restriction of activities)**

Limitation - bodily pain	
Limitation to moderate activities (e.g. s moving a table, pushing a vacuum cleaner, bowling, or playing golf) Limitation to walking more than a mile Limitation to lifting or carrying groceries Limitation to climbing one flight of stairs Limitation to walking one block	**Limitation to moderate activities (e.g. light housework)**
Limitation to walking several blocks Limitation to vigorous activities (e.g. running, lifting heavy objects, participating in strenuous sports) Limitation to climbing several flights of stairs	**Limitation to vigorous activities (e.g. running, lifting heavy objects, participating in strenuous sports)**
degree of induration	**Local perianal inflammation/induration assessed clinically**
MRI - Rectal wall involvement Wall thickness Contrast enhancement Oedema Decrease in bowel oedema on MRI Bowel oedema with mild peri lymphangitis	**MRI assessment of rectum (proctitis)**
LN > 1cm	**MRI features (luminal)**

LN size, and number LN enhancement Mural enhancement pattern Total length of disease in segment Mural thickness of bowel on MRI Pseudopolyps Ulcers Comb sign	
Mucus	**Mucus leakage**
Complications - nausea Nausea or feeling sick Nausea/Vomiting Complications - vomiting	**Nausea and vomiting**
Altered consciousness Peripheral neuropathy Constipation Neuropathic pain Late Adverse events - myalgia	**Neurological complications**
Creatinine	**Non-inflammatory blood markers**

Blood urea nitrate Nitrogen AST ALT Bilirubin Haemoglobin Hb Iron studies	
ESR Albumin Haematocrit Neutrophils Leukocytes Granulocytes WCC Immunological response (CD4/8 ratio) Plts Platelets	**Objective blood markers of inflammation**
Fistula improvement	**Partial fistula healing assessed clinically**

Detection of tracts ulceration or fistula with undermining skin	
Incontinence Score	**An incontinence score**
Patient perception of continence Change in continence Incontinence rates (undefined)	**Patient perception of continence compared to others OR baseline**
Complications - abscess Abscess Absence of perianal abscess	**Perianal abscess on clinical assessment after intervention**
Limitation to bathing or dressing yourself Limitation to bending, kneeling, or stooping	**Physically restricted in self care**
Early Adverse events - urticaria Late Adverse events - rash Cutaneous skin Early Adverse events - rash Alopecia	**Rash or other skin/hair problems**
Rectal mucosal healing	**Rectal mucosal healing**
Reduction in fistula drainage as reported by the patient Discharge	**Reduction in fistula drainage as reported by the patient**

Marked reduction in drainage as reported by the patient Patient reported fistula drainage Fistula	
Remission of Crohn's disease	**Remission of Crohn's disease**
Problems with sexual activity Restriction of sexual activity	**Restriction of sexual activity**
Safety	**Safety (adverse events) and toxicity**
Laboratory toxicity	
Limitation of emotional & physical health - affecting normal social activities with families, friends, neighbours, or groups Limitation during last month - interfered with social activity Limitation of pain - interfering normal work (including both work outside the home and housework)? How often during the last 2 weeks have you delayed or cancelled a social engagement because of your bowel problem? How often have you had to delay a social engagement because of your bowels	**Social interaction avoidance - *Stop leaving the house unless you have to (work but not friends)***
Steroid free remission	**Steroid free remission**
Surgical complications	

Complications	**Surgical complications specific to the surgical procedure (e.g. plug extrusion)**
Recurrence - reopening of the external tracts with active drainage or the development of an abscess at the site of the original fistula Surgical re-intervention	**Surgical re-intervention**
MRI T1 hyperintensity T1 enhancement on MRI	**T1 enhancement on MRI**
Going to the bathroom even though bowels empty How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?	**Tenesmus or incomplete evacuation - *Feeling like you need to go to the toilet all the time (even if just been)***
Time to loss of response for primary responders	**Time to loss of response to medical treatments**
Recurrence - a new fistula occurring after a symptom-free period Recurrence - reopening of the external tracts with active drainage or the development of an abscess at the site of the original fistula Recurrence (undefined) Recurrence - reopening of the external tracts with active drainage or the development of an abscess at the site of the original fistula	**Time to recurrence**
Systemic tolerance	**Tolerability of treatment**

Tolerance of the treatment (fistula plug) Tolerability of treatment	
Unable to attend to school/work	**Unable to attend to school/work**
Proteinuria Haematuria Complications - urinary dysfunction	**Urinary complications**
Taking constipating agents Anti-diarrhoeal drugs	**Use Anti diarrhoeal drugs**
Use of pads Accidental soiling of underpants Wears pads for continence	**Wearing a pad for continence/leakage**
Wearing a pad/plug	**Wearing a plug for continence/leakage**
Complications - wound infection Infection	**Wound infection**
≥50% tracts not draining on clinical examination ≥50% tracts not draining on clinical examination at least 2 visits post baseline	**≥50% tracts not draining on clinical examination**

1

2

Appendix D. Round one voting

Themes	Outcomes	R1 - Panel SuRa *importance*		R1 - Panel GaNu *importance*		R1 - Panel Pa *importance*		R1 - Overall *importance*		R1 results
		High (%)	Low (%)	High (%)	Low (%)	High (%)	Low (%)	High (%)	Low (%)	Domain retained
2	**Faecal diversion or proctectomy**	97	0	98	0	96	0	97	0	*yes*
6	**Death**	97	3	100	0	91	5	96	3	*yes*
2	**Development of a new fistula**	89	0	97	0	92	0	93	0	*yes*
2	**Incontinence to solid stool**	89	0	94	0	93	1	92	0	*yes*
2	**Perianal related hospitalisation**	89	0	94	0	91	3	91	1	*yes*
2	**Incontinence to liquid stool**	83	0	92	0	96	0	91	0	*yes*
2	**Perianal abscess on clinical assessment after intervention**	86	2	89	0	92	6	89	3	*yes*

2	**Surgical re-intervention**	89	2	91	0	86	5	89	2	*yes*
2	**Recurrence of fistula**	86	0	94	0	81	0	87	0	*yes*
6	**Medical complications specific to the immunosuppression (e.g. opportunistic infections, cancers)**	79	0	97	0	83	9	86	3	*yes*
3	**Unable attend school/work**	84	0	92	0	81	1	86	1	*yes*
6	**Safety (adverse events) and toxicity**	83	0	88	0	77	3	82	1	*yes*
2	**Pads for continence/leakage**	73	0	91	0	81	3	82	1	*yes*
3	**Social interaction avoidance**	65	3	82	0	89	6	79	3	*yes*
3	**Lifestyle alterations (pain/restriction of activities)**	76	2	85	0	75	8	78	3	*yes*
6	**Neurological complications**	73	6	85	6	76	12	78	8	*yes*
4	**Abscess on MRI following treatment**	73	5	91	0	68	3	77	2	*yes*
3	**Restriction of sexual activity**	63	3	79	0	86	3	77	2	*yes*
2	**Anal pain**	63	3	80	2	83	0	76	1	*yes*
4	**Fistula response on MRI imaging**	65	11	91	2	72	5	76	6	*yes*
6	**Cardio-respiratory complications**	70	3	76	6	81	7	76	5	*yes*
3	**Limitation to moderate activities**	70	0	74	0	79	1	74	1	*yes*

3	**Physically restricted in self care**	62	2	82	0	78	6	74	3	*yes*
4	**# Fistula T2 hyperintensity on MRI**	63	6	74	2	82	1	74	3	*yes*
1	**Patient-reported reduction in fistula drainage**	65	3	74	0	79	1	73	2	*yes*
3	**Feeling depressed & down and hopelessness**	59	5	79	2	79	7	73	4	*yes*
7	**Duration of healing/improvement**	73	3	80	0	66	16	73	7	*yes*
3	**Modifying how you walk, sit or stand because of your fistula**	60	5	68	2	83	9	71	5	*yes*
3	**Anxiety & worries**	57	8	74	3	81	1	71	4	*yes*
6	**Allergic reaction**	70	2	79	5	64	5	71	4	*yes*
3	**Avoidance of intimacy**	63	2	77	0	71	3	71	2	*yes*
3	**Change in lifestyle based on toileting needs**	65	0	68	0	77	5	70	2	*yes*
2	**# Wound infection**	43	6	74	2	90	0	70	2	*yes*
3	**Change in general health - psychological**	56	3	74	0	78	4	70	2	*yes*
6	**Surgical complications specific to the surgical procedure (e.g. plug extrusion)**	57	6	68	2	79	1	69	3	*yes*
3	**Embarrassment & feeling isolated**	62	2	74	2	68	8	68	4	*yes*
2	**Discrimination between passing stool and gas**	57	6	70	0	76	3	68	3	*yes*

1	**Complete fistula healing assessed clinically**	67	2	82	3	57	15	68	7	*yes*
3	**Concerns about and impact on fertility, birth, parenthood and family**	52	3	71	2	75	7	67	4	*yes*
4	**MRI assessment of fistula volume**	46	19	76	3	76	1	67	7	*yes*
4	**# Fistula T1 enhancement on MRI**	43	14	73	6	81	3	67	7	*yes*
3	**Change in general health - physical**	52	3	65	3	79	3	66	3	*yes*
6	**Grading system for surgical complications e.g. Clavien-Dindo**	59	11	62	14	76	5	66	10	*yes*
3	**Sleep disturbance**	51	6	64	8	80	4	66	6	*yes*
3	**# Lethargy and fatigue**	46	6	62	6	85	3	65	5	*yes*
5	**Fever**	49	10	74	5	71	4	65	6	*yes*
2	**Faecal urgency**	46	5	67	0	79	4	65	3	*yes*
3	**Tolerability of treatment**	56	2	64	5	73	5	64	4	*yes*
3	**A feeling of being unhygienic**	46	8	64	5	80	1	64	5	*yes*
1	**Rectal mucosal healing**	57	11	74	2	58	5	63	6	*yes*
6	**# Urinary complications**	44	0	59	5	84	3	63	3	*yes*
1	**Local perianal inflammation/induration assessed clinically**	48	5	58	3	82	0	63	3	*yes*

7	*** Biologic free remission**	68	2	56	14	64	6	63	7	*yes*
3	*** A quality of life score e.g. Short form survey 36 (SF-36)**	56	6	64	11	68	2	63	6	*yes*
2	**Plug for continence/leakage**	49	6	61	6	76	1	63	5	*yes*
3	**Modifying travel**	48	5	65	2	72	3	62	3	*yes*
2	**Mucus leakage**	44	3	68	2	71	0	62	1	*yes*
1	**Closure of internal opening**	54	19	56	11	71	6	61	12	*yes*
7	**Financial implications**	48	5	50	6	83	0	61	4	*yes*
5	**Time to loss of response to medical treatments**	38	13	68	6	72	4	60	8	*yes*
1	**Closure of all the external openings on clinical examination**	52	8	62	6	64	2	60	5	*no*
1	**Clinical assessment of drainage either spontaneously or on gentle finger pressure**	33	6	56	8	84	5	59	6	*yes*
4	*** An activity based MRI score e.g. Van Assche Score**	30	24	68	11	75	4	59	12	*yes*
1	**# Development of perianal features of Crohn's (other than fistula)**	49	16	52	8	72	10	59	11	*yes*
1	**# A validated score to assess perianal disease activity e.g. Perianal disease activity index (PDAI)**	38	22	58	8	77	3	59	11	*yes*
2	**Incontinence to wind**	44	13	61	5	69	0	58	6	*no*
7	**Recovery time after intervention**	40	6	55	3	77	0	58	3	*yes*

7	**Antibiotic free remission**	49	5	53	8	68	5	57	6	*no*
3	**Restricted clothing choices**	38	3	53	8	75	3	56	4	*yes*
7	**Increasing analgesia**	48	0	59	2	60	12	56	5	*no*
1	**≥50% tracts not draining on clinical examination**	37	22	50	5	75	11	56	12	*yes*
4	**MRI assessment of rectum (proctitis)**	32	29	50	11	82	0	56	13	*yes*
2	*** A combined faecal incontinence score e.g. the Vaizey Score, Cleveland Clinic Incontinence score, Faecal Incontinence Severity Index (FISI)**	40	21	62	11	62	0	55	10	*yes*
3	**Patient perception of continence compared to others OR baseline**	44	2	55	9	62	14	54	9	*no*
3	**Decisional regret of treatment choice**	44	6	56	3	59	5	53	5	*no*
3	**Body detachment**	40	6	58	5	61	6	53	6	*no*
3	**Concern over further intervention**	35	6	53	8	70	1	53	5	*yes*
3	**Irritable, frustrated and angry**	33	11	53	8	70	1	53	6	*yes*
2	**Tenesmus or incomplete evacuation**	37	8	52	5	67	1	52	4	*no*
2	**# Anal bleeding**	22	24	53	6	76	5	52	11	*yes*
3	**Limitation to vigorous activities (e.g. running, lifting heavy objects, participating in strenuous sports)**	32	6	53	5	67	10	51	7	*no*

1	**Partial fistula healing assessed clinically**	33	6	42	6	74	1	51	5	*yes*
4	**# Fistula response on endoanal USS**	17	43	58	20	71	2	49	21	*yes*
5	**Objective blood markers of inflammation**	25	24	48	12	65	1	47	12	*no*
2	**Increased frequency of loose stool**	27	10	50	3	59	4	46	6	*no*
6	**Rash or other skin/hair problems**	32	17	45	11	59	4	46	11	*no*
5	**C-reactive protein (CRP)**	24	27	47	12	62	11	46	16	*no*
6	**Nausea or vomiting**	38	14	50	15	48	6	46	12	*no*
5	**Non-inflammatory blood markers *(related biologics)***	27	25	45	18	61	3	45	15	*no*
7	**Cost effectiveness**	29	17	44	12	54	5	42	12	*no*
5	**Instability of weight (assessed by BMI)**	30	29	39	15	42	6	37	16	*no*
7	**Use anti-diarrhoeal drugs**	16	22	29	27	58	5	34	18	*no*

THEME KEY

1	Fistula response to treatment (symptoms)
2	Direct impact of fistula on the patient
3	Impact on the patient as a person
4	Assessment with imaging techniques (scans)

5	Fistula response to treatment (tests)
6	Safety implications related to treatment
7	Impact on patient over time

*SMG decision to change the name (or lay description) based on heterogeneity or comments by participants

Items were retained due to polarising views/heterogeneity or comments by participants

Appendix E. Round two voting

		R1 - Panel SuRa		R2 - Panel GaNu		R2 - Panel Pa		R2 - Overall		R2 results
		importance		*importance*		*importance*		*importance*		
Theme	**Outcome**	**High (%)**	**Low (%)**	**High (%)**	**Low (%)**	**High (%)**	**Low (%)**	**High (%)**	**Low (%)**	**Domain retained**
2	**Development of a new fistula**	98	0	100	0	98	0	98	0	*yes*
2	**Faecal diversion or proctectomy**	98	0	100	0	100	0	97	0	*yes*
6	**Death**	98	2	100	0	96	2	97	1	*yes*
2	**Perianal related hospitalisation**	96	0	98	0	98	0	97	0	*yes*
2	**Incontinence to solid stool**	98	0	98	0	98	2	97	1	*yes*
2	**Recurrence of fistula**	100	0	98	0	91	0	96	0	*yes*

2	**Perianal abscess on clinical assessment after intervention**	94	0	94	0	100	0	95	0	*yes*
2	**Incontinence to liquid stool**	91	0	98	0	98	2	94	1	*yes*
6	**Medical complications specific to the immunosuppression (e.g. opportunistic infections, cancers)**	92	0	98	0	92	2	94	1	*yes*
2	**Surgical re-intervention**	94	0	96	0	89	2	93	1	*yes*
3	**Unable attend school/work**	94	0	94	0	87	7	91	2	*yes*
2	**Pads for continence/leakage**	86	0	96	0	96	0	91	0	*yes*
6	**Safety (adverse events) and toxicity**	98	0	90	0	88	2	91	1	*yes*
3	**Lifestyle alterations (pain/restriction of activities)**	91	0	88	0	91	0	89	0	*yes*
6	**Neurological complications**	86	2	88	0	96	2	89	1	*yes*
7	**Duration of healing/improvement**	86	0	92	0	87	2	88	1	*yes*
4	**Abscess on MRI following treatment**	85	4	96	0	74	2	85	2	*yes*
4	**Fistula response on MRI imaging**	78	10	94	0	83	0	85	3	*yes*
3	**Social interaction avoidance**	75	2	86	0	98	2	85	1	*yes*
3	**Restriction of sexual activity**	72	2	92	0	91	4	85	2	*yes*
2	**Anal pain**	76	0	88	2	92	2	85	1	*yes*

6	**Cardio-respiratory complications**	83	2	79	0	96	2	85	1	*yes*
2	**Patient-reported reduction in fistula drainage**	76	0	84	0	89	2	82	1	*yes*
3	**Modifying how you walk, sit or stand because of your fistula**	76	2	78	0	91	4	81	2	*yes*
3	**Embarrassment & feeling isolated**	73	2	88	0	77	4	79	2	*yes*
3	**Limitation to moderate activities**	79	0	76	0	84	0	79	0	*yes*
2	**Complete fistula healing assessed clinically**	79	4	92	2	66	4	78	3	*yes*
3	**Feeling depressed & down and hopelessness**	68	4	82	0	87	9	78	4	*yes*
6	**Allergic reaction**	76	0	80	0	82	2	78	1	*yes*
3	**Change in general health - psychological**	73	2	80	0	83	2	78	1	*yes*
3	**Avoidance of intimacy**	71	0	84	0	78	2	77	1	*yes*
3	**Anxiety & worries**	71	6	69	0	93	0	77	2	*yes*
3	**Change in lifestyle based on toileting needs**	72	2	77	0	83	4	77	2	*yes*
2	**Discrimination between passing stool and gas**	62	2	76	0	90	2	75	1	*yes*
3	**Physically restricted in self care**	67	0	82	0	78	7	74	2	*yes*
4	**MRI assessment of fistula volume**	49	20	80	2	89	4	71	9	*yes*

3	**Change in general health - physical**	53	2	69	2	92	0	71	1	*yes*
2	**§ Reversal of defunctioning stoma**	82	2	70	5	76	9	71	5	*yes*
2	**#§ Need to access medical care**	51	7	67	3	*93*	2	69	4	*yes*
2	**#Wound infection**	30	0	*81*	2	*96*	0	68	1	*yes*
3	**Concerns about and impact on fertility, birth, parenthood and family**	51	2	*83*	0	*79*	5	68	2	*no*
3	**Sleep disturbance**	54	6	68	4	*85*	2	68	4	*no*
4	**#Hyperintensity on T2 weighted MRI**	67	6	63	0	*98*	0	67	2	*yes*
3	**§ Patient global satisfaction with management and outcome**	63	0	*79*	4	67	10	67	4	*no*
3	**Tolerability of treatment**	60	0	65	2	*78*	0	67	1	*no*
2	**Faecal urgency**	44	2	*70*	0	*88*	4	66	2	*no*
7	**Period of time off biologics/anti-TNFs/immunosuppression**	*75*	0	58	8	67	10	65	6	*no*
6	**Surgical complications specific to the surgical procedure (e.g. plug extrusion)**	56	4	*72*	0	*81*	2	64	2	*no*
3	**A feeling of being unhygienic**	42	8	64	4	*89*	4	64	5	*no*
2	**Rectal mucosal healing**	65	2	*77*	2	47	13	62	6	*no*
6	**#Urinary complications**	33	0	58	2	*98*	2	62	1	*yes*

2	**#Development of perianal features of Crohn's (other than fistula)**	52	8	46	4	*92*	0	62	4	*yes*
3	**#Lethargy and fatigue**	33	4	60	4	*96*	0	62	3	*yes*
3	**Modifying travel**	48	4	61	0	*78*	4	61	3	*no*
2	**Mucus leakage**	34	2	*76*	2	*77*	0	61	1	*no*
2	**Plug for continence/leakage**	40	2	63	2	*86*	2	60	2	*no*
2	**Closure of internal opening**	56	14	48	10	*80*	4	60	9	*no*
2	**Local perianal inflammation/induration assessed clinically**	35	4	61	0	*85*	2	59	2	*no*
5	**Time to loss of response to medical treatments**	22	4	*75*	0	*86*	0	59	1	*no*
5	**Fever**	32	12	*71*	4	*76*	2	59	6	*no*
2	**Clinical assessment of drainage either spontaneously or on gentle finger pressure**	17	4	68	6	*87*	2	56	4	*no*
5	**§ Non-inflammatory blood markers for therapeutic drug monitoring (biologics- efficacy)**	28	14	60	11	*84*	0	55	7	*no*
2	**§ Need for ongoing seton**	40	14	49	5	*82*	8	54	9	*no*
3	***A global assessment of quality of life**	42	6	54	6	*70*	6	54	6	*yes*
7	**Financial implications**	42	2	39	0	*83*	6	54	3	*no*
4	**#Fistula T1 enhancement on MRI**	20	10	*71*	2	*91*	0	54	4	*yes*

6	**Grading system for surgical complications e.g. Clavien-Dindo**	50	9	45	11	*83*	10	53	9	*no*
2	***A validated score to assess perianal disease activity e.g. Perianal disease activity index (PDAI)**	21	23	59	2	*79*	6	52	10	*yes*
7	**Recovery time after intervention**	30	2	47	2	*79*	8	51	4	*no*
4	***An activity based MRI score e.g. Van Assche Score**	10	24	67	6	*83*	0	51	10	*yes*
2	**≥50% tracts not draining on clinical examination**	18	16	48	8	*87*	0	50	8	*no*
3	**Restricted clothing choices**	29	4	42	8	*81*	2	49	5	*no*
2	***A global assessment of incontinence that covers all aspects of leakage**	19	15	69	4	60	7	48	8	*yes*
4	**MRI assessment of rectum (proctitis)**	22	32	37	12	*85*	0	47	14	*no*
3	**Irritable, frustrated and angry**	20	16	42	8	*83*	4	47	9	*no*
2	**#Anal bleeding**	8	16	32	4	*94*	0	44	7	*yes*
3	**Concern over further intervention**	24	6	35	4	*71*	6	42	5	*no*
2	**Partial fistula healing assessed clinically**	18	9	33	0	*76*	2	42	4	*no*
4	**Fistula response on endoanal Ultrasound**	2	55	44	13	69	16	35	27	*no*

THEME KEY

1	Fistula response to treatment (symptoms)
2	Direct impact of fistula on the patient
3	Impact on the patient as a person
4	Assessment with imaging techniques (scans)
5	Fistula response to treatment (tests)
6	Safety implications related to treatment
7	Impact on patient over time

§ De novo outcomes added after round one

*Outcomes which did not meet consensus but were retained by SMG

Retained due to a high patient scoring (≥90%)

1

2 ## Appendix F. Round three voting

		R3 - Panel SuRa		R3 - Panel GaNu		R3 - Panel Pa		R3 - Overall		R3 results
		importance		*importance*		*importance*		*importance*		
THEME	**OUTCOME**	**High (%)**	**Low (%)**	**High (%)**	**Low (%)**	**High (%)**	**Low (%)**	**High (%)**	**Low (%)**	**Domain retained**
2	**Development of a new fistula**	97%	2%	98%	2%	97%	3%	97%	2%	*yes*
6	**Death**	97%	2%	97%	2%	90%	10%	95%	3%	*yes*

2	**Recurrence of fistula**	95%	3%	97%	2%	93%	3%	95%	2%	*yes*
2	**Faecal diversion or proctectomy**	95%	2%	95%	2%	92%	5%	94%	2%	*yes*
3	**Unable attend school/work**	95%	2%	95%	2%	80%	8%	90%	3%	*yes*
7	**Duration of healing/improvement**	95%	0%	84%	5%	90%	8%	90%	3%	*yes*
6	**Safety (adverse events) and toxicity**	95%	2%	86%	6%	81%	8%	87%	3%	*yes*
2	**Incontinence to solid stool**	93%	2%	97%	3%	95%	5%	95%	2%	*yes*
2	**Perianal related hospitalisation**	93%	3%	97%	3%	92%	7%	94%	3%	*yes*
3	**Lifestyle alterations (pain/restriction of activities)**	92%	2%	92%	2%	90%	5%	91%	2%	*yes*
6	**Medical complications specific to the immunosuppression (e.g. opportunistic infections, cancers)**	92%	2%	91%	2%	92%	7%	91%	3%	*yes*
2	**Surgical re-intervention**	92%	5%	94%	2%	86%	12%	91%	4%	*yes*
4	**Abscess on MRI following treatment**	92%	7%	94%	2%	83%	7%	90%	4%	*yes*
2	**Reversal of defunctioning stoma**	90%	3%	81%	3%	69%	8%	80%	4%	*yes*
2	**Perianal abscess on clinical assessment after intervention**	88%	7%	97%	2%	93%	7%	93%	3%	*yes*
2	**Incontinence to liquid stool**	87%	5%	95%	3%	93%	5%	92%	2%	*yes*

1	**Patient-reported reduction in fistula drainage**	87%	2%	84%	2%	93%	5%	88%	2%	*yes*
1	**Complete fistula healing assessed clinically**	87%	2%	83%	6%	81%	7%	84%	4%	*yes*
2	**Pads for continence/leakage**	85%	2%	95%	2%	95%	3%	92%	2%	*yes*
3	**Social interaction avoidance**	83%	2%	80%	3%	92%	7%	85%	3%	*yes*
3	**Restriction of sexual activity**	83%	2%	88%	2%	81%	8%	84%	3%	*yes*
3	**Modifying how you walk, sit or stand because of your fistula**	82%	3%	88%	2%	90%	7%	86%	3%	*yes*
6	**Neurological complications**	82%	8%	88%	6%	86%	10%	85%	6%	*yes*
2	**Anal pain**	82%	3%	83%	2%	88%	8%	84%	3%	*yes*
3	**Avoidance of intimacy**	82%	5%	86%	2%	83%	5%	84%	3%	*yes*
3	**Change in lifestyle based on toileting needs**	82%	3%	80%	2%	80%	10%	80%	4%	*yes*
3	**Physically restricted in caring for oneself**	80%	5%	88%	2%	78%	8%	82%	4%	*yes*
3	**Embarrassment & feeling isolated**	80%	2%	83%	5%	80%	5%	81%	3%	*yes*
3	**Limitation to moderate activities**	80%	3%	78%	2%	83%	5%	80%	3%	*yes*
2	**Discrimination between passing stool and gas**	78%	3%	78%	3%	88%	7%	81%	3%	*yes*
6	**Cardio-respiratory complications**	78%	10%	80%	8%	86%	10%	81%	7%	*yes*

3	**Feeling depressed & down, hopelessness and unable to cope**	77%	7%	83%	3%	86%	10%	82%	6%	*yes*
6	**Allergic reaction**	77%	3%	73%	6%	78%	10%	76%	5%	*yes*
4	**Hyperintensity on T2 weighted MRI**	77%	8%	56%	5%	88%	7%	73%	5%	*yes*
4	**Fistula response on MRI imaging**	75%	15%	89%	3%	90%	5%	85%	5%	*yes*
3	**Change in general health - psychological**	75%	5%	80%	3%	83%	8%	79%	4%	*yes*
3	**Anxiety & worries**	73%	8%	70%	3%	86%	7%	77%	5%	*yes*
1	**Development of other perianal features**	68%	7%	61%	6%	92%	2%	73%	4%	*yes*
3	**Change in physical ability to do things**	65%	3%	72%	6%	86%	8%	74%	4%	*yes*
4	**MRI assessment of fistula volume**	52%	13%	80%	2%	86%	5%	73%	6%	*yes*
3	**A global assessment of quality of life**	48%	8%	69%	6%	75%	12%	64%	8%	*yes*
3	**Lethargy and fatigue**	43%	10%	56%	8%	83%	7%	61%	7%	*yes*
6	**Urinary complications**	37%	7%	61%	8%	85%	10%	61%	6%	*yes*
2	**Wound infection**	28%	7%	78%	5%	92%	3%	66%	3%	*yes*
1	**A validated score to assess perianal disease activity e.g. Perianal disease activity index (PDAI)**	27%	17%	52%	9%	81%	10%	53%	11%	*yes*
2	**A global assessment of incontinence that covers all aspects of leakage**	20%	10%	78%	5%	69%	8%	56%	6%	*yes*

4	**Fistula T1 enhancement on MRI**	17%	10%	55%	3%	86%	5%	52%	5%	*yes*
2	**Anal bleeding**	12%	17%	36%	8%	86%	5%	44%	9%	*yes*
4	**An activity based MRI score e.g. Van Assche Score**	10%	18%	64%	5%	78%	5%	51%	9%	*yes*

THEME KEY

1	Fistula response to treatment (symptoms)
2	Direct impact of fistula on the patient
3	Impact on the patient as a person
4	Assessment with imaging techniques (scans)
5	Fistula response to treatment (tests)
6	Safety implications related to treatment
7	Impact on patient over time

1

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