Heterogeneity in outcome selection, definition and measurement in studies assessing the treatment of cryptoglandular anal fistula: findings from a systematic review

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Abstract
Background  Treatment for cryptoglandular anal fistula (AF) is challenging and a lack of uniform outcomes in the literature prevents direct comparison of treatments. This can be addressed by developing a core outcome set, a standardised set of outcomes reported in all interventional studies for a specific condition. The aim of this systematic review is to assess the range of outcomes, their definitions, and the measurement instruments currently utilised in interventional studies for adult patients with AF. This will inform the development of an AF core outcome set.

Methods  Medline, Embase and The Cochrane Library were searched to identify all patient- and clinician-reported outcomes in studies assessing medical, surgical or combination treatment of adult patients with AF published from January 2008 to May 2020. The resulting outcomes were categorized according to the Core Outcome Measurement in Effectiveness Trials (COMET) taxonomy to better understand their distribution.

Results  In total, 155 studies were included, 552 outcomes were extracted, with a median of three outcomes (interquartile range 2–5) per study. Only 25% of studies demonstrated high-quality outcome reporting. The outcomes were merged into 52 unique outcomes and structured into four core areas and 14 domains, with the majority in the domain of physiological or clinical (gastrointestinal) outcomes. The most commonly reported outcomes were healing (77%), incontinence (63%), and recurrence (40%), with no single outcome assessed across all studies. There was a wide variation in outcome definitions and measurement instruments used.

Conclusions  There is substantial heterogeneity in outcomes, definitions, and measurement instruments reported in interventional studies for cryptoglandular anal fistula. This emphasises the need for standardised outcome reporting and measurement.

Keywords Cryptoglandular anal fistula · Systematic review · Outcome assessment · Core outcome set

Introduction
Cryptoglandular anal fistula (AF) is a challenging condition to manage. The symptom burden can be severe and can have wide-ranging impact on physical functioning and quality of life [1]. For clinicians, the difficulties of balancing treatment efficacy with minimal impairment of continence have been well documented [2, 3], particularly for complex and recurrent cases. In an attempt to address the dichotomy in achieving these key treatment aims, numerous sphincter-preserving procedures have been developed in recent decades. These procedures have now made their way into common clinical practice, leading to wide variation in the techniques used according to surgical expertise, preference, and geographical area [4]. Along with the expansion of procedures, numerous interventional studies have been conducted to assess success rates and determine treatment superiority. Attempts have been made to meta-analyse data from multiple studies, however, difficulties in doing so reliably are frequently reported, due to inadequate follow-up, lack of randomized controlled trials, and non-uniform reporting of outcomes [4–6]. This limits the development of treatment guidelines for AF.
The selection of relevant and appropriate outcomes is crucial to any study on treatment effectiveness [7], however, the lack of a systematic approach results in the reporting of numerous outcomes with varied definitions, multiple measurement instruments, and inconsistencies in the timing of assessment. Furthermore, selective reporting of outcomes based on significant results is a recognised problem and can overestimate the size of the treatment effect [8, 9]. Such outcome reporting bias can lead to ill-informed decisions with the potential to cause patient harm [10].

One way of addressing such issues is to develop a core outcome set (COS); an agreed, standardised set of outcomes to be measured in all interventional studies for a specific health condition [9]. The importance and value of a COS in disease areas with heterogeneity in outcome reporting is being increasingly recognised. However, a COS has not yet been developed for cryptoglandular AF. We believe that this is an important step in addressing the challenges in developing evidence-based management strategies.

According to the Core Outcome Measurement in Effectiveness Trials (COMET) initiative, the first stage in the development of a COS is to determine what to measure, which can be partially achieved by identifying potential outcomes from the existing literature [7]. The primary aim of this systematic review was to identify all patient- and clinician-reported outcomes in studies assessing medical, surgical or combination treatment of adult patients with cryptoglandular AF, to inform the development of a cryptoglandular Anal Fistula Core Outcome Set (AFCOS) [11]. The secondary aim is to assess outcome definitions and identify the measurement instruments used.

### Materials and methods

A systematic review of studies assessing medical, surgical, and combined interventions for cryptoglandular AF was performed in accordance with a registered protocol (PROSPERO-ID CRD42018102778).

### Search strategy

An electronic search strategy was developed by an information specialist prior to execution. The following electronic databases were searched, adjusting vocabulary and syntax for each: Medline (Ovid), Embase (Ovid), and The Cochrane Library. Validated terms for ‘Perianal Fistula’ were used, ensuring that all interventional studies for AF could be captured. If MeSH terms or subject headings existed, these were included in the search strategy and supplemented with free-text searches of the same databases. To avoid limiting the scope of outcomes identified, no study design filter was applied. The search was restricted to full-text articles in English published from January 2008 to May 2020 and to studies conducted in human subjects aged ≥ 18 years. The full search strategy can be found in Table 1.

| Table 1  | Search strategy |
|----------|-----------------|
| Embase (Ovid) | Anus fistula/  
2 | Rectum fistula/  
3 | ((Anus or anal or anorectal or rectal or rectum or perianal) adj4 fistul*).m_titl  
4 | Fistula ani.m_titl  
5 | Fistula-in-ano.m_titl  
6 | 1 or 2 or 3 or 4 or 5  
7 | Limit 6 to (full text and human and year = “2008–current”) |
| The Cochrane library | MeSH descriptor: (rectal fistula) this term only  
2 | (Anus or anal or anorectal or rectal or rectum or perianal) near/4 (fistul*):ti  
3 | Fistula ani:ti  
4 | Fistula-in-ano:ti  
5 | #1 or #2 or #3 or #4  
| Publication date from January 2008 to May 2020 |
| Medline (Ovid) | Rectal fistula/  
2 | ((Anus or anal or anorectal or rectal or rectum or perianal) adj4 fistul*).m_titl  
3 | Fistula ani.m_titl  
4 | Fistula-in-ano.m_titl  
5 | 1 or 2 or 3 or 4  
6 | Limit 5 to (full text and humans and year = “2008–current”) |
Study selection

Four members of the study management group (AM, NI, KS, SA) identified and screened titles and abstracts using Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia, available at https://www.covidence.org/home), with each abstract and full-text publication screened by two independent group members. The following predefined selection criteria were used: (1) Prospective [including randomised controlled trials (RCTs), cohort comparisons, case controls and case series], retrospective, and observational studies including ≥ 10 patients and systematic reviews published between January 2008 and May 2020; (2) including ≥ 10 adult patients (aged ≥ 18 years) with cryptoglandular AF; (3) assessing medical, surgical, or combined interventions for cryptoglandular AF; (4) and reporting ≥ one outcome. Studies were excluded if they were abstract only or if they reported on interventions that were only assessed on fistulas that were not perianal or not of cryptoglandular origin. Systematic reviews were included and individual studies were checked for eligibility. Disagreements were resolved through discussion with recourse to the senior authors (PT, SB) if necessary.

Data extraction

Two members of the study management group (AM, NI) extracted data from eligible studies using a predefined data extraction sheet created in Microsoft Excel. Extracted data included study publication year, design, interventions, patients, outcomes (primary and secondary), outcome definitions and measurement instruments used. In keeping with COMET recommendations, all data were extracted verbatim [7]. The quality of describing and reporting outcomes was assessed using Harman’s criteria [12], which are presented in (Table 2). Disagreements were resolved through discussion with recourse to the senior authors (PT, SB) if necessary.

Data synthesis

Outcome categorisation

The resulting list of outcomes was reviewed by the study management group, including patient representatives (AM, NI, GK, RW, HG, MK, UG, PT, SB) to enable those with similar wording or meaning to be reduced to a single outcome. These were then mapped according to the COMET taxonomy developed for outcomes in medical research [13]. In this taxonomy, the measurable aspects of health conditions can be structured into five core areas, namely death, physiological or clinical, life impact, resource use, and adverse events, and further subdivided into 38 domains.

Data analysis

Primary, secondary, and overall outcome reporting were analysed. Results were summarised using frequencies and percentages. The frequency of outcome domain reporting was calculated. The interventions studied, number of outcome definitions and measurement instruments used were collated and analysed.

Results

Search strategy and study selection

The electronic databases Medline (Ovid), Embase (Ovid), and The Cochrane Library were searched in May 2018, followed by an updated search in May 2020, identifying a total of 2583 records. A schematic overview of the inclusion and exclusion of articles, including reasons provided for exclusion, is presented in Fig. 1. Full-text screening resulted in the inclusion of 143 articles, including 15 systematic reviews. The systematic reviews were individually screened for any additional studies that were not captured by the initial search and this yielded 27 articles, resulting in a final number of 155 articles from which data were extracted.

Study characteristics

An overview of the 155 included studies is presented in Table 2. Interventions for cryptoglandular AF were assessed on a total of 11,819 patients (mean 76, range 10–462 participants per study). The majority of studies were prospective studies (52%) and assessed the effectiveness of sphincter-preserving procedures, of which fistula plugs (19%) and ligation of intersphincteric fistula tract (LIFT) procedures (19%) were assessed most frequently. The characteristics of the included studies are presented in Table 3. The quality of outcome reporting for each individual study was assessed using Harman’s criteria [12] and reported in Table 2. The criteria involve assessing whether: (1) The primary outcome for a study is clearly stated, (2) The primary outcome is clearly defined so that other researchers can reproduce its measurement, (3) The secondary outcomes are clearly stated, (4) The secondary outcomes are clearly defined, (5) The authors explain the use of the outcomes they have selected and (6) Any methods were used to enhance the quality of outcome measurement. The average number of criteria met across all studies was two, with only 38 of 155 studies (25%) meeting ≥ four criteria, indicating high-quality outcome reporting in just a quarter of the studies assessed.
In total, 552 patient- and clinician-reported outcomes were extracted from 155 studies, with studies reporting a median of three outcomes (interquartile range 2–5) per study. Duplicate and analogous terms were merged to form 52 outcomes, of which healing (77%), incontinence (63%), recurrence (40%), and pain (26%) were reported most frequently (Table 4). Outcomes such as healing and recurrence were sometimes measured at different time points within the same study but referred to as primary or secondary outcomes. This resulted in some studies reporting outcomes of healing and recurrence more than once.
### Table 2  Overview of the included studies

| First author     | Title                                                                 | Year of publication | Study design   | Intervention(s)               | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|------------------|-----------------------------------------------------------------------|---------------------|----------------|------------------------------|------------------------|----------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|------------------------------------------|-------------------------------------------------------------|
| A ba-baike-re    | Randomized controlled trial of minimally invasive surgery using acellular dermal matrix for complex anorectal fistula | 2010                | RCT            | ADM ERAF                     | 90                     | 6                    | Yes                             | Yes                             | Yes                             | Yes                             | No                                        | Yes                                        |
| Abcarian         | Ligation of intersphincteric fistula tract: early results of a pilot study | 2012                | Prospective study | LIFT procedure              | 40                     | 3                    | Yes                             | No                              | Yes                             | No                              | No                                        | No                                        |
| Abdelnaby        | Drained mucosal advancement flap versus rerouting seton around the internal anal sphincter in treatment of high trans-sphincteric anal fistula: a randomized trial | 2019                | RCT            | Advancement flap and drainage seton around EAS Seton around IAS | 97                     | 6                    | Yes                             | Yes                             | Yes                             | Yes                             | No                                        | No                                        |
| First author | Title                                                                 | Year of publication | Study design     | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|------------------|-----------------|------------------------|----------------------|-------------------------------|--------------------------------|----------------------------------|------------------------------------------|-----------------------------------------------------------|
| Aboulian     | Early result of ligation of the intersphincteric fistula tract for fistula-in-ano | 2011                | Retrospective review | LIFT procedure  | 25                     | 5                    | Yes                           | No                             | Yes                              | No                                       | Yes                                                      | No                                                        |
| Adams        | Long-term outlook after successful fibrin glue ablation of cryptoglandular transphincteric fistula-in-ano | 2008                | Retrospective review | Fibrin glue     | 36                     | 2                    | Yes                           | No                             | Yes                              | No                                       | No                                                      | No                                                        |
| Adamina      | To plug or not to plug: a cost-effectiveness analysis for complex anal fistula | 2010                | Prospective study  | AFP ERAF         | 24                     | 2                    | Yes                           | Yes                           | N/A                              | N/A                                      | Yes                                                      | No                                                        |
| Altomare     | Seton or glue for transphincteric anal fistulae: a prospective randomized crossover clinical trial | 2011                | RCT               | Fibrin glue Seton | 64                     | 5                    | Yes                           | No                             | Yes                              | Yes                                      | No                                                      | No                                                        |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------|---------------------------------------------------------------------------------|------------------------|------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------------------|-------------------------------------------------|
| Alvandipour  | Efficacy of 10% sucralfate ointment after anal fistulotomy: a prospective, double-blind, randomised, placebo-controlled trial | 2016                | RCT          | Fistulotomy and 10% sucralfate Fistulotomy and placebo                           | 41                     | 2                      | Yes                              | Yes                               | Yes                               | Yes                             | No                                             | No                                             |
| Anan         | Fistulotomy with or without marsupialisation of wound edges in treatment of simple anal fistula: a randomised controlled trial | 2019                | RCT          | Fistulotomy Fistulotomy and marsupialisation                                    | 60                     | 5                      | Yes                              | Yes                               | Yes                               | Yes                             | No                                             | No                                             |
| Arawatti     | Standardisation and clinical evaluation of nimba ksharsutra in the management of bhagandar (fistula in ano) | 2012                | RCT          | Seton Seton                                                                      | 40                     | 5                      | Yes                              | Yes                               | No                                | N/A                             | No                                             | No                                             |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)          | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------|--------------------------|------------------------|----------------------|-------------------------------|-------------------------------|-----------------------------------|-----------------------------------|------------------------------------|--------------------------------------------------|
| Arroyo      | Photodynamic therapy for the treatment of complex anal fistula        | 2017                | Prospective study | Photodynamic therapy     | 10                     | 4                    | Yes                           | Yes                           | Yes                               | Yes                               | No                                 | No                                |
| Arroyo      | Fistulotomy and sphincter reconstruction in the treatment of complex fistula-in-ano: long-term clinical and manometric results | 2012                | Prospective study | FISR                     | 70                     | 2                    | Yes                           | No                            | Yes                               | No                                | No                                 | Yes                               |
| First author | Title                                                                 | Year of publication | Study design            | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly defined? | Secondary outcomes clearly stated? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|-------------------------|-------------------------------------------------------------------------------|-----------------------|-----------------------|--------------------------------|----------------------------------|-----------------------------------|---------------------------------|---------------------------------------------|----------------------------------------------------------|
| Atkin        | For many high anal fistulas, lay open is still a good option          | 2011                | Retrospective review    | EUA Drainage of abscess Fistulotomy (and marsupialization) Seton Fibrin glue Advancement flap Transperineal core-out and repair Martius flap Sphincter repair Defunctioning stoma Proctectomy and permanent colostomy | 180                   | 3                     | Yes                             | No                               | Yes                               | No                             | No                                         | No                                                     |
| Attaallah    | Should we consider topical silver nitrate irrigation as a definitive nonsurgical treatment for perianal fistula | 2014                | Prospective study      | Irrigation and 1% silver nitrate                                               | 56                    | 3                     | Yes                             | Yes                              | Yes                               | Yes                             | No                                         | Yes                                                    |
| First author | Title                                                                 | Year of publication | Study design   | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|----------------|------------------|------------------------|----------------------|-------------------------------|---------------------------------|----------------------------------|-----------------------------------|------------------------------------------------|--------------------------------------------------|
| Bleier       | Ligation of the intersphincteric fistula tract: an effective new technique for complex fistulas | 2010                | Retrospective review | LIFT procedure   | 39                     | 3                    | Yes                           | No                              | Yes                              | No                                | No                                | No                                               |
| Boeniecke    | Advancement flap for treatment of complex cryptoglandular anal fistula: prediction of therapy success or failure using anamnestic and clinical parameters | 2017                | Prospective study  | Advancement flap | 61                     | 2                    | Yes                           | Yes                             | Yes                              | Yes                               | No                                | No                                               |
| Bondi        | Randomized clinical trial comparing collagen plug and advancement flap for transsphincteric anal fistula | 2017                | RCT             | AFP Advancement flap | 94                     | 4                    | Yes                           | Yes                             | Yes                              | Yes                               | No                                | Yes                                               |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|------------------------------------------------------------------------|---------------------|--------------|---------------------------------------------------------------------------------|------------------------|----------------------|-------------------------------|----------------------------------|---------------------------------|----------------------------------|-------------------------------------------------|-------------------------------------------------|
| Browder      | Modified Hanley procedure for management of complex horseshoe fistulae | 2009                | Retrospective review | Modified Hanley procedure, drainage and setons                                  | 23                     | 4                    | Yes                           | No                               | Yes                             | No                               | No                               | No                               |
| Chalya       | Fistulectomy versus fistulotomy with marsupialisation in the treatment of low fistula-in-ano: a prospective randomized controlled trial | 2013                | RCT          | Fistulectomy Fistulotomy and marsupialisation                                   | 162                    | 9                    | Yes                           | Yes                              | Yes                             | Yes                              | No                               | No                               |
| Chan         | Initial experience of treating anal fistula with the Surgisis anal fistula plug | 2012                | Prospective study | AFP                                                                             | 44                     | 2                    | Yes                           | Yes                              | Yes                             | No                               | No                               | No                               |
Table 2 (continued)

| First author | Title                                                                 | Year of publication | Study design       | Intervention(s)                      | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|--------------------|--------------------------------------|------------------------|-----------------------|---------------------------------|----------------------------------|----------------------------------|----------------------------------------|-------------------------------------------------------------|
| Chen         | High ligation of the fistula track by lateral approach: a modified sphincter-saving technique for advanced anal fistulas | 2012                | Prospective study  | Modified LIFT procedure               | 10                     | 4                     | No                              | No                               | N/A                              | N/A                                    | Yes                                        | No                                             |
| Chowbey      | Minimally invasive anal fistula treatment (MAFT)—an appraisal of early results in 416 patients | 2015                | Prospective study  | MAFT                                 | 416                    | 3                     | Yes                             | No                               | No                               | N/A                                    | No                                        | No                                             |
| Chung        | Anal fistula plug and fibrin glue versus conventional treatment in repair of complex anal fistulas | 2009                | Retrospective review | AFP Fibrin glue Advancement flap Seton | 232                    | 1                     | Yes                             | Yes                              | N/A                              | N/A                                    | No                                        | No                                             |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|--------------|-----------------|------------------------|----------------------|--------------------------------|-----------------------------------|--------------------------------|----------------------------------|------------------------------------------------|------------------------------------------------|
| Choi         | Patient-performed seton irrigation for the treatment of deep horseshoe fistula | 2010                | Retrospective review | Seton           | 24                     | 4                    | Yes                             | Yes                               | No                              | N/A                              | No                                | No                                             |
| Choi         | Autologous adipose tissue-derived stem cells for the treatment of complex perianal fistulas not associated with Crohn’s disease: a phase II clinical trial for safety and efficacy | 2017                | Prospective study  | ASC             | 15                     | 5                    | Yes                             | Yes                               | Yes                             | Yes                              | No                                | Yes                                           |
| Christosforidis | Treatment of complex anal fistulas with the collagen fistula plug       | 2008                | Retrospective review | AFP             | 47                     | 1                    | Yes                             | No                               | N/A                             | N/A                              | No                                | No                                             |
| First author | Title                                                                 | Year of publication | Study design       | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------------|-----------------|------------------------|----------------------|---------------------------------|----------------------------------|----------------------------------|--------------------------------------|--------------------------------------------------|
| Christoforidis | Treatment of trans sphincteric anal fistulas by endorectal advancement flap or collagen fistula plug: a comparative study | 2009                | Retrospective review | ERAFAFP          | 80                     | 3                    | Yes                             | Yes                              | Yes                              | No                                   | No                                               |
| Cintron      | Treatment of fistula-in-ano using a porcine small intestinal submucosa anal fistula plug | 2013                | Prospective study  | AFP              | 73                     | 2                    | Yes                             | Yes                              | Yes                              | No                                   | No                                               |
| Daodu        | Draining setons as definitive management of fistula-in-ano          | 2018                | Retrospective study | Seton            | 76                     | 2                    | Yes                             | Yes                              | No                               | N/A                                  | No                                               |
### Table 2 (continued)

| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|--------------|-----------------|------------------------|----------------------|-------------------------------|---------------------------------|-----------------------------------|---------------------------------|--------------------------------------------------|---------------------------------------------------------------|
| De La Portilla | Platelet-rich plasma (PRP) versus fibrin glue in cryptogenic fistula-in-ano: a phase III single-center, randomized, double-blind trial | 2019                | RCT          | PRP Fibrin glue  | 56                     | 5                    | Yes                           | Yes                             | Yes                               | No                              | No                               | Yes                                         |
| De La Portilla | Treatment of transsphincteric fistula-in-ano with growth factors from autologous platelets: results of a phase II clinical trial | 2017                | Prospective study | PRGF            | 36                     | 5                    | Yes                           | Yes                             | No                                | N/A                             | No                               | No                                           |
| De La Portilla | Evaluation of a new synthetic plug in the treatment of anal fistulas: results of a pilot study | 2011                | Prospective study | AFP             | 19                     | 4                    | Yes                           | No                             | No                                | N/A                             | No                               | No                                           |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|---------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|------------------------------------------|--------------------------------------------------|
| Dubsky       | Endorectal advancement flaps in the treatment of high anal fistula of cryptoglandular origin: full thickness vs mucosal rectum flaps | 2008 | Retrospective review | Advancement flap Advancement flap | 54 | 2 | No | N/A | No | N/A | No | No |
| Dozois       | Early results of a phase I trial using an adipose-derived mesenchymal stem cell-coated fistula plug for the treatment of transsphincteric cryptoglandular fistulas | 2019 | Prospective study | AFP | 15 | 3 | Yes | No | Yes | Yes | No | Yes |
| Ege          | Hybrid seton for the treatment of high anal fistulas: results of 128 consecutive patients | 2014 | Retrospective review | Seton | 128 | 5 | Yes | No | No | N/A | No | No |
| First author | Title                                                                 | Year of publication | Study design          | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|-----------------------|-----------------|------------------------|----------------------|--------------------------------|---------------------------------|-------------------------------------|---------------------------------|-----------------------------------------------|------------------------------------------------|
| Eitan        | The use of the loose seton technique as a definitive treatment for recurrent and persistent high trans-sphincteric anal fistulas: a long-term outcome | 2009                | Retrospective review  | Seton           | 41                     | 3                    | Yes                            | Yes                             | No                                  | N/A                             | No                             | No                                             |
| Ellis        | Outcomes with the use of bioprosthetic grafts to reinforce the ligation of the intersphincteric fistula tract (BioLIFT procedure) for the management of complex anal fistulas | 2010                | Retrospective review  | BioLIFT procedure | 31                     | 2                    | Yes                            | Yes                             | N/A                                 | N/A                             | No                             | No                                             |
| First author | Title                                                                 | Year of publication | Study design       | Intervention(s)       | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------------|-----------------------|------------------------|----------------------|----------------------------------|-----------------------------------|--------------------------------------|--------------------------------------|---------------------------------------------|-------------------------------------------------|
| Ellis        | Long-term outcomes with the use of bioprosthetic plugs for the management of complex anal fistulas | 2010                | Retrospective review | AFP                   | 63                     | 1                    | Yes                              | No                                | No                                   | N/A                                  | No                                           | No                                              |
| Fabiani      | Permacol collagen paste injection for the treatment of complex anal fistula: 1-year follow-up | 2017                | Prospective study | Collagen paste injection | 21                     | 3                    | Yes                              | No                                | Yes                                  | No                                   | No                                           | No                                              |
| Fung         | Operative strategy for fistula-in-ano without diversion of the anal sphincter | 2013                | Retrospective review | Partial fistulotomy and seton | 46                     | 3                    | Yes                              | Yes                              | Yes                                  | Yes                                  | Yes                                           | No                                              |
| First author  | Title                                                                 | Year of publication | Study design | Intervention(s)                        | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------|----------------------------------------|------------------------|----------------------|----------------------------------|-----------------------------------|--------------------------------------|---------------------------------|--------------------------------------------------|--------------------------------------------------|
| Garcia-Arranz | Autologous adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistula: a randomized clinical trial with long-term follow-up | 2020                | RCT          | ASC and fibrin glue Fibrin glue         | 57                     | 4                    | Yes                              | Yes                               | N/A                                  | N/A                              | No                                | Yes                                             |
| Garcia-Olmo  | Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial | 2009                | RCT          | Fibrin glue Fibrin glue ASC             | 49                     | 4                    | Yes                              | No                                | No                                   | N/A                              | No                                | No                                              |
| First author | Title                                                                 | Year of publication | Study design       | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------------|-----------------|------------------------|----------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|--------------------------------------------------|
| Garg         | PERFACT procedure (Proximal superficial cauterization, emptying regularly of fistula tracts and curettage of tracts): A new concept to treat highly complex anal fistula | 2015                | Prospective study  | PERFECT procedure | 51                     | 3                    | Yes                             | No                              | No                              | N/A                              | No                               | No                                 |
| Garg         | To determine the efficacy of anal fistula plug in the treatment of high fistula-in-ano: an initial experience | 2009                | Prospective study  | AFP              | 21                     | 7                    | No                              | N/A                             | No                              | N/A                              | No                               | No                                 |
| Gautier      | Easy clip to treat anal fistula tracts: a word of caution           | 2015                | Retrospective study| Clip             | 17                     | 10                   | Yes                             | No                              | No                              | N/A                              | No                               | No                                 |
| First author | Title                                                                 | Year of publication | Study design     | Intervention(s)          | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|----------------------|------------------|---------------------------|------------------------|-----------------------|---------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Giamundo     | Fistula-tract laser closure (FiLaC): long-term results and new operative strategies | 2015                 | Retrospective study | FiLaC                     | 45                     | 5                     | Yes                             | Yes                               | Yes                               | Yes                                  | No                                                   | No                                                                 |
| Gottgens     | Ligation of the intersphincteric fistula tract for high transsphincteric fistula yields moderate results at best: is the tide turning? | 2019                 | Retrospective study | LIFT, BioLIFT             | 46                     | 5                     | Yes                             | Yes                               | Yes                               | No                                   | No                                                   | No                                                                 |
| Gottgens     | Long-term results of mucosal advancement flap combined with platelet-rich plasma for high cryptoglandular perianal fistulas | 2014                 | Retrospective study | Advancement flap and platelet-rich plasma | 25                     | 2                     | Yes                             | Yes                               | Yes                               | Yes                                  | No                                   | No                                                   | No                                                                 |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|----------------------|-----------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------------------|------------------------------------------------------------------|
| Grolich      | Role of video-assisted anal fistula treatment in our management of fistula-in-ano | 2014         | Retrospective review | VAAFT           | 30                     | 2                    | Yes                         | No                            | No                              | No                              | N/A                           | No                                      |
| Gupta        | Topical sucralfate treatment of anal fistulotomy wounds: a randomized placebo-controlled trial | 2011         | RCT           | Fistulotomy and 7% sucralfate Fistulotomy and placebo | 80                     | 3                    | Yes                         | Yes                           | Yes                             | Yes                             | No                           | No                                      |
| Haim         | Long-term results of fibrin glue treatment for cryptogenic perianal fistulas: a multicenter study | 2011         | Retrospective review | Fibrin glue      | 23                     | 3                    | Yes                         | Yes                           | Yes                             | Yes                             | No                           | Yes                                      |
| Hall         | Outcomes after operations for anal fistula: results of a prospective, multicenter, regional study | 2014         | Retrospective review | Fistulotomy LIFT procedure Seton Advancement flap AFP | 240                    | 2                    | Yes                         | No                            | No                              | N/A                            | No                           | No                                      |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|---------------------|-------------------------------|-------------------------------|--------------------------------|---------------------------------|--------------------------------|--------------------------------------------------|
| Hammond      | Manage-ment of idiopathic anal fistula using cross-linked collagen: a prospective phase 1 study | 2011 | Prospective study | Collagen paste injection Fibrin glue | 29 | 6 | Yes | Yes | Yes | Yes | No | No |
| Han          | Ligation of intersphincteric fistula tract vs ligation of the intersphincteric fistula tract plus a bioprosthetic anal fistula plug procedure in patients with transsphincteric anal fistula: early results of a multicenter prospective randomized trial | 2016 | RCT | LIFT procedure LIPT-plug procedure | 237 | 5 | Yes | Yes | No | N/A | No | No |
| First author | Title                                                                 | Year of publication | Study design  | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|---------------|-----------------|------------------------|----------------------|-------------------------------|---------------------------------|----------------------------------|---------------------------------|-------------------------------------------------|-------------------------------------------------|
| Han          | Long-term outcomes of human acellular dermal matrix plug in closure of complex anal fistulas with a single tract | 2011                | Retrospective study | ADM             | 114                    | 2                    | Yes                           | Yes                             | No                               | N/A                             | No                               | No                               |
| Han          | Ligation of the intersphincteric fistula tract plus bioprosthetic anal fistula plug (LIFT-Plug): a new technique for fistula-in-ano | 2013                | Prospective study | LIFT-plug procedure | 21                    | 3                    | Yes                           | Yes                             | Yes                              | Yes                             | No                               | No                               |
| Herold       | Results of the Gore Bio-a fistula plug implantation in the treatment of anal fistula: a multicentre study | 2016                | Prospective study | AFP              | 60                    | 6                    | Yes                           | Yes                             | Yes                              | Yes                             | No                               | Yes                             |
| First author | Title                                                                                     | Year of publication | Study design     | Intervention(s)                                | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|-------------|-------------------------------------------------------------------------------------------|---------------------|------------------|------------------------------------------------|------------------------|----------------------|-------------------------------|----------------------------------|---------------------------------|---------------------------------|-----------------------------------------------|--------------------------------------------------------|
| Herreros    | Autologous expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas: a phase III randomized clinical trial (FATT 1: fistula advanced therapy trial 1) and long-term evaluation | 2012                | RCT              | ASC ASC and fibrin glue Fibrin glue           | 183                    | 4                    | Yes                           | Yes                              | No                              | No                              | No                                            | No                                                   |
| Hirschburger| Fistulectomy with primary sphincter reconstruction in the treatment of high trans-sphincteric anal fistulas | 2014                | Retrospective review | FISR             | 50                     | 4                    | No                            | N/A                             | No                              | N/A                             | No                                            | No                                                   |
| First author | Title                                                                 | Year of publication | Study design       | Intervention(s)                                      | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|--------------------|-----------------------------------------------------|------------------------|----------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------------------------|-----------------------------------------------------------|
| Han          | Ligation of the intersphincteric fistula tract plus a bioprosthetic anal fistula plug (LIFT-plug): a new technique for fistula-in-ano | 2013                | Prospective study  | LIFT-plug procedure                                 | 46                     | 5                    | No                              | N/A                             | Yes                             | No                              | No                                      | No                                      |
| Heydari      | Bioabsorbable synthetic plug in the treatment of anal fistulas          | 2013                | Retrospective review | AFP                                                  | 48                     | 3                    | Yes                             | No                              | No                              | N/A                             | No                                      | No                                      |
| Hyman        | Outcomes after fistulotomy: results of a prospective, multicenter regional study | 2009                | Prospective study  | Fistulotomy Seton Fistulotomy AFP Fibrin glue Advancement flap | 245                    | 3                    | Yes                             | Yes                             | Yes                             | Yes                             | No                                      | No                                      |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|----------------------|--------------|---------------------------------------------------------------------------------|------------------------|------------------------|--------------------------------|---------------------------------|---------------------------------|--------------------------------|-----------------------------------------------|-------------------------------------------------|
| Jain         | Comparison of a fistulotomy and a fistulotomy with marsupialization in the management of a simple anal fistula: a randomized, controlled pilot trial | 2012                 | RCT          | Fistulectomy Fistulotomy and marsupialization                                    | 40                     | 9                      | Yes                           | No                              | No                              | No                              | No                             | No                             |
| Jivapaisarnpong | Core out fistulotomy, anal sphincter reconstruction and primary repair of internal opening in the treatment of complex anal fistula | 2009                 | Prospective study | FISR                                                                                           | 33                     | 4                      | No                             | N/A                             | No                              | N/A                             | No                             | No                             |
| Jarrar       | Advancement flap repair: a good option for complex anorectal fistulas | 2011                 | Retrospective study | Advancement flap                                                                                       | 98                     | 3                      | Yes                           | No                              | Yes                             | No                              | No                             | No                             |
Table 2 (continued)

| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------|--------------------------------------------------------------------------------|------------------------|------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------------------|----------------------------------------------------------------|
| Jayne        | Anal fistula plug versus surgeon’s preference for surgery for trans-sphincteric anal fistula: the FIAT RCT | 2019                | RCT          | AFP Surgeon’s preference (fistulotomy, seton, advancement flap or LIFT)         | 304                    | 6                      | Yes                             | Yes                             | No                              | No                              | Yes                                         | No                                           |
| Jiang        | Video-assisted anal fistula treatment (VAAFT) for complex anal fistula: a preliminary evaluation in China | 2017                | Retrospective review | VAAFT                                               | 52                     | 4                      | Yes                             | Yes                             | No                              | N/A                             | No                                           | No                                           |
| Kalim        | Comparison of mean healing time and mean pain scores between fistulotomy and fistulotomy for the treatment of low fistula in ano | 2017                | RCT          | Fistulotomy Fistulotomy                                                          | 304                    | 3                      | Yes                             | No                              | Yes                             | No                              | No                                           | No                                           |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|---------------------|-------------------------------|-------------------------------|----------------------------------|----------------------------------|----------------------------------|--------------------------------------------------|
| Ky           | Collagen fistula plug for the treatment of anal fistula | 2008 | Prospective study | AFP            | 45                     | 3                   | Yes                           | Yes                           | No                               | No                               | N/A                               | No                              |
| Kelly        | The role of loose seton in the management of anal fistula: a multicenter study of 200 patients | 2014 | Retrospective review | Seton          | 200                   | 3                   | Yes                           | No                           | No                               | No                               | N/A                               | No                              |
| Khafagy      | Treatment of anal fistula by partial rectal wall advancement flap or mucosal advancement flap: a prospective randomized study | 2010 | Prospective study | Advancement flap | 40                    | 5                   | Yes                           | No                           | No                               | No                               | N/A                               | No                              |
| Kochhar      | Video-assisted anal fistula treatment | 2014 | Retrospective review | VAAFT          | 82                    | 5                   | Yes                           | Yes                          | Yes                              | Yes                              | Yes                              | Yes                             |
| First author | Title                                                                 | Year of publication | Study design     | Intervention(s)   | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|------------------|-------------------|------------------------|-----------------------|---------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|------------------------------------------|--------------------------------------------------|
| Lara         | Platelet-rich fibrin sealant as a treatment for complex perianal fistulas: a multicentre study | 2015                | Prospective study | PRF                | 60                     | 3                     | Yes                             | Yes                               | No                                | N/A                               | No                                        | Yes                                              |
| Lawes        | Early experience with the bioabsorbable anal fistula plug          | 2008                | Retrospective review | AFP                | 20                     | 2                     | Yes                             | No                                | No                                | N/A                               | No                                        | No                                                |
| Leventoglu   | Treatment for horseshoe fistula with the modified Hanley procedure using a hybrid seton: results of 21 cases | 2013                | Prospective study | Modified Hanley procedure | 21                     | 7                     | Yes                             | No                                | Yes                               | No                                | No                                        | Yes                                              |
| Liu          | Long-term results of ligation of intersphincteric fistula tract (LIFT) for fistula-in-ano | 2013                | Retrospective review | LIFT procedure      | 38                     | 5                     | Yes                             | Yes                               | No                                | N/A                               | No                                        | No                                                |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Lupinacci    | Treatment of fistula-in-ano with the Surgisis AFP anal fistula plug    | 2010                | Prospective study | AFP             | 15                     | 2                    | Yes                             | Yes                             | Yes                             | Yes                             | No                              | No                              |
| Lo           | Ligation of intersphincteric fistula tract procedure for the management of cryptoglandular anal fistulas | 2012                | Prospective study | LIFT procedure   | 25                     | 5                    | Yes                             | Yes                             | No                              | N/A                             | No                              | No                              |
| Lehman       | Efficacy of LIFT for recurrent anal fistula                           | 2013                | Prospective study | LIFT procedure   | 17                     | 2                    | No                              | N/A                             | No                              | N/A                             | Yes                             | No                              |
| Lobo         | A comparative clinical study of Snahi Ksheera Sutra, Tilanala Kshara Sutra and Apamarga Kshara Sutra in Bhagandara (fistula in ano) | 2012                | Prospective study | Seton Seton       | 33                     | 3                    | Yes                             | Yes                             | No                              | N/A                             | No                              | No                              |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                         | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Madbouly     | Ligation of intersphincteric fistula tract versus mucosal advancement flap in patients with high transsphincteric fistula-in-ano: a prospective randomized trial | 2014                | RCT          | LIFT procedure Advancement flap                         | 70                      | 6                    | Yes                         | Yes                              | No                                | No                               | No                                             | No                                             |
| Malakorn     | Ligation of intersphincteric fistula tract for fistula in ano: lessons learned from a decade of experience | 2017                | Retrospective review | LIFT procedure                                      | 251                     | 1                    | Yes                         | Yes                              | N/A                               | N/A                              | No                                             | No                                             |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Mansour      | Medical intervention treatment of adult fistula-in-ano. A pilot study for curative response of intra-tract injections of Ceftazidime and Metronidazole | 2016 | RCT          | Ceftazidime and Metronidazole injection                                          | 25                     | 2                     | No                             | N/A                             | No                              | N/A                             | No                              | No                                             |
| Mascagni     | OTSC proctology vs. fistulectomy and primary sphincter reconstruction as a treatment for low trans-sphincteric anal fistula in a randomized controlled pilot trial | 2019 | Retrospective study | Clip Fistulectomy                                                                | 30                     | 3                     | No                             | N/A                             | No                              | N/A                             | No                              | No                                             |
| First author | Title                                                                 | Year of publication | Study design       | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|------------------------------------------------------------------------|---------------------|--------------------|------------------|------------------------|-----------------------|-------------------------------|----------------------------------|----------------------------------|---------------------------------|-----------------------------------------------|---------------------------------------------------------|
| Mascagni     | Total fistulectomy, sphincteroplasty and closure of the residual cavity for trans-sphincteric perianal fistula in the elderly patient | 2017                | Retrospective review | FISR             | 86                     | 6                     | No                            | N/A                              | No                               | N/A                             | No                              | No                                          |
| McGee        | Tract length predicts successful closure with anal fistula plug in cryptoglandular fistulas | 2010                | Prospective study  | AFP              | 41                     | 2                     | Yes                           | No                               | No                               | N/A                             | No                              | No                                          |
| Meinero      | Video-assisted anal fistula treatment: a novel sphincter-saving procedure for treating complex anal fistulas | 2011                | Retrospective review | VAAFT            | 136                    | 3                     | No                            | N/A                              | No                               | N/A                             | No                              | No                                          |
| First author | Title                                                                 | Year of publication | Study design          | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Meinero     | Video-assisted anal fistula treatment: a new concept of treating anal fistulas | 2014                | Retrospective review  | VAAFT            | 203                    | 5                    | No                            | N/A                           | No                               | N/A                              | No                                          | No                                             |
| Mennigen    | The OTSC proctology clip system for the closure of refractory anal fistulas | 2015                | Retrospective review  | Clip            | 10                     | 4                    | Yes                           | Yes                           | No                               | N/A                              | No                                          | No                                             |
| Mishra      | The role of fibrin glue in the treatment of high and low fistulas in ano | 2013                | Prospective study    | Fibrin glue      | 30                     | 4                    | No                            | N/A                           | No                               | N/A                              | No                                          | No                                             |
| Mitalas     | Does rectal mucosal blood flow affect the outcome of transanal advancement flap repair? | 2009                | Prospective study    | Advancement flap | 54                     | 3                    | No                            | N/A                           | No                               | N/A                              | Yes                                         | No                                             |
| First author       | Title                                                                 | Year of publication | Study design | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Mushaya           | Ligation of intersphincteric fistula tract compared with advancement flap for complex anorectal fistulas requiring initial seton drainage | 2012               | RCT          | LIFT procedure Advancement flap                                                | 39                     | 6                     | No                            | N/A                             | No                             | N/A                             | No                                   | Yes                                             |
| Naeer             | Better option for the patients of low fistula in ano: fistulotomy or fistulotomy | 2012               | RCT          | Fistulotomy Fistulectomy                                                       | 150                    | 5                     | No                            | N/A                             | No                             | N/A                             | No                                   | No                                              |
| Nordholm-Carstensen | Treatment of complex fistula-in-ano with nitinol proctology clip       | 2017               | Retrospective review | Clip                                                          | 35                     | 2                     | Yes                           | Yes                             | Yes                            | Yes                             | Yes                                   | No                                             |
### Table 2 (continued)

| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Omar         | Drainage seton versus external anal sphincter-sparing seton after rerouting of the fistula tract in the treatment of complex anal fistula: a randomized controlled trial | 2019                | RCT          | Seton Rerouting of fistula tract and seton around internal anal sphincter       | 60                     | 6                    | Yes                           | Yes                               | Yes                                 | Yes                                      | No                                           | No                                          |
| Ommer        | Gore BioA fistula plug in the treatment of high anal fistulas - initial results from a German multicenter study | 2012                | Retrospective review | AFP                                                              | 40                     | 1                    | No                            | N/A                               | N/A                                 | N/A                                      | Yes                                          | No                                           |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Ortiz       | Randomized clinical trial of anal fistula plug versus endorectal advancement flap for the treatment of high cryptoglandular fistula in ano | 2009                | RCT          | AFP ERAF        | 32                     | 2                    | Yes                           | No                              | Yes                             | Yes                             | Yes                           | No                                         |
| Ortiz       | Length of follow-up after fistulotomy and fistulectomy associated with endorectal advancement flap repair for fistula in ano | 2008                | Prospective study | Fistulotomy and ERAF | 206                   | 2                    | No                            | N/A                             | N/A                             | N/A                             | No                           | No                                         |
| Owen        | Plugs unplugged. Anal fistula plug: the Concord experience           | 2010                | Retrospective review | AFP            | 32                     | 1                    | Yes                           | Yes                             | N/A                             | N/A                             | No                           | No                                         |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|--------------|-----------------|-----------------------|----------------------|--------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|---------------------------------|-------------------------------------------------|
| Ooi          | Managing fistula-in ano with ligation of the intersphincteric fistula tract procedure: the Western Hospital experience | 2012                | Prospective study | LIFT procedure  | 25                    | 2                    | Yes                             | Yes                               | Yes                               | Yes                               | Yes                             | No                               |
| Ozturk       | Treatment of recurrent anal fistula using an autologous cartilage plug: a pilot study | 2015                | Prospective study | AFP             | 10                    | 5                    | No                              | N/A                               | No                                | N/A                              | Yes                             | No                               |
| Ozturk       | Laser ablation of fistula tract a sphincter-preserving method for treating fistula-in ano | 2014                | Retrospective review | Laser ablation | 37                    | 1                    | Yes                             | Yes                               | N/A                               | N/A                              | Yes                             | No                               |
| Proost       | Short-term outcomes of a novel endoscopic clipping device for closure of the internal opening in 100 anorectal fistulas | 2016                | Retrospective review | Clip            | 96                    | 2                    | No                              | N/A                               | No                                | N/A                              | No                              | No                               |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------|-----------------|------------------------|----------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|
| Ratto        | Fistulotomy with end-to-end primary sphincteroplasty for anal fistula: results from a prospective study | 2013                | Prospective study | FISR            | 72                     | 2                    | No                           | N/A                           | No                           | No                            | No                             | No                             |
| Roig         | Changes in anorectal morphologic and functional parameters after fistula-in-ano surgery | 2009                | Prospective study | Fistulotomy FISR Seton Fistulectomy and advancement flap | 120                    | 4                    | No                           | N/A                           | No                           | N/A                           | Yes                            | No                             |
| Roig         | Fistulectomy and sphincteric reconstruction for complex cryptoglandular fistulas | 2010                | Retrospective review | ERAF FISR       | 146                    | 7                    | No                           | N/A                           | No                           | N/A                           | No                             | No                             |
| Safar        | Anal fistula plug: initial experience and outcomes                  | 2009                | Retrospective review | AFP             | 35                     | 1                    | No                           | N/A                           | No                           | N/A                           | Yes                            | No                             |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)                                      | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Sanad        | A randomized controlled trial on the effect of topical phenytoin 2% on wound healing after anal fistulotomy | 2019                | RCT          | Fistulotomy and phenytoin Fistulotomy               | 60                     | 6                     | Yes                           | Yes                           | Yes                                 | Yes                                 | No                                             | No                                                                                          |
| Schulze      | Management of complex anorectal fistulas with seton drainage plus partial fistulotomy and subsequent ligation of intersphincteric fistula tract (LIFT) | 2015                | Prospective study | Seton Fistulotomy and LIFT procedure                | 75                     | 5                     | Yes                           | Yes                           | N/A                                 | N/A                                 | No                                             | No                                                                                          |
| Schwandner   | Surgical treatment of complex anal fistulas with the anal fistula plug: a prospective, multicenter study | 2009                | Prospective study | AFP                                                   | 60                     | 4                     | No                            | N/A                           | No                                  | N/A                                  | No                                             | No                                                                                          |
| First author | Title                                                                 | Year of publication | Study design  | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
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| Schwandner   | Randomized clinical trial comparing a small intestinal submucosa anal fistula plug to advancement flap for the repair of complex anal fistulas | 2018                | RCT           | AFP Advancement flap | 82                   | 5                    | Yes                           | Yes                             | Yes                             | Yes                             | No                                             | No                                             |
| Seneviratne  | Quality of life following surgery for recurrent fistula-in-ano       | 2009                | Prospective study | Fistulotomy Fistulectomy Seton | 21                   | 1                    | No                            | N/A                             | N/A                             | N/A                             | No                                             | No                                             |
| Seow-En      | An experience with video-assisted anal fistula treatment (VAAFT) with new insights into the treatment of anal fistulae | 2016                | Retrospective review | VAAFT             | 41                   | 3                    | Yes                           | Yes                             | N/A                             | N/A                             | Yes                                            | No                                             |
| First author | Title                                                                 | Year of publication | Study design        | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|---------------------|---------------------------------------------------------------------------------|------------------------|------------------------|-------------------------------|----------------------------------|----------------------------------|----------------------------------|-----------------------------------------------|-------------------------------------------------|
| Shafik       | Combined partial fistulectomy and electrocauterization of the intersphincteric tract as a sphincter-sparing treatment of complex anal fistula: clinical and functional outcome | 2014                | Prospective study   | Fistulectomy and electrocauterization                                             | 53                     | 4                      | No                            | N/A                              | No                               | N/A                              | No                                             | No                                              |
| Shanwani     | Ligation of the intersphincteric fistula tract (LIFT): a sphinctersaving technique for fistula-in-ano | 2010                | Prospective study   | LIFT procedure                                                            | 45                     | 4                      | No                            | N/A                              | No                               | N/A                              | No                                             | No                                              |
| Sileri       | Surgery of fistula-in-ano in a specialist colorectal unit: a critical appraisal | 2011                | Prospective study   | Seton Fistulotomy LIFT procedure Advancement flap                             | 247                    | 6                      | No                            | N/A                              | No                               | N/A                              | No                                             | No                                              |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|---------------------|-------------------------------|-------------------------------|---------------------------------|---------------------------------|-----------------------------------------------|-----------------------------------------------|
| Sileri       | Ligation of the intersphincteric fistula tract (LIFT) to treat anal fistula: early results from a prospective observational study | 2011 | Prospective study | LIFT procedure | 18 | 4 | No | N/A | No | N/A | No | No |
| Stamos       | Prospective multicenter study of a synthetic bioabsorbable anal fistula plug to treat cryptoglandular transsphincteric anal fistulas | 2015 | Prospective study | AFP | 93 | 5 | No | N/A | No | N/A | No | No |
| Stroumza     | Surgical treatment of transsphincteric anal fistulas with the Fat GRAFT technique: a minimally invasive procedure | 2017 | Prospective study | Fat grafting | 11 | 3 | Yes | Yes | Yes | No | Yes | No |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|----------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|--------------------------------------------|---------------------------------------------------------------|
| Sugrue       | Sphincter-sparing anal fistula repair: are we getting better? | 2017 | Retrospective review | LIFT procedure, Fibrin glue, Advancement flap, AFP, Advancement flap and AFP, Advancement flap | 462 | 1 | Yes | No | N/A | N/A | Yes | No |
| Shanwari     | Ligation of the intersphincteric fistula tract (LIFT): a sphincter-saving technique for fistula-in-ano | 2010 | Prospective study | LIFT procedure, Advancement flap and AFP, Advancement flap and advancement flap | 45 | 4 | Yes | Yes | No | N/A | No | Yes |
| Schwandner   | Initial experience on efficacy in closure of cryptoglandular and Crohn’s trans-sphincteric fistula by the use of the anal fistula plug | 2008 | Prospective study | AFP | 19 | 3 | Yes | Yes | Yes | Yes | No | No |
| First author       | Title                                                                 | Year of publication | Study design      | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|-------------------|-----------------------------------------------------------------------|---------------------|-------------------|--------------------------------------------------------------------------------|------------------------|----------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|------------------------------------------------|------------------------------------------------|
| Sirikurnpiboon    | Ligation of intersphincteric fistula tract and its modification: results from treatment of complex fistula | 2013                | Prospective study | LIFT procedure and fistulectomy                                                  | 41                     | 6                    | No                            | N/A                            | No                             | N/A                             | No                                            | No                                              |
| Sungurtekin       | Loose seton: a misnomer of cutting seton                               | 2016                | Prospective study | Seton                                                                            | 50                     | 3                    | Yes                           | Yes                            | Yes                            | Yes                             | No                                            | No                                              |
| Tan               | To LIFT or to flap? Which surgery to perform following seton insertion for high anal fistula? | 2012                | Retrospective review | ERAF LIFT procedure                                                             | 31                     | 2                    | No                            | N/A                            | No                             | N/A                             | Yes                                           | No                                              |
| Tan               | The anatomy of failures following the ligation of intersphincteric tract technique for anal fistula: a review of 93 patients over 4 years | 2011                | Retrospective review | LIFT procedure                                                                  | 93                     | 3                    | No                            | N/A                            | No                             | N/A                             | Yes                                           | No                                              |
| First author | Title                                                                 | Year of publication | Study design          | Intervention(s)   | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|-----------------------|-------------------|------------------------|----------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|-------------------------------------------------|
| Terzi        | Closing perianal fistulas using a laser: long-term results in 103 patients | 2018                | Retrospective review  | FiLaC             | 103                    | 2                    | No                              | N/A                             | No                              | N/A                             | No                              | No                                              |
| Tobisch      | Total fistulectomy with simple closure of the internal opening in the management of complex cryptoglandular fistulas: long-term results and functional outcome | 2012                | Retrospective review  | Fistulectomy and closure of internal opening | 252                    | 2                    | No                              | N/A                             | No                              | N/A                             | Yes                              | No                                              |
| Tokunaga     | Clinical role of a modified seton technique for the treatment of transsphincteric and suprasphincteric anal fistulas | 2013                | Retrospective review  | Seton             | 239                    | 2                    | No                              | N/A                             | No                              | N/A                             | Yes                              | Yes                                             |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|----------------|------------------------|---------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|-------------------------------------------------|
| Tozer        | Fistulotomy in the tertiary setting can achieve high rates of fistula cure with an acceptable risk of deterioration in continence | 2013 | Retrospective review | Fistulotomy | 50 | 3 | No | N/A | No | N/A | No | No |
| Tan          | Early experience of reinforcing the ligation of the intersphincteric fistula tract procedure with a bioprosthetic graft (BioLIFT) for anal fistula | 2014 | Retrospective study | BioLIFT procedure | 13 | 4 | No | N/A | No | N/A | No | No |
| Thekkinkattil | Efficacy of the anal fistula plug in complex anorectal fistulae | 2009 | Prospective study | AFP | 43 | 2 | Yes | Yes | No | N/A | No | No |
| Tsunoda      | Anal function after ligation of the intersphincteric fistula tract | 2013 | Prospective study | LIFT procedure and seton | 20 | 3 | No | N/A | No | N/A | Yes | No |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s)       | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|--------------|-----------------------|------------------------|----------------------|-------------------------------|----------------------------------|---------------------------------|----------------------------------|--------------------------------|---------------------------------------------------------------|
| Van Koperen  | The anal fistula plug versus the mucosal advancement flap for the treatment of anorectal fistula (PLUG trial) | 2008                | RCT          | AFP Advancement flap   | 60                     | 4                    | No                            | N/A                              | No                              | N/A                              | Yes                             | No                                             |
| Van Koperen  | Fibrin glue and transanal rectal advancement flap for high transsphincteric perianal fistulas; is there any advantage? | 2008                | Retrospective study | Fibrin glue and advancement flap | 80                     | 2                    | Yes                           | Yes                              | Yes                             | No                              | Yes                             | No                                             |
| Van Koperen  | The anal fistula plug treatment compared with the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistula: a double-blinded multicenter randomized trial | 2011                | RCT          | AFP Advancement flap   | 60                     | 5                    | No                            | N/A                              | No                              | N/A                              | No                              | No                                             |
| First author | Title                                                                 | Year of publication | Study design          | Intervention(s)                              | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly defined? | Secondary outcomes explained? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|-------------|----------------------------------------------------------------------|---------------------|-----------------------|----------------------------------------------|------------------------|----------------------|-------------------------------|-------------------------------|-------------------------------------|----------------------------------|------------------------------------------------|----------------------------------------------------------------|
| Van Koperen | Long-term functional outcome and risk factors for recurrence after surgical treatment for low and high perianal fistulas of cryptoglandular origin | 2008                | Retrospective review  | Fistulotomy and advancement flap             | 179                    | 3                     | No                            | N/A                           | No                                  | Yes                              | No                            | No                                                                          |
| Van Onkelen | Treatment of anal fistulas with high intersphincteric extension      | 2013                | Retrospective review  | Advancement flap and drainage of abscess     | 14                     | 3                     | No                            | N/A                           | No                                  | No                              | Yes                           | No                                                                          |
| Van Onkelen | Is it possible to improve the outcome of transanal advancement flap repair for high transsphincteric fistulas by additional ligation of the intersphincteric fistula tract? | 2012                | Prospective study    | LIFT procedure and advancement flap          | 41                     | 2                     | No                            | N/A                           | No                                  | Yes                              | No                            | No                                                                          |
| First author       | Title                                                                 | Year of publication | Study design      | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|-------------------|----------------------------------------------------------------------|---------------------|-------------------|------------------|------------------------|----------------------|---------------------------------|-----------------------------------|----------------------------------|-------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|
| Van Onkelen       | Ligation of the intersphincteric fistula tract in low transphincteric fistula: a new technique to avoid fistulotomy | 2013                | Retrospective study | LIFT procedure   | 22                     | 2                    | Yes                             | Yes                               | No                               | N/A                                 | No                                                       | No                                                       |
| Van Onkelen       | Predictors of outcome after transanal advancement flap repair for high transphincteric fistulas | 2014                | Retrospective review | Advancement flap | 252                   | 2                    | No                              | N/A                               | No                               | N/A                                 | Yes                                                      | No                                                       |
| Visscher          | Long-term follow-up after surgery for simple and complex cryptoglandular fistulas: fecal incontinence and impact on quality of life | 2015                | Retrospective study | Fistulotomy      | 116                   | 2                    | No                              | N/A                               | No                               | N/A                                 | Yes                                                      | Yes                                                      |
| First author | Title                                                   | Year of publication | Study design     | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|---------------------------------------------------------|---------------------|------------------|-----------------|------------------------|---------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|--------------------------------|--------------------------------------------------|
| Walega       | VAAFT: a new minimally invasive method in the diagno-     | 2014                | Prospective      | VAAFT           | 18                     | 5                   | No                             | No                              | N/A                             | N/A                             | No                               | No                                             |
|              | stics and treatment of anal fistulas—initial results    |                     | study            |                 |                        |                     |                                 |                                 |                                 |                                 |                                 |                                                 |
| Wallin       | Does ligation of the intersphincteric fistula tract     | 2012                | Retrospective    | LIFT procedure   | 93                     | 4                   | No                             | N/A                             | No                              | No                              | No                               | No                                             |
|              | raise the bar in fistula surgery?                       |                     | review            |                 |                        |                     |                                 |                                 |                                 |                                 |                                 |                                                 |
| Wang         | Traditional Chinese surgical treatment for anal fis-    | 2012                | RCT              | Suture dragging and pad compression Fistulotomy | 60         | 6                   | Yes                            | No                              | Yes                             | No                              | No                               | No                                             |
|              | tulae with secondary tracks and abscess                 |                     |                  | Fistulotomy      |                        |                     |                                 |                                 |                                 |                                 |                                 |                                                 |
| Wang         | Management of low transsphincteric anal fistula with    | 2016                | Retrospective    | Seton Fistulotomy | 26                    | 2                   | Yes                            | Yes                            | N/A                             | N/A                             | No                               | No                                             |
|              | serial setons and interval muscle-cutting fistulotomy  |                     | study            |                 |                        |                     |                                 |                                 |                                 |                                 |                                 |                                                 |
| First author | Title                                                                 | Year of publication | Study design   | Intervention(s)   | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|----------------|-------------------|------------------------|----------------------|-------------------------------|-------------------------------------|----------------------------------------|----------------------------------------|------------------------------------------------|------------------------------------------------|
| Wang         | Treatment of transsphincteric anal fistulas: are fistula plugs an acceptable alternative? | 2009                | Retrospective study | AFP Advancement flap | 55                     | 1                    | No                            | N/A                                 | No                                      | N/A                                    | No                                      | No                                      |
| Wilhelm      | A new technique for sphincter-preserving anal fistula repair using a novel radial emitting laser probe | 2011                | Retrospective study | FiLaC           | 11                     | 2                    | Yes                           | Yes                                 | Yes                                     | Yes                                     | Yes                                     | No                                      |
| Wilhelm      | Five years of experience with the FiLaC laser for fistula-in-ano management: long-term follow-up from a single institution | 2017                | Prospective study | FiLaC           | 117                    | 2                    | No                            | N/A                                 | No                                      | N/A                                    | Yes                                     | No                                      |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|--------------|-----------------|------------------------|----------------------|---------------------------------|----------------------------------|----------------------------------|----------------------------------|---------------------------------------------|---------------------------------------------------------------|
| Yan          | Clinical effect of tunnel-like fistulectomy plus draining seton combined with incision of internal opening of anal fistula (TFSIA) in the treatment of high-transsphincteric anal fistula | 2020 | RCT         | TFSIA Seton     | 80                    | 7                    | No                              | N/A                              | No                               | N/A                              | No                                           | No                                           |
| Ye           | Early experience with the modified approach of ligation of the intersphincteric fistula tract for high transsphincteric fistula | 2015 | Retrospective review | Modified LIFT procedure | 43 | 3 | Yes | Yes | Yes | Yes | Yes | No | No |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|---------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Yuan         | Clinical study on herbal fumigation of detumescence and pain relieving shengji decoction in wound repair after anal fistula surgery | 2017 | RCT | Shengji decoction Potassium permanganate | 90 | 6 | No | N/A | No | N/A | No | No |
| Zarin        | VAAFT: video-assisted anal fistula treatment: bringing revolution in fistula treatment | 2015 | Prospective study | VAAFT | 40 | 3 | Yes | Yes | N/A | N/A | Yes | No |
| Zubaidi      | Anal fistula plug in high fistula-in-anor: an early Saudi experience | 2009 | Prospective study | AFP | 22 | 1 | Yes | No | No | N/A | No | No |
| First author | Title                                                                 | Year of publication | Study design          | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-----------------------------------------------------------------------|---------------------|-----------------------|-----------------|------------------------|----------------------|----------------------------------|---------------------------------|------------------------------------|----------------------------------------|------------------------------------------|--------------------------------------------------|
| Zwiep       | Comparison of ligation of the intersphincteric fistula tract and BioLIFT for the treatment of transsphincteric anal fistula: a retrospective analysis | 2020                | Retrospective review  | LIFT, BioLIFT    | 119                    | 4                    | Yes                              | Yes                             | Yes                                | Yes                                    | No                                       | No                                          |
| Total        |                                                                       |                     |                       |                 | 11,819 patients        | 552 outcomes         | 65.8%                            | 67.6%                           | 39.7%                              | 64.3%                                  | 20.0%                                    | 11.0%                                     |
| Adegbola     | Short-term efficacy and safety of three novel sphincter-sparing techniques for anal fistulae: a systematic review | 2017                | Systematic review     |                 |                        |                      |                                  |                                  |                                    |                                        |                                          |                                                |
| Alasari      | Overview of anal fistula and systematic review of ligation of the intersphincteric fistula tract (LIFT) | 2014                | Systematic review     |                 |                        |                      |                                  |                                  |                                    |                                        |                                          |                                                |
| First author | Title                                                                 | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|-------------|----------------------------------------------------------------------|---------------------|--------------|-----------------|------------------------|---------------------|-------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Cirocchi    | The treatment of anal fistulas with biologically derived products: is innovation better than conventional surgical treatment? An update | 2013                | Systematic review |                |                        |                     |                               |                                    |                                     |                                        |                                              |                                                            |
| Cirocchi    | Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano | 2010                | Systematic review |                |                        |                     |                               |                                    |                                     |                                        |                                              |                                                            |
| Garg        | The efficacy of anal fistula plug in fistula-in-ano: a systematic review | 2010                | Systematic review |                |                        |                     |                               |                                    |                                     |                                        |                                              |                                                            |
| Hong        | Ligation of intersphincteric fistula tract (LIFT) to treat anal fistula: systematic review and meta-analysis | 2014                | Systematic review |                |                        |                     |                               |                                    |                                     |                                        |                                              |                                                            |
| First author | Title                                                                 | Year of publication | Study design       | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|------------------------------------------------------------------------|---------------------|-------------------|-------------------------------------------------------------------------------|------------------------|------------------------|-------------------------------|---------------------------------|----------------------------------|---------------------------------|---------------------------------|----------------------------------------------------------------|
| Jacob        | Surgical intervention for anorectal fistula                           | 2010                | Systematic review |                                                                                   |                        |                        |                               |                                 |                                   |                                 |                                 |                                                                 |
| Malik        | Incision and drainage of perianal abscess with or without treatment of anal fistula | 2010                | Systematic review |                                                                                   |                        |                        |                               |                                 |                                   |                                 |                                 |                                                                 |
| O’Riordan    | A systematic review of the anal fistula plug for patients with Crohn’s and non-Crohn’s related fistula-in-ano | 2012                | Systematic review |                                                                                   |                        |                        |                               |                                 |                                   |                                 |                                 |                                                                 |
| Pu           | Fistula plug versus conventional surgical treatment for anal fistulas: a systematic review and meta-analysis | 2012                | Systematic review |                                                                                   |                        |                        |                               |                                 |                                   |                                 |                                 |                                                                 |
| First author | Title                                                                 | Year of publication | Study design                        | Intervention(s)                                                                 | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|----------------------------------------------------------------------|---------------------|-------------------------------------|---------------------------------------------------------------------------------|------------------------|-----------------------|---------------------------------|-------------------------------|-----------------------------------------|---------------------------------|---------------------------------------------|--------------------------------------------------|
| Ratto        | Fistulotomy or fistulectomy and primary sphincteroplasty for anal fistula (FIPS): a systematic review | 2015                | Systematic review                   |                                                                                 |                        |                       |                                 |                               |                                          |                                 |                                             |                                                  |
| Ritchie      | Incontinence rates after cutting seton treatment for anal fistula    | 2009                | Systematic review                   |                                                                                 |                        |                       |                                 |                               |                                          |                                 |                                             |                                                  |
| Sirany       | The ligation of the intersphincteric fistula tract procedure for anal fistula: a mixed bag of results | 2015                | Systematic review                   |                                                                                 |                        |                       |                                 |                               |                                          |                                 |                                             |                                                  |
| Soltani      | Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano | 2010                | Systematic review                   |                                                                                 |                        |                       |                                 |                               |                                          |                                 |                                             |                                                  |
| First author | Title | Year of publication | Study design | Intervention(s) | Number of participants | Number of outcome(s) | Primary outcome clearly stated? | Primary outcome clearly defined? | Secondary outcomes clearly stated? | Secondary outcomes clearly defined? | The use of the selected outcomes explained? | Methods used to enhance the quality of outcome measurement? |
|--------------|-------|---------------------|--------------|-----------------|------------------------|---------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Vial         | Faecal incontinence after seton treatment for anal fistulae with and without surgical division of internal anal sphincter: a systematic review | 2010 | Systematic review | | | | | | | | | |

**RCT** randomized controlled trial, **ADM** acellular dermal matrix, **ERAF** endorectal advancement flap, **LIFT** ligation of intersphincteric fistula tract, **EAS** external anal sphincter, **IAS** internal anal sphincter, **AFP** anal fistula plug, **FISR** fistulectomy/fistulotomy and immediate sphincter reconstruction, **EUA** examination under anaesthetic, **MAFT** minimally invasive anal fistula treatment, **ASC** adipose-derived stem cells, **PRP** platelet-rich plasma, **PRGF** plasma-rich growth factor, **PERFACT** proximal superficial cauterization, emptying regularly fistula tracts and curettage of tracts, **FiLaC** fistula laser closure, **VAAFT** video-assisted anal fistula treatment, **PRF** platelet-rich fibrin, **TFSIA** tunnel-like fistulectomy plus draining seton combined with incision of internal opening of anal fistula
Table 3 Study characteristics

| Study included | N (%) |
|----------------|-------|
| Total included | 155 (100) |

Study types contributing to data synthesis

| Study type | N (%) |
|------------|-------|
| Retrospective studies | 66 (43) |
| Prospective studies (RCT) | 89 (57) |

| Publication year | N (%) |
|------------------|-------|
| 2008–2010 | 40 (25) |
| 2011–2013 | 50 (32) |
| 2014–2016 | 35 (23) |
| 2017–2019 | 27 (17) |
| 2020 | 3 (2) |

| Intervention(s) | Control(s) | N (%) |
|-----------------|------------|-------|
| AFP | No control | 30 (19) |
| LIFT | No control | 29 (19) |
| LIFT-plug | LIFT-plug | 6 (4) |
| BioLIFT | Advancement flap | 6 (4) |
| Modified LIFT | LIFT and fistulectomy | 6 (4) |
| LIFT and seton | BioLIFT | 6 (4) |
| LIFT and advancement flap | LIFT and advancement flap | 6 (4) |
| LIFT and fistulectomy | LIFT and advancement flap | 6 (4) |
| Seton | No control | 12 (8) |
| Fistulotomy | No control | 10 (7) |
| Fistulotomy and sucralfate | Advancement flap | 6 (4) |
| Partial fistulotomy and seton | Fistulotomy | 6 (4) |
| Fistulotomy and phenytoin | Fistulotomy and placebo sucralfate | 6 (4) |
| Fistulotomy and ERAF | Fistulotomy and seton | 6 (4) |
| Fistulotomy and marsupialization | Fistulotomy | 6 (4) |
| VAAFT | No control | 8 (5) |
| Fibrin glue | No control | 6 (4) |
| Fibrin glue and advancement flap | Seton | 3 (3) |
| Fibrin glue and ASC | Fistulotomy | 3 (3) |
| Fistulotomy and electro-cauterization | Fistulotomy | 3 (3) |
| Fistulotomy and closure of internal fistula opening | Fistulotomy and marsupialization | 3 (3) |
| TFSIA | Seton | 3 (3) |
| FISR | No control | 5 (3) |
| FiLaC or laser ablation | No control | 5 (3) |
| Clip | No control | 5 (3) |
Table 3 (continued)

| Intervention(s)                          | Control(s)                                           | n (%) |
|-----------------------------------------|------------------------------------------------------|-------|
| ERAF                                    | AFP, LIFT, FISR                                      | 3 (2) |
| ASC                                     | No control, ASC, fibrin glue, and fibrin glue, Fibrin glue | 3 (2) |
| ADM                                     | No control, ERAF                                     | 2 (1) |
| Modified Hanley                         | No control                                           | 2 (1) |
| Modified Hanley, drainage, and setons   |                                                      |       |
| Collagen paste injection                | No control, Fibrin glue                              | 2 (1) |
| PRGF                                    | No control                                           | 1 (1) |
| PERFECT procedure                       | No control                                           | 1 (1) |
| PRF                                     | No control                                           | 1 (1) |
| MAFT                                    | No control                                           | 1 (1) |
| Irrigation and silver nitrate           | No control                                           | 1 (1) |
| PRP                                     | Fibrin glue                                          | 1 (1) |
| ≥ 4 interventions compared              |                                                      | 7 (5) |
| Other                                   |                                                      | 5 (3) |
| Total                                   |                                                      | 155 (100) |

AFP anal fistula plug, ERAF endorectal advancement flap, LIFT ligation of intersphincteric fistula tract, VAAFT video-assisted anal fistula treatment, ASC adipose-derived stem cells, TFSIA tunnel-like fistulectomy plus draining seton combined with incision of internal opening of anal fistula, FISR fistulotomy/fistulotomy and immediate sphincter reconstruction, FiLaC fistula laser closure, ADM acellular dermal matrix, PRGF plasma-rich growth factor, PERFECT proximal superficial cauterezation, emptying regularly fistula tracts and curettage of tracts, PRF platelet-rich fibrin, MAFT minimally invasive anal fistula treatment, PRP platelet-rich plasma

Outcome categorisation

The outcomes were categorized into core areas and domains according to the COMET taxonomy, with guidance from a member of COMET. The frequency of these outcomes and their categorisation is shown in Table 5. Adverse event outcomes are categorised under their appropriate taxonomy and identified as a harm outcome [13]. Cryptoglandular AF treatment rarely impacts lifespan, therefore the core area death was excluded from categorisation. Some outcomes were categorised in multiple domains, as the study management group considered their impact to be broad. For instance, ‘problems related to sexual function’ was included in the domains physical, social and emotional functioning and well-being. Outcomes belonging to the core area of ‘physiological or clinical’ were placed in domains according to their underlying cause or affected body system [13]. Whilst categorisation highlighted the spread of outcomes across all relevant domains, the majority focused on the physiological or clinical impact, particularly in the domain of gastrointestinal outcomes (99%), whereas only 12% of outcomes were related to the impact on physical, role and social functioning and emotional functioning and wellbeing (Table 5).

Outcome definitions

Significant heterogeneity in outcome definition and overlap between definitions was noted in the outcomes of ‘healing’, ‘recurrence’, and ‘treatment failure’.

Healing

Healing was reported in 120 studies (77%) and was synonymous with terms such as ‘healing rate’, ‘fistula closure’, ‘success’, ‘cure’, ‘effectiveness’, and ‘complete clinical response’. There was considerable heterogeneity in the definitions of healing, however, overlap between the components of each definition meant that all could be defined by using one or more of the components presented in Table 6. Considering the ways in which components could be combined, 34 different definitions were found. Healing was most frequently defined as ‘healing of the external fistula
## Table 4  Frequency of outcome reporting

| Outcome                          | Reported as primary outcome (n) | Reported as secondary outcome (n) | Unstated (n) | Number of studies reporting outcome (n) (%) |
|----------------------------------|--------------------------------|----------------------------------|-------------|--------------------------------------------|
| Healing                          | 80                             | 12                               | 38          | 120 (77)                                   |
| Incontinence                     | 24                             | 35                               | 39          | 98 (63)                                    |
| Recurrence                       | 16                             | 21                               | 27          | 62 (40)                                    |
| Pain                             | 12                             | 16                               | 12          | 40 (26)                                    |
| Complications                    | 15                             | 10                               | 11          | 36 (23)                                    |
| Closure time                     | 13                             | 3                                | 9           | 25 (16)                                    |
| Treatment failure                | 4                              | 4                                | 14          | 22 (14)                                    |
| Quality of life                  | 6                              | 12                               | 4           | 22 (14)                                    |
| Duration of treatment            | 4                              | 7                                | 1           | 12 (8)                                     |
| Morbidity                        | 1                              | 3                                | 7           | 11 (7)                                     |
| Return to work                   | 2                              | 2                                | 3           | 7 (5)                                      |
| Patient satisfaction             | 2                              | 2                                | 3           | 7 (5)                                      |
| Anorectal manometry              | 0                              | 0                                | 6           | 6 (4)                                      |
| Pus discharge                    | 2                              | 3                                | 0           | 5 (3)                                      |
| Hospital stay                    | 1                              | 2                                | 2           | 5 (3)                                      |
| Adverse effects                  | 2                              | 3                                | 0           | 5 (3)                                      |
| Fistula persistence              | 3                              | 1                                | 0           | 4 (3)                                      |
| Reinterventions                  | 0                              | 1                                | 3           | 4 (3)                                      |
| Safety                           | 1                              | 3                                | 0           | 4 (3)                                      |
| Plug dislodgement rates          | 1                              | 2                                | 0           | 3 (2)                                      |
| Symptoms                         | 3                              | 0                                | 0           | 3 (2)                                      |
| Unit cutting time                | 2                              | 0                                | 0           | 2 (1)                                      |
| Size of operative wound          | 0                              | 2                                | 0           | 2 (1)                                      |
| Postoperative perineal sepsis    | 1                              | 0                                | 1           | 2 (1)                                      |
| Postoperative bleeding           | 0                              | 0                                | 2           | 2 (1)                                      |
| Cost-effectiveness               | 1                              | 1                                | 0           | 2 (1)                                      |
| Difficulty of technique          | 2                              | 0                                | 0           | 2 (1)                                      |
| Impact on daily life             | 0                              | 2                                | 0           | 2 (1)                                      |
| Endoanal ultrasound              | 0                              | 0                                | 2           | 2 (1)                                      |
| Radiological healing             | 0                              | 1                                | 0           | 1 (1)                                      |
| Anorectal deformity rate         | 0                              | 1                                | 0           | 1 (1)                                      |
| Burning sensation                | 0                              | 1                                | 0           | 1 (1)                                      |
| Itching                          | 0                              | 1                                | 0           | 1 (1)                                      |
| Length of time until seton removal| 0                             | 1                                | 0           | 1 (1)                                      |
| Fraction of patients showing ≥ 50% decrease in fistula size | 0 | 1 | 0 | 1 (1) |
| Investigator’s satisfaction score| 0                              | 1                                | 0           | 1 (1)                                      |
| Amount of mucosal covering       | 0                              | 1                                | 0           | 1 (1)                                      |
| Asymptomatic                     | 1                              | 0                                | 0           | 1 (1)                                      |
| Subjective parameters            | 0                              | 1                                | 0           | 1 (1)                                      |
| Glue reaction                    | 0                              | 0                                | 1           | 1 (1)                                      |
| Median mucosal blood flow        | 0                              | 0                                | 1           | 1 (1)                                      |
| Problems related to sexual function | 0                         | 0                                | 1           | 1 (1)                                      |
| Pudendal nerve terminal motor latency | 0                  | 0                                | 1           | 1 (1)                                      |
| Duration for return to normal activity | 1                          | 0                                | 0           | 1 (1)                                      |
| Duration of immobilisation       | 1                              | 0                                | 0           | 1 (1)                                      |
| Emerging of a secondary abscess  | 1                              | 0                                | 0           | 1 (1)                                      |
| Need for a new wave of drainage  | 1                              | 0                                | 0           | 1 (1)                                      |
| Removal or migration of the clip | 1                              | 0                                | 0           | 1 (1)                                      |
In nine studies, a radiological assessment was needed to confirm or refute healing [14–22], whereas another study identified ‘radiological healing’ as a separate outcome [23]. Five of these 10 studies included the radiological description required to demonstrate healing [14, 15, 18, 21, 22]. In 21 studies, the definition of healing was dependent upon a time period after which the fistula should be assessed, or for the duration of which the components of healing should be present, which in themselves demonstrated significant variation, ranging from 2 weeks [24] to 12 months [16, 25] after the procedure.

**Recurrence, treatment failure and persistence**

The terms recurrence, treatment failure, and persistence were used interchangeably to describe a spectrum of clinical manifestations, ranging from no evidence of closure or persistence of fistula and symptoms [26–29], to temporary closure followed by re-appearance of the original fistula [26], to the development of additional fistulas [20, 30–32]. Similar to healing, the definitions were broken down into components which are presented in Table 7. The most frequently used definitions were ‘persistence or recurrence of symptoms’ (n = 21), followed by ‘persistence or reappearance of the external fistula opening’ (n = 13). There were 19 different definitions of recurrence and treatment failure. In 10 studies, the definition was qualified by a time period at or after which the fistula had to be assessed, ranging from within the first month [20] to 12 months after treatment [33].

**Outcome measurement instruments**

Heterogeneity was noted amongst the measurement instruments used for the most frequently reported outcomes (Table 8). Combinations of measurement instruments were frequently used. Furthermore, the instruments for each outcome were not always clearly stated and many studies used unspecified questionnaires.

**Discussion**

This systematic review is the first study to provide an overview of the outcomes reported in interventional studies for AF. We identified 552 outcomes from 155 studies published in the last 12 years, which were merged into 52 unique outcomes, of which healing was reported most frequently (77%). Our results demonstrate heterogeneity in outcome definition and measurement, making the use of such studies to supplement current understanding of fistula management and guide treatment pathways much more challenging.

The lack of consistency and clarity in definitions of success, treatment failure, and recurrence after fistula treatment has been previously noted [34]. Despite being one of the most frequently reported outcomes, healing was variably defined in terms of anatomical features, absence of a specific set of symptoms or healing of the (surgical) wound. This highlights the difficulty of data synthesis across different studies, particularly when a fistula has healed in one study simply by closure of the external fistula opening [35], but would be considered persistent in another, where both the external and internal fistula openings, and an absence of symptoms are required [36]. The addition of radiological healing provides additional complexity, as it is well documented that deep tissue healing of perianal fistula as assessed on magnetic resonance imaging lags behind clinical healing by a period of months [37–39]. Nevertheless, radiological outcomes and objective measures of the disease have been frequently used in studies of AF, and their potential inclusion in a COS warrants further discussion and involvement of radiological expertise.

The various definitions of recurrence, persistence, and treatment failure demonstrated overlap, however, in line with previous suggestions [34], we determined that treatment failure and persistence of the fistula, i.e. no change in the morphology and symptomatology of the original fistula, should be differentiated from fistula recurrence, which describes reappearance of the fistula after a period of resolution, and
| Core area                  | Domain                        | Outcomes                                                                 | No. studies reporting outcomes (%) |
|----------------------------|-------------------------------|--------------------------------------------------------------------------|------------------------------------|
| Physiological or clinical  | Gastrointestinal outcomes    | Healing                                                                  | 154 (99)                           |
|                            |                               | Incontinence (harm)                                                     |                                    |
|                            |                               | Recurrence (harm)                                                       |                                    |
|                            |                               | Pain                                                                     |                                    |
|                            |                               | Treatment failure (harm)                                                 |                                    |
|                            |                               | Closure time                                                             |                                    |
|                            |                               | Pus discharge                                                            |                                    |
|                            |                               | Anorectal manometry                                                      |                                    |
|                            |                               | Fistula persistence (harm)                                               |                                    |
|                            |                               | Plug dislodgement rates (harm)                                           |                                    |
|                            |                               | Unit cutting time                                                        |                                    |
|                            |                               | Symptoms                                                                 |                                    |
|                            |                               | Radiological healing                                                     |                                    |
|                            |                               | Anorectal deformity rate (harm)                                          |                                    |
|                            |                               | Burning sensation                                                        |                                    |
|                            |                               | Itching                                                                  |                                    |
|                            |                               | Fraction of patients showing ≥ 50% decrease in fistula size              |                                    |
|                            |                               | Amount of mucosal covering                                               |                                    |
|                            |                               | Asymptomatic                                                             |                                    |
|                            |                               | Subjective parameters                                                    |                                    |
|                            |                               | Glue reaction (harm)                                                     |                                    |
|                            |                               | Endoanal ultrasound                                                      |                                    |
|                            |                               | Pudendal nerve terminal motor latency                                    |                                    |
|                            |                               | Removal or migration of the clip (harm)                                  |                                    |
|                            |                               | Perianal incision wound healing                                          |                                    |
|                            |                               | Conversion into intersphincteric fistula (harm)                          |                                    |
|                            |                               | Keyhole like anomaly (harm)                                              |                                    |
| General outcomes           |                               | Morbidity (harm)                                                         | 11 (7)                             |
| Infection and infestation outcomes |                           | Postoperative perineal sepsis (harm)                                     | 3 (2)                              |
|                            |                               | Emerging of a secondary abscess (harm)                                   |                                    |
| Vascular outcomes          |                               | Median mucosal blood flow                                                | 2 (1)                              |
|                            |                               | Postoperative bleeding (harm)                                             |                                    |
Table 5 (continued)

| Core area                        | Domain                        | Outcomes                                                                 | No. studies reporting outcomes (%) |
|----------------------------------|-------------------------------|---------------------------------------------------------------------------|-----------------------------------|
| Life impact                      | Physical functioning          | Problems related to sexual functioning                                     | 5 (3)                             |
|                                  |                               | Duration for return to normal activity                                     |                                   |
|                                  |                               | Duration of immobilisation                                                  |                                   |
|                                  |                               | Impact daily life                                                           |                                   |
|                                  | Social functioning            | Problems related to sexual functioning                                     | 3 (2)                             |
|                                  |                               | Impact daily life                                                           |                                   |
|                                  | Role functioning              | Return to work                                                              | 8 (5)                             |
|                                  |                               | Impact daily life                                                           |                                   |
|                                  | Emotional functioning or well-being | Problems related to sexual functioning                                     | 3 (2)                             |
|                                  |                               | Impact daily life                                                           |                                   |
|                                  | Global quality of life        | Quality of life                                                             | 22 (14)                           |
|                                  | Delivery of care              | Treatment failure                                                           | 32 (22)                           |
|                                  |                               | Duration of treatment                                                       |                                   |
|                                  |                               | Patient satisfaction                                                        |                                   |
|                                  |                               | Size of operative wound                                                     |                                   |
|                                  |                               | Length of time until seton removal                                          |                                   |
|                                  |                               | Investigator’s satisfaction score                                          |                                   |
| Resource use                     | Economic                      | Cost-effectiveness                                                          | 2 (1)                             |
|                                  | Hospital                      | Hospital stay                                                               | 5 (3)                             |
|                                  | Need for further intervention | Reinterventions                                                            | 6 (4)                             |
|                                  |                               | Need for a new wave of drainage                                             |                                   |
|                                  |                               | Analgesic requirement                                                       |                                   |
| Adverse events                   | Adverse events and/or effects | Complications                                                               | 44 (28)                           |
|                                  |                               | Adverse effects                                                             |                                   |
|                                  |                               | Safety                                                                      |                                   |

Table 6 Components used, in varying combinations, to define the outcome ‘healing’

| Component                                           | Times used |
|-----------------------------------------------------|------------|
| Absence of symptoms                                | 70         |
| Closure of the external fistula opening             | 61         |
| Absence of abscess or infection or inflammation or sepsis | 27         |
| Closure of the (surgical) wound                     | 24         |
| Closure of the internal fistula opening             | 15         |
| Closure of the fistula tract                        | 14         |
| No additional intervention required                 | 8          |
| Absence of recurrence or persistence or treatment failure | 8          |
| Absence of anal sphincter injury                    | 1          |

Table 7 Components used, in varying combinations, to define the outcomes ‘recurrence’ and ‘treatment failure’

| Component                                           | Times used |
|-----------------------------------------------------|------------|
| Persistence or recurrence of symptoms               | 21         |
| Reappearance of the fistula after healing            | 16         |
| Persistence or reappearance of the external fistula opening | 13         |
| Absence of wound healing                            | 8          |
| Abscess or infection                                 | 6          |
| Absence of fistula closure or persistence            | 6          |
| Non-healing fistula                                  | 3          |
| Additional intervention required                     | 3          |
| Additional fistula                                   | 2          |
that development of new fistulas should be considered separately. However, persistence and recurrence of fistulas could simply be the same problem viewed at different time points, and from a patient’s perspective 1 year after the intervention, the difference is probably minimal. This would be an interesting area to explore during the generation of the COS.

The quality of studies eligible for data extraction was assessed using Harman’s criteria [12], however, only a quarter of the studies demonstrated high-quality outcome reporting using this method. Whilst the majority of studies clearly stated their measured outcomes, few went as far as defining whether the outcomes were primary or secondary. Only 20% of the studies explained their reasoning for selecting their outcomes. This may be due to the fact that healing, incontinence, and recurrence, the most commonly reported outcomes, require little explanation for their selection to fistula surgeons or patients, as the ultimate aim of any fistula treatment is frequently cited as healing with minimal impact on continence, and minimal risk of recurrence.

The outcomes summarised in this systematic review were categorised according to the COMET taxonomy. Although all relevant domains are represented, the vast majority of outcomes are related to the pathophysiology of disease and treatment. Only 10% of the outcomes reported by all studies in the last 12 years were related to the impact of disease in terms of its influence on patients’ physical, social and role functioning, in other words their quality of life. Whilst the inclusion of outcomes such as these is encouraging and should be recognised, their use is infrequent and gives a narrow reflection of the wide-ranging impact that fistula symptoms or treatments have for patients. For example, whilst the impact on sexual functioning has been recognised, the wider effects on personal and social relationships have not been recorded, as well as the influence of symptoms on non-work-related activities. Whilst the pathophysiological aspects of the disease are inevitably interrelated with life impact and use of resources, focusing only on the physical symptoms fails to address adequately the wider impact of living with AF. Earlier studies have identified that patients and surgeons allocate importance to different aspects of quality of life associated with anal fistula and its treatment. Surgeons rated continence, leakage, pain, cure and sepsis, whereas patients identified independent activity, good health, pain, continence, psychological health and leakage as their most important aspects of quality of life [40]. We are currently conducting further qualitative work to explore patients’ experiences of disease further, and patient involvement in deciding the final COS and how these outcomes should be prioritised is crucial to ensure that the COS remains representative of all stakeholders [7] and centred around relevance to patients.

The current study reported the range of outcome measurement instruments used for the most frequently reported outcomes. Validated measures were largely used for outcomes such as incontinence and quality of life, allowing the benefit of comparison across studies, as well as with other chronic health conditions [41]. However, the broad range of validated measures across studies for AF makes it difficult to compare these specific outcomes across interventions. This supports the need for a systematic method of selecting appropriate Outcome Measurement Instruments (OMIs) once the final COS is established [7, 42]. Furthermore, most measurement instruments of quality of life were generic. Disease-specific measures are known to be more sensitive to change and can directly detect the specific concerns of particular clinical groups, which may be underrepresented in generic measurement instruments [43]. Planned qualitative work will help to determine whether the concerns of patients with AF are adequately addressed by these instruments, or whether the development of a disease-specific Patient-Reported Outcome Measure (PROM) is needed.

The strength of this systematic review is that with the range of studies reviewed, it is well placed to inform a long list of items for the development of a COS. However, it is limited by the lack of outcomes related to the quality of life, suggesting that the additional qualitative feedback from patients required by COMET to supplement this longlist is crucial. Although it is possible that not all relevant studies have been captured due to the eligibility criteria used, the sheer number of outcomes extracted from the included studies make it likely that saturation has been reached and that any additional outcomes would be procedure specific, and, therefore, not eligible for a generic COS representing a minimum set of outcomes to be adopted by all studies, regardless of intervention used. A further limitation is the English language inclusion criterion, although no abstracts or full texts were excluded based on the language criterion alone, rather they studied the wrong population or were review articles or commentaries. The lack of non-English papers may limit the generalisability of these findings across cultural and ethnic groups. This may be effectively countered through the subsequent longlisting and consensus processes, which will include a broad ethnic and cultural diversity.

**Conclusions**

This systematic review highlights the need for consensus amongst researchers and clinicians regarding the outcomes that are essential in determining successful fistula treatment, and how they should be defined and measured. The under-representation of outcomes relating to the quality of life needs to be challenged, and qualitative exploration of the patient experience, as well as active engagement of patients in determining a COS are crucial.
Table 8 Measurement instruments used, in varying combinations, to assess the most frequently reported outcomes

| Outcome | Instruments (used in various combinations) | Times used |
|---------|--------------------------------------------|------------|
| Healing | Clinical examination, including digital rectal examination | 88         |
|         | (Telephone) interview                        | 16         |
|         | MRI                                         | 9          |
|         | (3D) endoanal ultrasound                     | 7          |
|         | Medical record review                        | 7          |
|         | Anoscopy or proctoscopy or rectoscopy        | 7          |
|         | (Un)specified questionnaire                  | 6          |
|         | Digital photograph of the external fistula opening | 2         |
|         | Transanal ultrasound                         | 1          |
|         | Examination under anaesthetic                | 1          |
|         | Anal endosonography                          | 1          |
| Incontinence/sphinicter function            | Wexner Cleveland Clinic Florida incontinence score | 48         |
|         | Patient-reported                             | 9          |
|         | Vaizey incontinence score                    | 9          |
|         | Fecal Incontinence Quality of Life Scale     | 6          |
|         | (Un)specified questionnaire                  | 5          |
|         | Anorectal manometry                          | 5          |
|         | Endoanal ultrasound                          | 4          |
|         | Specified grading system                     | 3          |
|         | Clinical examination, including digital rectal examination | 3 |
|         | Colorectal functional outcome questionnaire  | 3          |
|         | (Telephone) interview                        | 3          |
|         | Medical record review                        | 2          |
|         | German Society of Coloproctology score       | 1          |
|         | Williams grade                               | 1          |
|         | Fecal Incontinence Severity Index            | 1          |
| Recurrence | Clinical examination                            | 43         |
| Treatment failure | (Telephone) interview                         | 7          |
|         | MRI                                         | 6          |
|         | Medical record review                        | 6          |
|         | (Un)specified questionnaire                  | 3          |
|         | Endorectal ultrasound                        | 2          |
|         | Anoscopy or proctoscopy                      | 2          |
|         | 3D endoanal ultrasound                       | 1          |
|         | Anal endosonography                          | 1          |
|         | Patient-reported                             | 1          |
| Quality of life | Fecal Incontinence Quality of Life Scale     | 6          |
|         | Short Form-36 health survey (SF-36)           | 6          |
|         | EQ-5D                                       | 4          |
|         | Short Form-12 health survey (SF-12)           | 2          |
|         | Cleveland global quality of life             | 2          |
|         | Gastrointestinal Quality of Life Index       | 2          |
|         | (Un)specified questionnaire                  | 2          |
|         | Quality of Life Scale                        | 1          |
|         | Visual Analogue Scale (VAS)                  | 1          |
|         | Fecal Incontinence Severity Index            | 1          |
| Pain    | VAS                                         | 31         |
|         | Patient-reported                             | 2          |
|         | Specified grading system                     | 1          |
|         | Medical record review                        | 1          |
|         | Number of analgesics used                    | 1          |

MRI magnetic resonance imaging, VAS Visual Analogue Scale, EQ-5D EuroQol five-dimensions questionnaire
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**Code availability** Not applicable.

**Declarations**

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