NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of bioprosthetic plug insertion for anal fistula

An anal fistula is a narrow tunnel that forms between the end of the bowel and the skin near the anus. It may cause pain or discomfort, and leak blood or pus. In this procedure, a plug is put into the fistula and stitched in place. The plug is made from animal tissue (bioprosthetic). The aim is to block the fistula.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2018 and updated in May 2019.

Procedure name

- Bioprosthetic plug insertion for anal fistula

Specialist societies

- Association of Coloproctology of Great Britain and Ireland
- Royal College of Surgeons of England
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow.

Description of the procedure

Indications and current treatment

An anal fistula is an abnormal tract between the anal canal and the skin around the anus. It usually results from previous anal abscesses (cryptoglandular), and can be associated with other conditions such as inflammatory bowel disease and cancer. It may cause symptoms such as pain or discomfort in the anal area, and leakage of blood or pus.

Anal fistulas can be classified according to their anatomical relationship with the external sphincter. Intersphincteric fistulas are the most common type and cross only the internal sphincter. Trans-sphincteric fistulas pass through the internal and external sphincter.

Treatment of anal fistulas commonly involves surgery. The type of surgery depends on the location and complexity of the fistula. For intersphincteric and low trans-sphincteric anal fistulas, the most common treatment is a fistulotomy or laying open of the fistula track. For deeper fistulas that involve more muscle, and for recurrent fistulas, a seton (a piece of suture material or rubber sling) may be

used, either alone or with fistulotomy. Setons can be loose (designed to drain the sepsis but not for cure), or snug or tight (designed to cut through the muscles in a slow controlled fashion). Fistulas that cross the external sphincter at a high level are sometimes treated with a mucosal advancement flap or other procedures to close the internal opening. Other options for treating anal fistulas are to fill the tract with glue or paste.

What the procedure involves

Bioprosthetic plug insertion for anal fistula aims to leave the sphincter muscles intact, allowing the use of subsequent treatments if needed.

The procedure is usually done using general anaesthesia. The fistula tract is identified using a probe or by imaging techniques, and it may be irrigated. A conical plug, usually made of porcine intestinal submucosa, is pulled into the tract until it blocks the internal opening. It is sutured in place at the internal opening. The external opening is not completely sealed so that drainage of the fistula can continue. The plug acts as a scaffold into which new tissue can grow.

Efficacy summary

Successful fistula closure

In a systematic review and meta-analysis of 10 studies including 778 patients having a bioprosthetic anal fistula plug (AFP, n=294) or a mucosal advancement flap (MAF, n=484), there was no statistically significant difference in the overall healing rate between the AFP and MAF procedures (odds ratio [OR]: 0.79, 95% confidence interval [CI] 0.36 to 1.73, p = 0.55, n=8 studies). [1]

In a randomised controlled trial (RCT) of 106 patients having seton removal combined with AFP (n=54) or seton removal only (n=52), the rate of fistula closure was not statistically significantly different between groups at 12 weeks: 31.5% (17/54) compared with 23.1% (12/52), relative risk [RR] 1.31; 95% CI 0.59 to 4.02; p=0.19. In the same study, there were no statistically significant differences between groups in the median Van Assche MRI scores (that assess the healing of the fistula tract on MRI) at 12 weeks (6 compared with 8) and at 12 months (3 compared with 3). [2]

In an RCT of 82 patients having AFP (n=43) or MAF (n=39), the healing rates were not statistically significant between groups at 6 months (68% compared with 73%, p=0.59) or at 12 months (67% compared with 76%, p=0.80).[4]

In a systematic review and meta-analysis of 11 studies including 810 patients having the AFP (n=327) or the rectal advancement flap (RAF, n=483) procedure, there was no significant difference in the healing rates between the AFP and RAF

groups based on the pooled result of the 5 RCTs (OR: 0.46, 95% CI 0.16 to 1.34, I^2=79%, p=0.16) and 4 non-RCTs (OR: 0.64, 95% CI 0.25 to 1.64, I^2=66%, p=0.35). In the same study, at a median follow-up of 11 months, the AFP group had a statistically significantly lower healing rate than the RAF group (OR: 0.32, 95% CI 0.13 to 0.78, I^2=60%, p=0.01, 4 RCTs).[10]

In a systematic review of 12 studies including 84 patients having the AFP procedure, the total successful fistula closure rate was 58% (49/84, 95% CI 47 to 69) in all studies combined. In patients with a recurrent anal fistula from previous treatments, the successful closure rate was 40% (2/5, 95% CI 5 to 85).[11]

In a retrospective case series of 126 patients, the success rate of a first plug procedure was 24% (30/126) at more than 8-month follow-up.[6]

In a retrospective case series of 114 patients, the overall success rate was 54% (62/114) at 6 months. Of 40 patients who had a cutting seton placement after plug failure, 33 (82.5%) reported a successful outcome and 12 patients refused further surgery. [7]

In a case series of 46 patients, the overall healing rate was 43% (20/46). 11% (5/46) of patients had a repeat AFP procedure including 1 patient who had 2 repeat procedures. [8]

In a case series of 15 patients, the complete clinical healing rate was 20% (3/15) and the partial healing rate was 53% (8/15) at 6 months after the procedure. Radiographic improvement was seen in 73% (11/15) of patients.[12]

Recurrence

In the systematic review and meta-analysis of 10 studies including 778 patients having a bioprosthetic anal fistula plug (AFP, n=294) or a mucosal advancement flap (MAF, n=484), there was no statistically significant difference in the recurrence rate between the AFP and MAF procedures (OR: 2.29, 95% CI 0.59 to 8.88, p=0.23, n=7 studies). [1]

In a non-inferiority RCT of 91 patients having the AFP (n=46) or the MAF (n=45) procedure, the fistula recurrence rate at 1 year was statistically significantly higher in the AFP group (66% [27/41]) compared with the MAF group (38% [15/40]), p=0.006 (p=0.979 for non-inferiority analysis). [3]

In the RCT of 82 patients having AFP (n=43) or MAF (n=39), the fistula tract reopened after documentation of closure in 9% (4/43) of patients in the AFP group compared with 3% (1/39) of patients in the MAF group (p=0.36). [4]

In an RCT of 60 patients, there was no statistically significant difference in the recurrence rate at median 11 months between AFP (71% [22/31]) and MAF (52% [15/29]), p=0.126. [5]

In the systematic review and meta-analysis of 11 studies including 810 patients, there was no significant difference in the recurrence rates between the AFP (n=245) and RAF (n=404) groups based on the pooled result of the 4 RCTs (OR: 2.10, 95% CI 0.38 to 11.74, I^2=86%, p=0.40) and 4 non-RCTs (OR: 2.75, 95% CI 0.46 to 16.43, I^2=81%, p=0.27). In the same study, at a median follow-up of 11 months, the AFP group had a statistically significantly higher recurrence rate than the RAF group (OR: 4.45, 95% CI 1.45 to 13.65, I^2=60%, p=0.009, 3 RCTs).[10]

In the systematic review of 12 studies including 84 patients, the recurrence rate was 14% (3/22) in 5 studies.[11]

In the case series of 46 patients, the overall recurrence rate was 57% (26/46) and the median time to recurrence was 24.8 months (95% CI 9.4 to 73.8 months). The recurrence rates were 31% at 6 months, 40% at 1 year and 48% at 2 years. [8]

Clinical remission

In the RCT of 106 patients having seton removal and AFP (n=54) or seton removal only (n=52), there were no statistically significant differences in the clinical remission (defined as the absence of any drainage by all fistula openings occurring spontaneously or after gentle finger compression [grade 0 on the 5-grade scale] and the absence of perianal abscess) rates between groups at 4 weeks (30% [16/54] compared with 37% [19/52]), 8 weeks (30% [16/54] compared with 29% [15/52]), 6 months (35% [19/54] compared with 31% [16/52]) and 12 months (28% [15/54] compared with 23% [12/52]). [2]

Clinical response

In the RCT of 106 patients having seton removal and AFP (n=54) or seton removal only (n=52), there were no statistically significant differences in the clinical response (defined as at least 50% of fistula tracts without any drainage by the external openings and no occurrence of perianal abscess, fistula tract healing at MRI, and tolerance of AFP between inclusion and month 12) rates between groups at 4 weeks (19% [10/54] compared with 10% [5/52]), 8 weeks (15% [8/54] compared with 8% [4/52]), 6 months (4% [2/54] compared with 12% [6/52]) and 12 months (7% [4/54] compared with 6% [3/52]).[2]

Perianal disease severity

In the RCT of 106 patients having seton removal and AFP (n=54) or seton removal only (n=52), there were no statistically significant differences between groups in the median perianal disease activity index scores at 4 weeks (4 compared with 4), 8 weeks (4 compared with 5), 12 weeks, (4 compared with 5), 6 months (3 compared with 3) and 12 months (3 compared with 5), p=0.38. [2]

Anal pain relief

In the non-inferiority RCT of 91 patients having the AFP (n=46) or the MAF (n=45) procedure, anal pain statistically significantly improved in both groups from before the procedure to 3 months after the procedure. In the AFP group the mean visual analogue score (VAS) improved from 3.5 (95% CI 2.7 to 4.2) to 2.4 (95% CI 11.7 to 3.1) compared with 2.9 (95% CI 2.2 to 3.7) to 1.8 (95% CI 1.1 to 2.5) in the MAF group (p≤0.001). There was no statistically significant decline in the reported VAS score from 3 to 12 months in either group and no statistically significant differences in VAS score between the 2 groups.[3]

Quality of life

In the RCT of 106 patients having seton removal and AFP (n=54) or seton removal only (n=52), there were no statistically significant differences between groups in the median inflammatory bowel disease questionnaire scores at 12 weeks (182 compared with 174.5) and at 12 months (194 compared with 187). [2]

In the RCT of 82 patients having AFP (n=43) or MAF (n=39), there were no statistically significant differences between groups for the mean EQ-5D scores at baseline (0.37 compared with 0.31), 3 months (0.19 compared with 0.26), 6 months (0.06 compared with 0.28) and at 12 months (0.04 compared with 0.38). In the same study, there were no statistically significant differences between groups in the faecal incontinence quality of life score at any assessment, with all scores ranging from 3.5 to 3.9. [4]

In the RCT of 60 patients comparing AFP with MAF, there were no statistically significant differences between groups for the SF-36 and EQ-5D scores before surgery and at 16 weeks. For AFP, the EQ-5D scores were 0.796 before surgery and 0.830 after surgery (p=not statistically significant and no further details reported). [5]

In the case series of 46 patients, the median physical summary score of the short form-36 health survey, version 2 (SF-26 v2, range from 1 to 81, highest scores indicate the best possible condition) statistically significantly increased from 47.2 before surgery to 56.2 at 6 months ($p < 0.001$). The median mental summary score of the SF-36 v2 (SF-26 v2, range from 9 to 82, highest scores indicate the best possible condition) statistically significantly increased from 48.5 before surgery to 55.3 at 6 months ($p = 0.013$). At 6 months, none of the patients felt

''much worse'' compared with before surgery, 11% (4/35) felt ''somewhat worse'', 31% (11/35) felt ''equal'', 14% (5/35) felt ''somewhat better'' and 43% (15/35) felt ''much better'' (p=0.005 for the comparison with before surgery). [8]

Safety summary

Overall complication rate

In the systematic review and meta-analysis of 10 studies including 778 patients having a bioprosthetic anal fistula plug (AFP, n=294) or a mucosal advancement flap (MAF, n=484), there was no statistically significant difference in the rate of fistula complication between the AFP and the MAF procedures (OR: 1.10, 95% CI 0.58 to 2.09, p=0.78, n=8 studies). [1]

In the systematic review and meta-analysis of 11 studies including 810 patients, there was no significant difference in the fistula complication rates between the AFP and RAF groups in the pooled results of the 3 RCTs (OR: 1.16, 95% CI 0.34 to 3.94, I^2=0%, p=0.81) or 4 non-RCTs (OR: 1.61, 95% CI 0.17 to 15.14, I^2=64%, p=0.68). In the same study, at a median follow-up of 11 months, there was no statistically significant difference in the fistula complication rates between the AFP and RAF groups (OR: 0.47, 95% CI 0.08 to 2.74, I^2=0%, p=0.40, 2 RCTs).[10]

Faecal incontinence

Faecal incontinence happened less frequently in the AFP group compared with the MAF group in the systematic review and meta-analysis of 10 studies including 778 patients having a bioprosthetic anal fistula plug (AFP, n=294) or a mucosal advancement flap (MAF, n=484) (OR: 0.16, 95% CI 0.03 to 0.95, p=0.04, n=3 studies). Three studies were included in this meta-analysis showing absolute rates of incontinence in the 2 groups as follows: (0/27, 1/45 and 0/31 in AFP group and 9/23, 4/45 and 0/29 in MAF group).[1]

The mean St Mark's scores (range from 0 (fully continent) to 24 (total incontinence)) were not statistically significantly different between AFP and MAF before the procedure (5.1 compared with 4.7), at 3 months (5.3 compared with 4.6) and at 12 months (5.7 compared with 4.1) in a non-inferiority RCT of 91 patients having the AFP (n=46) or the MAF (n=45) procedure (p=not statistically significant at each time point). [3]

The mean (±standard deviation [SD]) Vaizey scores (range from 0 to 24, complete continence to complete incontinence) were not statistically significantly different before and after the procedure for AFP (6.7 [±3.3] compared with 7.2 [±3.7]) and for MAF (7.0 [±3.9] compared with 7.7 [±3.2]) (p=0.618) in an RCT of

60 patients who had an AFP (n=31) or a MAF (n=29). In the same study, the mean ± SD colorectal functional outcome scores (COREFO, range from 0 to 100, a higher score represents an increased level of continence disturbance) and the median (range) Wexner scores (range from 0 (perfect continence) to 20 (complete incontinence)) were also not statistically significantly different before and after the procedure. The mean COREFO scores for AFP were 16.3 (±14.5) before the procedure and 18.7 (±16.0) after the procedure compared with 15.1 (±13.5) and 14.8 (±12.7) for MAF respectively. The median Wexner scores for AFP were 5.50 (0 to 16) before the procedure and 5.50 (0 to 14) after the procedure compared with 7.00 (0 to 12) and 6.50 (0 to 16) for MAF respectively. There were also no statistically significant differences between groups after surgery.[5]

The incontinence rate 6 months after the procedure (or just before placement of a cutting seton) was 2% (2/114) and the median Wexner score was 0 in the overall study population in a case series of 114 patients. [7]

Anal continence (measured using the faecal incontinence score index) statistically significantly improved from a median of 19 points before surgery to 12 points at 6-month follow-up (p = 0.008). No statistically significant difference was found for urgency for the comparison before surgery with 6-week or 6-month follow-up.[8]

Abscess or infection

Abscess was reported in 4 patients in each group at 12 weeks and in 11 patients in the AFP group compared with 10 patients in the control group at 1 year in the RCT of 106 patients having seton removal and AFP (n=54) or seton removal only (n=52).[2]

Perianal infection was reported in 1 patient in the AFP group compared with none of the patients in the MAF group before 3-month follow-up and in 12 patients compared with 5 patients respectively before the 12-month follow-up in the non-inferiority RCT of 91 patients having the AFP (n=46) or the MAF (n=45) procedure (p value not reported). The patients needed a further operation. [3]

Infection or abscess involving the fistula was reported in 7% (3/43) of patients with an AFP compared with 8% (3/39) of patients with a MAF in the RCT of 82 patients. [4]

Perianal abscess was reported in 1 patient day after surgery in the AFP group in the RCT of 60 patients who had an AFP (n=31) or a MAF (n=29). The plug was removed, and the abscess drained. There were none in the MAF group. [5]

Perianal abscess occurred in 13% (2/15) of patients within 30 days after the procedure in the case series of 15 patients and both cases needed surgical drainage.[12]

Sepsis was reported in 8% (9/114) of patients in the case series of 114 patients. 8 cases happened between 10 to 24 days after the procedure and 1 case happened 120 days after the procedure.[7]

No abscess was reported in the case series of 46 patients.[8]

Induration, redness, or swelling

Induration, redness, or swelling affecting the external opening was reported in 5% (2/43) of patients with an AFP compared with 5% (2/39) of patients with a MAF (p=1.0) in the RCT of 82 patients. [4]

Plug extrusion

Plug avulsion was reported in 5 patients at 12 weeks and in 6 patients at 1 year in the RCT of 106 patients having seton removal and AFP (n=54) or seton removal only (n=52).[2]

The plug fell out or the flap failed in none of the patients with an AFP compared with 5% (2/39) of patients with a MAF (p=0.22). [4]

Plug extrusion was reported in 13% (4/31) of patients within 10 days of the procedure in the RCT of 60 patients who had an AFP (n=31) or a MAF (n=29). [5]

Plug extrusion was reported in 10% (11/114) of patients within 2 weeks of the procedure in the case series of 114 patients. [7]

Plug extrusion was reported in 7% (3/460) of patients within 4 days of the procedure in the case series of 46 patients. 2 patients out of 3 had a successful repeat AFP procedure; the third patient declined to have a repeat AFP.[8]

Pain

Abdominal pain was reported in 1 patient in the AFP group compared with none of the patients in the control group at 12 weeks and in 2 patients in the AFP group compared with 3 patients in the control group at 1 year in the RCT of 106 patients having seton removal and AFP (n=54) or seton removal only (n=52).[2]

Median VAS scores were not statistically significantly different between the AFP and the MAF groups on the day of the procedure (21 compared with 25.5,

p=0.74), at hospital discharge (10.5 compared with 16.5, p=0.33) and 2 weeks after surgery (9.0 compared with 10.5, 0.13) in the RCT of 82 patients. [4]

Mean VAS scores were 3 (±3) in the AFP group compared with 4 (±2.5) in the MAF group 1 day after surgery in the RCT of 60 patients comparing AFP (n=31) with MAF (n=29) (p=0.143). In the same study, abdominal pain was reported in none of the patients in the AFP group compared with 1 patient in the MAF group.[5]

Bleeding

Light bleeding from the external wound, bleeding from the fistula, or new apparent fistula forming was reported in 2% (1/43) of patients with an AFP compared with 5% (2/39) of patients with a MAF in the RCT of 82 patients (p=0.60). [4]

Bleeding was reported in none of the patients in the AFP group compared with 1 patient in the MAF group, 10 days after surgery in the RCT of 60 patients comparing AFP (n=31) with MAF (n=29). [5]

Abdominal wall seroma

Abdominal wall seroma was reported in 1 patient within 30 days after the procedure in the case series of 15 patients. No intervention was needed, and the seroma resolved without complications.[12]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly happen, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: ‘’plugs seem sometimes to make the fistula wider and increase symptoms’’.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to bioprosthetic plug insertion for anal fistula. The following databases were searched, covering the period from their start to 20 May 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries

and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with an anal fistula.
Intervention/test	Bioprosthetic plug insertion for anal fistula
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 2,455 patients from 3 systematic reviews[1, 10, 11], 4 RCTs[2-5], 4 case series[6-8, 12] and 1 unpublished NIHR Health Technology Assessment report on the Fistula-in-ano trial (FIAT).[9]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on bioprosthetic plug insertion for anal fistula

Study 1 Xu Y (2016)

Details

Study type	**Systematic review and meta-analysis**
Country	Systematic review and meta-analysis: China Studies included: America (3), Spain (1), England (1), Canada (1), China (1), New Zealand (1), Switzerland (1), and Netherlands (1).
Recruitment period	Date of search not reported
Study population and number	n= **778 (294 AFP versus 484 MAF)** patients from 10 studies with complex anal fistulas
Age and sex	AFP group: 50% (146/294) male MAF group: 55% (266/484) male Age not reported
Patient selection criteria	Inclusion criteria: All randomised and non-randomised controlled clinical trials that compared AFP with MAF treatment methods for anal fistula and that reported clinical healing rate, complication, recurrence and incontinence. Exclusion criteria: Abstracts, letters, case reports, comments and conference proceedings. Studies on patients with rectovaginal fistula, rectal fistula, Crohn's disease or infected with human immunodeficiency virus who were treated with fistula plugs and patients undergoing additional procedures along with the fistula plug. Studies reporting patients with anal fistulas treated with fibrin glue or fibrin sealant.
Technique	AFP or MAF.
Follow-up	**AFP group: median 1 to 44 months** **MAF group: 0.25 to 161 months**
Conflict of interest/source of funding	Not reported

Analysis
Study design issues:

- A fistula was considered 'complex' when the fistula was high, was anterior in a female, had multiple tracts or if the patient had pre-existing incontinence, a history of local irradiation or Crohn's disease.
- Healing was defined as a closed external opening in the absence of symptoms at a minimal follow-up time.
- Recurrence was defined as the presence of an abscess arising in the area or obvious evidence of fistulation.
- 3 of the trials included were randomised using computer randomisation. 5 of the trials included were retrospective studies; 1 study compared the healing and complication rates of a prospective cohort of AFP patients to a retrospective cohort of patients that had the endoanal AFP, and 1 study did not describe the design method.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **778 (294 AFP versus 484 MAF)** **Healing rate** (8 studies) There was no statistically significant difference in the overall healing rate between the AFP and MAF procedures**.** OR: 0.79, 95% CI 0.36 to 1.73, p = 0.55. [I^2 = 74%, p=0.0004] **Recurrence** (7 studies) There was no statistically significant difference in the recurrence rate between the AFP and MAF procedures**.** OR: 2.29, 95% CI 0.59 to 8.88, p = 0.23. [I^2 = 83%, p<0.00001] **Fistula healing time** (1 study) The fistula healing time was statistically shorter in the AFP group compared with the MAF group (p < 0.05). **Hospital length of stay** (3 studies) The median hospital length of stay was statistically significantly shorter after AFP compared with MAF (p < 0.001).	**Complications** (8 studies) There was no statistically significant difference in the rate of fistula complication between the AFP and the MAF procedures. OR: 1.10, 95% CI 0.58 to 2.09, p = 0.78. [I^2 = 44%, p=0.12] **Pain after surgery** (1 study) Postoperative pain was statistically significantly shorter in the AFP group compared with the MAF group (p < 0.05). **Faecal incontinence** (3 studies) The faecal incontinence rate was statistically significantly lower in the AFP group compared with the MAF group**.** OR: 0.16, 95% CI 0.03 to 0.95, **p = 0.04**. [I^2 = 0%, p=0.66].
Abbreviations used: AFP, anal fistula plug; CI, confidence interval; MAF, mucosal advancement flap; OR, odds ratio	

Study 2 Senejoux A (2016)

Details

Study type	**Open-label RCT**
Country	France (14 sites) and Belgium (2 sites)
Recruitment period	2008 to 2011
Study population and number	n**= 106 (54 seton removal and AFP versus 52 seton removal only)** patients with non- or mildly active Crohn's disease having at least 1 ano-perineal fistula tract drained for more than 1 month
Age and sex	AFP: Mean 34 years; 33% (18/54) male Control: Mean 37 years; 38% (20/52) male
Patient selection criteria	Inclusion criteria: at least 18 years old and had CD confirmed by endoscopy and histology. The CD Activity Index [CDAI] had to be 250 or less. Patients had at least 1 active ano-perineal fistula track [between the anus or low rectum and the perineum or vulva] for at least 2 months with seton drainage for at least 1 month. Treatments with azathioprine, 6-mercaptopurine, methotrexate, thalidomide, or anti- TNF were permitted providing the dose was stable for more than 3 months, and treatment with aminosalicylates at a stable dose for more than 1 month. Oral corticosteroids were tolerated given at stable dose for at least 2 weeks at equal or less than 15 mg/day equivalent prednisone or 6 mg/day budesonide. Exclusion criteria: anal abscess, recto-vaginal fistula, anal or rectal stricture, anal surgery within the past month, rectovaginal fistula, severe proctitis, corticosteroids > 15 mg/day or budesonide > 6 mg/day, anti-TNF started in the past 6 months or with dose or interval modification in the past 2 administrations, ciclosporin or tacrolimus in the past 3 months, previous use of AFP for fistulising anoperineal-CD, pregnancy, or refusal to receive a porcine device.
Technique	AFP: Broad-spectrum parenteral antibiotic was given on induction of anaesthesia according to French Society of Anaesthesia and Reanimation protocols. All setons were removed during the procedure. In case of multiple fistulous tracks, several plugs could be inserted. All patients were advised to avoid any strenuous activity and to observe sexual abstinence for 2 weeks. Control: Patients had a clinical examination with setons removal without general anaesthesia.
Follow-up	**1 year**
Conflict of interest/source of funding	The study was supported by Société Nationale Française de Gastro-Entérologie [SNFGE] [research grant], Association François Aupetit [research grant], and Cook Biotech [supply of the plugs]. The study design, performance, analysis, and reporting were conducted without any influence of Cook Biotech Laboratories.

Analysis

Follow-up issues:

- Visits were planned at Weeks 4, 8, and 12 and Months 6 and 12. At each visit, patients had a clinical examination without general anaesthesia. For each external opening, draining was assessed on a 5-grade ordinal scale from 0 [no draining] to 4 [passage of stools]. Perianal Disease Activity Index [PDAI] was assessed at each visit, and the Inflammatory Bowel Disease Questionnaire [IBDQ] was recorded at Week 12 and Month 12. MRI was performed in case of clinical remission between Weeks 12 and 16 and at Month 12.
- At Week 12, 99 (48 versus 51) patients were available for evaluation and the remaining 7 were considered as treatment failures.

Study design issues:

- The primary end point was fistula closure at 12 weeks.
- At 12 weeks, AFP was proposed to all patients who did not achieve clinical remission, whatever the treatment they were assigned by randomisation.
- Randomisation was centralised using permutations tables in a ratio 1:1, stratified both on centre and on stratum, predefined as simple or complex fistula. The numbers were allocated sequentially in the order of enrolment. Patients could not be included twice in the study. After obtaining informed consent, investigators used a specific form sent by fax, which assigned the eligible patient to the next randomisation number for the centre and stratum concerned.
- Healing of the fistula tract on MRI was defined according to Van Assche criterias [absence of T2 hyperintensity, absence of cavities/ abscesses, and absence of rectal wall involvement].

- The sample size calculation was based on the assumption that AFP would be superior to seton removal alone. A minimum of 102 patients [51 per arm] would provide a 90% power to detect a 30% difference in remission rate between AFP and control groups, based on a two-sided test with type I error of 5%, from the 20% assumed rate of remission in controls.
- Analysis was made on an intent-to-treat basis.

Study population issues:

- 96% (52/54) of patients in the AFP group and 98% (51/52) of patients in the control group had previous fistula surgery.
- 72% (39/54) of patients in the AFP group and 75% (39/62) of patients in the control group had a simple fistula.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **106 (54 seton removal and AFP versus 52 seton removal only**

Primary endpoint

Fistula closure at 12 weeks: 31.5% (17/54) versus 23.1% (12/52) (RR stratified on AGA classification: 1.31; 95% confidence interval: 0.59 to 4.02; p = 0.19)

Response rate

	AFP group	Control group	p value
Clinical remission*			
4 weeks	30% (16/54)	37% (19/52)	0.67
8 weeks	30% (16/54)	29% (15/52)	0.82
6 months	35% (19/54)	31% (16/52)	0.24
12 months	28% (15/54)	23% (12/52)	0.43
Clinical response**			
4 weeks	19% (10/54)	10% (5/52)	0.27
8 weeks	15% (8/54)	8% (4/52)	0.36
6 months	4% (2/54)	12% (6/52)	0.16
12 months	7% (4/54)	6% (3/52)	1.00
PDAI score (median [IQR])			
4 weeks	4 [3; 7]	4 [3; 6]	0.38[a]
8 weeks	4 [3; 7]	5 [3; 7]	-
12 weeks	4 [3; 7]	5 [3; 7]	-
6 months	3 [2; 4]	3 [2.25; 4]	-
12 months	3 [2; 4]	5 [2.5; 6.5]	-
Van Assche MRI score (median [IQR])			
12 weeks	6 [4; 10]	8 [3; 12]	0.63
12 months	3 [1; 7.5]	3 [1; 7.5]	0.97
IBDQ score (median [IQR])			
12 weeks	182 [128; 195.5]	174.5 [138; 192]	0.96
12 months	194 [173; 198.5]	187 [166; 194]	0.62

*Clinical remission was defined as the absence of any drainage by all fistula openings occurring spontaneously or after gentle finger compression [grade 0 on the 5-grade scale] and the absence of perianal abscess.

**Clinical response was defined as at least 50% of the fistula tracts without any drainage by the external openings and no occurrence of perianal abscess, fistula tract healing at MRI, and tolerance of AFP between inclusion and Month 12.

[a] Based on a Poisson regression model incorporating time.

Safety

Adverse events (Number of adverse events [number of patients])

	AFP group (n=54)	Control group (n=52)
At 12 weeks	25 (17)	11 (8)
Abscesses	6 (4)	4 (4)
Plug avulsions	5 (5)	0
CD flare	1 (1)	0
Abdominal pain	1 (1)	0
Miscellaneous	12 (6)	7 (4)
After 1-year follow-up	56 (27)	48 (21)
Abscesses	20 (11)	13 (10)
Plug avulsions	8 (6)	5 (5)
CD flare	2 (2)	5 (4)
Abdominal pain	2 (2)	3 (3)
Miscellaneous	24	22

Abbreviations used: AFP, anal fistula plug; AGA, American gastroenterological association; CD, Crohn's disease; IBDQ, inflammatory bowel disease questionnaire; PDAI, perianal disease activity index; RR, relative risk.

Study 3 Bondi J (2017)

Details

Study type	**Non-inferiority RCT**
Country	Norway (1 centre) and Sweden (2 centres)
Recruitment period	2009 to 2015
Study population and number	n= **91 (46 AFP versus 45 MAF)** patients with an anal fistula
Age and sex	AFP group: Mean 42 years; 46% (21/46) male; mean BMI 28 kg/m^2 MAF group: Mean 53 years; 49% (22/45) male; mean BMI 28 kg/m^2
Patient selection criteria	Inclusion criteria: patients with fistula involving more than one-third of the external anal sphincter (not suited for direct fistulotomy); single, continuous fistula tract at time of inclusion; able to complete an informed written consent, understand its implications and contents, and participate in follow-up. Exclusion criteria: fistula tract<2cm; complex fistula tract system (branching of fistula tract); more than 1 previous fistula operation: age<18 years: pregnancy; HIV positivity: fistula caused by malignancy: tuberculosis: hidradenitis suppurativa: pilonidal sinus disease: no internal fistula opening found: unable to undergo or contraindications to MRI: Crohn's disease and ulcerative proctitis.
Technique	All patients were pretreated with a draining seton at least 6 weeks before surgery. Perioperative antibiotics were given for 5 days in both groups. Anal fistula plugs were from Surgisis® (Cook Medical) and the procedure was done according to the manufacturer's recommendations.
Follow-up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Patients had clinical examinations at 3 and 12 months. In case of symptoms or failure that needed surgical involvement before 12 months, follow-up was set to the time of intervention.
- 94 patients (48 versus 46) were initially randomised. 2 patients in the AFP group and 1 in the MAF group did not receive the intervention after randomisation. At 3 months, there were 3 patients in the AFP group and 2 patients in the MAF group who were lost to follow-up. At 12 months, 2 more patients in the AFP group and 3 in the MAF group were lost to follow-up. Finally, 41 patients in the AFP group and 40 in the MAF group were analysed for primary outcome.

Study design issues:

- The primary outcome was the fistula recurrence rate (defined as a total absence of secretion, a dry scar at the external fistula opening and the absence of deep infection or cavities at 1 year. Anal pain (visual analogue scale), anal incontinence (St Mark's score) and quality of life (Short Form 36 questionnaire) were also reported.
- Initially, randomisation to treatment with AFP or MAF surgery was done by opening sealed envelopes, with 5 envelopes per block. During the early stage of the study, this was changed to computer block randomisation with random block sizes, accessed on the study's own webpage. Randomisation was done in the operating room, when the final preoperative anal examination had been done by the surgeon, to ensure that the patient fulfilled the inclusion criterion of a single fistula tract without extensions. The patient was not informed of the outcome of randomisation.
- For power calculations, the margin of difference for the 2 treatment methods was set at 10%. For a power of 80% and level of significance of 5%, 88 patients were needed in the study, with a success rate for standard treatment of 60%.

Study population issues: 10 patients in the AFP group and 13 in the in the MAF group had previous fistula surgery.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **94 (48 AFP versus 46 flap)**

Fistula recurrence rate at 1 year

AFP: 66% (27/41)

MAF: 38% (15/40)

p=0.006

p=0.979 for non-inferiority analysis

Anal pain (mean VAS score)

	AFP	MAF
Before the procedure	3.5 (95% CI 2.7 to 4.2)	2.9 (95% CI 2.2 to 3.7)
3 months	2.4 (95% CI 11.7 to 3.1)	1.8 (95% CI 1.1 to 2.5)
p value	**0.001**	**<0.001**

There was no statistically significant decline in the reported VAS score from 3 to 12 months in either group. There were no statistically significant differences in VAS score between the 2 groups.

Quality of life (SF-36 scores)

-There were no statistically significant differences between groups.

- Patients reported an increased quality of life in all 8 SF-36 categories after 3 months compared with preoperative scores in both groups. There was no further increase in quality of life reported after 12 months.

Safety

There were no intraoperative complications.

One patient with a known heart condition died from acute myocardial infarction 1 month after operation; this was not related to the fistula surgery.

Adverse events

	AFP (number of patients)	MAF (number of patients)
Perianal infection before 3-month follow-up	1	0
Perianal infection before 12-month follow-up	12	5

The patients had a further operation.

Faecal incontinence (St Mark's score, mean [95% CI])

	AFP	MAF	p value
Before the procedure	5·1 (3·7 to 6·4)	4·7 (3·4, 6·0)	0.673
3 months	5·3 (3·8 to 6·7)	4·6 (3·2, 5·9)	0.432
12 months	5·7 (3·8 to 7·5)	4·1 (2·4, 5·8)	0.211

The total St Mark's score ranges from 0 (fully continent) to 24 (total incontinence).

Abbreviations used: AFP, anal fistula plug; BMI, body mass index; CI, confidence interval; MAF, mucosal advancement flap; VAS, visual analogue score;

Study 4 Schwandner T (2018)

Details

Study type	**Open-label RCT**
Country	Germany (6 centres)
Recruitment period	2008 to 2012
Study population and number	n= **82 (43 AFP versus 39 advancement flap)** patients with trans-sphincteric anal fistulas
Age and sex	AFP: mean 45 years; 77% (33/43) male; mean BMI: 28.3 Advancement flap: mean 50 years; 59% (23/39) male; mean BMI: 28.4
Patient selection criteria	Inclusion criteria: 18 years or older with primary, persistent anal fistulas eligible for surgical repair. Exclusion criteria: patients presenting with evidence of abscess, infection, or acute inflammation were excluded until the tract matured and the infection resolved. Patients with Crohn's disease, ulcerative colitis, human immunodeficiency virus, other disorders of the immune system, collagen disease, a history of anorectal radiation therapy, superficial fistulas conventionally treated with fistulotomy or fistulectomy, recurrent fistula tracts, J-pouch fistulas, and those with porcine allergies or religious or cultural objections to the use of pig tissue were also were ineligible.
Technique	Patients in both groups received identical preoperative and postoperative care. A seton or vessel loop was placed in the fistula tract for a minimum of 6 weeks before surgery. Patients received a single, preoperative dose of cephalosporin and metronidazole. AFP: The Biodesign Anal Fistula Plug (cook Medical) was used.
Follow-up	**1 year**
Conflict of interest/source of funding	Cook Biotech Incorporated funded this study. All participating clinical centres received compensation and fistula plug devices from Cook Biotech Incorporated to support the research. Cook Biotech Incorporated has provided honoraria to Dr. Schwandner and Dr. Roland Scherer. Jason P. Hodde is an employee of Cook Biotech Incorporated.

Analysis

Follow-up issues:

- Patients with evidence of continued fistula drainage at the 6-month postoperative visit were withdrawn from the study. Those who declined follow-up examinations, patients treated with the plug in whom the plug dislodged, and those needing additional surgical or nonsurgical interventions affecting the treatment area were also withdrawn.
- 95% of patients in each group completed the 6-month follow-up.
- 77% (33/43) of patients in the AFP group and 85% (33/39) of patients in the advancement flap group completed the 12-month follow-up.

Study design issues:

- Randomisation was done immediately before the operation so that the patient did not know before surgery their assignment. A computer-generated sequence using a random block size of 4 or 6 patients, blocked on clinical study site, was used to ensure relatively equal assignment of patients across all sites and both treatments. A contract research organization coordinated subject randomisation, provided data management, and oversaw quality control and data monitoring.
- Study endpoints included healing rates, health-related quality of life, continence-related quality of life, pain, and safety at the time of surgery and 2 weeks, 3, 6, and 12 months following surgery.
- Healing was prospectively defined as closure of the external opening with no evidence of abscess, drainage, or pain.
- 2 groups of 47 patients each were needed to demonstrate a 25% difference between the interventions, with α=0.05, β=0.80, and a non-inferiority margin of 10%. The total enrolment target was 106 patients (53 per group) based on the assumption of a 12% attrition rate.

Study population issues:

- Study enrolment was stopped early due to difficulties in patient recruitment.
- 91% (39/43) of patients in the AFP group and 95% (37/39) of patients in the advancement flap group had a radial fistula (p>0.99).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **82 (43 AFP versus 39 advancement flap)**

Technical failure

- AFP: 0%
- Advancement flap: 5% (2/39)

Healing rate

	AFP	Advancement flap	p value
6 months	68%	73%	0.59
12 months	67%	76%	0.80

- The non-inferiority analysis confirmed that the healing rate for patients treated with the plug met the 10% margin of equivalence (p= 0.47), with evidence of equivalence also observed at the 6-month evaluation (p= 0.67).
- Healing rates were significantly better for patients with a higher BMI (p=0.03), shorter fistula length (p=0.01), and no previous colorectal surgeries (p < 0.001), regardless of treatment group.

Quality of life (mean overall EQ-5D scores)

	AFP	Advancement flap
Baseline	0.37	0.31
3 months	0.19	0.26
6 months	0.06	0.28
12 months	0.04	0.38

There were no statistically significant differences between treatment groups for the mean EQ-5D scores.

Reopening of fistula tract after documentation of closure

- AFP: 9% (4/43)
- Advancement flap: 3% (1/39)

p=0.36

Faecal Incontinence Quality of Life (FIQL)

There were no statistically significant differences between groups at any assessment, with all scores ranging from 3.5 to 3.9.

Safety

There were no intraoperative complications.

Pain scores (median VAS scores [range])

	AFP	Advancement flap	p value
Day of the procedure	21.0 (0 to 84)	25.5 (0 to 95)	0.74
At discharge	10.5 (0 to 49)	16.5 (0 to 49)	0.33
2 weeks after surgery	9.0 (0 to 61)	10.5 (o to 91)	0.13

Adverse events

	AFP	Advancement flap	p value
Induration, redness, or swelling affecting the external opening	5% (2/43)	5% (2/39)	1.0
Infection or abscess involving the fistula	7% (3/43)	8% (3/39)	1.0
Flap failed or plug fell out	0%	5% (2/39)	0.22
Light bleeding from external wound, bleeding from fistula, or new apparent fistula forming	2% (1/43)	5% (2/39)	0.60

Faecal Incontinence Score Index (FISI)

There were no statistically significant differences between groups in the composite score for faecal incontinence or the subscales for gas, mucus, liquid stool, and solid stool.

Abbreviations used: AFP, anal fistula plug; BMI, body mass index; EQ-5D, EuroQual-5 dimensions; VAS, visual analogue scale.

Study 5 van Koperen p J (2011)

Details

Study type	**Double-blinded RCT**
Country	The Netherlands (6 centres)
Recruitment period	2006 to 2008
Study population and number	n= **60 (31 AFP versus 29 MAF)** patients with high trans-sphincteric fistulas
Age and sex	AFP group: Median 45 years; 74% (23/31) male; median BMI 25 kg/m^2 MAF group: Median 42 years; 66% (19/29) male; median BMI 27 kg/m^2
Patient selection criteria	Inclusion criteria: age above 18 years, high perianal fistulas of cryptoglandular origin as established during surgery (trans-sphincteric, upper two-thirds of the sphincter complex that was confined by the puborectal sling and the end of the anal canal), and informed consent. Exclusion criteria: no internal opening found during surgery, HIV positivity, Crohn's disease, malignancy, or other causes.
Technique	Patients were randomly assigned during surgery to either the AFP group or the MAF group. The AFP from Surgisis (Cook Surgical Inc.) was used. Prophylactic broad spectrum antibiotics were administered only before surgery. Patients in both groups were advised to refrain from physical labour, cycling, and sports for 2 weeks.
Follow-up	**Median 11 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Patients visited the outpatient department at 2, 4, and 16 weeks after surgery. Follow-up ended when fistula closure was achieved. At the final follow-up, the closure rate was determined by clinical examination in the outpatient clinic by a colorectal surgeon blinded to the intervention.
- The fistula was rated closed if the external and the internal openings were closed and if no discharge and pain were experienced. Otherwise, it was considered as a persistent fistula.
- There were no patients lost to follow-up in either group.

Study design issues:

- The outcome measures included closure rate, postoperative pain, continence (colorectal functional outcome (COREFO), Vaizey, and Wexner scores), and quality of life. The COREFO questionnaire is a validated questionnaire with 27 questions to assess colorectal functional outcome. Five categories were assessed: incontinence, social impact, defecation frequency, stool-related aspects and use of medication. A total score was calculated from these categories, ranging from 0 to 100. A higher score represents an increased level of continence disturbance. The Vaizey scale consists of 3 items about the type and frequency of incontinence (all scored from 0 to 4) and 4 additional items that address alteration in lifestyle (0 to 4), the need to wear a pad or plug (0 or 2), the use of constipating medication (0 or 2), and the lack of ability to defer defecation for 15 minutes (0 or 4). The total score on the Vaizey scale ranges from 0 (complete continence) to 24 (complete incontinence).
- Patients were blinded for the type of intervention.
- The computer randomisation was done centrally in the Academic Medical Centre in Amsterdam, the Netherlands. Block randomisation with random block sizes (4 and 6) was used. Stratification was done for the randomising centres.
- Data were collected via datasheets on paper. Postoperative questionnaires on pain were filled in by patients. Four months after surgery, questionnaires were sent to the patients to assess continence and quality of life.
- To detect an increase in success rate from 40% to 80%, using a significance level of 0.05, at least 46 patients had to be randomly assigned to achieve a power of 80%.

Study population issues:

IP overview: Bioprosthetic plug insertion for anal fistula

- 74% (23/31) of patients in the AFP group and 69% (20/29) in the MAF group had previous fistula surgery.
- 26 % (8/31) of patients in the AFP group and 31% (9/29) in the MAF group had a seton drainage before the procedure.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 60 (31 AFP versus 29 MAF)

Recurrence rate at median 11 months
AFP: 71% (22/31)
MAF: 52% (15/29)
p=0.126
All the patients with a recurrent fistula were symptomatic.

Quality of life (SF-36 and EQ-5D)
-There were no statistically significant differences between groups before surgery and at 16 weeks.
-AFP group:
EQ-5D score before surgery: 0.796
EQ-5D score after surgery: 0.830
p=NS</td><td>There were no intraoperative complications.

Complications after surgery (number of patients)
<table>
<tr><th></th><th>AFP</th><th>MAF</th></tr>
<tr><td>Perianal abscess 1 day after surgery</td><td>1
The plug was removed and the abscess drained.</td><td>0</td></tr>
<tr><td>Abdominal pain 4 days after surgery</td><td>0</td><td>1
The patient was admitted for observation and was discharged after 1 week without a re-intervention.</td></tr>
<tr><td>Bleeding 10 days after surgery</td><td>0</td><td>1
The patient needed a new procedure.</td></tr>
</table>
Pain after surgery (mean VAS scores)
<table>
<tr><th></th><th>AFP</th><th>MAF</th></tr>
<tr><td>VAS score 1 day after surgery</td><td>3 (±3)</td><td>4 (±2.5)</td></tr>
</table>
Overall, there was no statistically significant difference between groups in postoperative pain (p=0.143).

Plug extrusion: 13% (4/31) [All within 10 days of the procedure.]

Incontinence
<table>
<tr><th></th><th colspan="2">AFP</th><th colspan="2">MAF</th></tr>
<tr><td>Scale</td><td>Before</td><td>After</td><td>Before</td><td>After</td></tr>
<tr><td>Vaizey[a] (Total)</td><td>6.7 (±3.3)</td><td>7.2 (±3.7)</td><td>7.0 (±3.9)</td><td>7.7 (±3.2)</td></tr>
<tr><td>COREFO[b] (Total)</td><td>16.3 (±14.5)</td><td>18.7 (±16.0)</td><td>15.1 (±13.5)</td><td>14.8 (±12.7)</td></tr>
<tr><td>Wexner score[c]</td><td>5.50 (0–16)</td><td>5.50 (0–14)</td><td>7.00 (0–12)</td><td>6.50 (0–16)</td></tr>
</table>
aThe values shown are mean (SD). The mean score ranges from 0 to 24 (complete continence to complete incontinence) for the total score.
bThe values shown are mean (SD). The higher score represents an increased level of continence disturbance. The total score scale ranges from 0 to 100.
cThe values shown are median (range). The median score ranges from 0 (perfect continence) to 20 (complete incontinence).
There were no statistically significant differences pre- and postoperatively in the COREFO (p=0.373), Vaizey (p=0.618), and Wexner (p=0.947) scores. There were also no statistically significant differences between groups after surgery.</td></tr>
<tr><td colspan="2">Abbreviations used: AFP, anal fistula plug; BMI, body mass index; COREFO, colorectal functional outcome; MAF, mucosal advancement flap; NS, not statistical significance; VAS, visual analogue scale.</td></tr>
</table>

Study 6 Blom (2014)

Details

Study type	**Retrospective case series**
Country	Sweden (4 centres)
Recruitment period	2006 to 2010
Study population and number	n= **126** patients with an anal fistula
Age and sex	Mean 47 years 63% (80/126) male
Patient selection criteria	Inclusion criteria: Every patient (no exclusions) who had received the first anal fistula plug (Biodesign) operation before 30 June 2010.
Technique	The operation was done according to the recommendations of the manufacturer of the AFP (Cook Biotech). All patients, except 4, had had a pre-treatment of the fistula with a seton to settle inflammation. Antibiotic prophylaxis was not used for the first few patients but was then given following subsequent recommendation. Most patients were off work for 1–2 weeks after the procedure.
Follow-up	**Median 13 months**
Conflict of interest/source of funding	Not reported

Analysis
Follow-up issues: The success of the procedure was assessed by chart review done a minimum of 8 months after plug insertion.
Study design issues:

- Cox proportional-hazards models were used to assess the associations of various factors with fistula healing.
- A closed external opening, without tenderness and with no discharge, was regarded as a successful anal fistula plug operation. Any record of secondary surgery for anal fistula was an obvious failure of the plug procedure. Abscess formation, patient observation of plug discharge, or statement of recurrent or persistent discharge from an external fistula opening, were also regarded as failure.

Study population issues:

- 85% of fistulae were cryptoglandular.
- A mean of 2.9 previous fistulae procedures had been performed.

Key efficacy and safety findings

Efficacy
Number of patients analysed: **126** **First plug-insertion success at more than 8-month follow up**: 24% (30/126) **Cox regression analysis of the association of background factors with fistula closure** • There was no statistically significant difference in success between the 4 participating hospitals (p = 0.39), and Cox regression analysis showed no effect of hospital. • There was no association between sex, age, duration of fistula or the number of operations for fistula and the result of the first plug-insertion procedure. • Success rate of anterior fistula: 12% (5/43) • Success rate of posterior fistula: 32% (16/50) (OR = 2.98, 95% CI: 1.01 to 8.78, posterior fistula compared with anterior fistula) • Success rate of lateral fistula: 41% (7/17) (OR = 2.76; 95% CI: 1.03 to 13.75, lateral fistula compared with anterior fistula). **Re-operation with a further procedure** • 28 failures had a second plug procedure and 5 had a third with an undetermined healing rate. Other patients had a variety of secondary treatments, including fistulotomy and mucosal advancement flap.
Abbreviations used: AFP, anal fistula plug; OR, odds ratio

Study 7 Han JG (2011)

Details

Study type	**Retrospective case series**
Country	China (1 centre)
Recruitment period	2007 to 2010
Study population and number	n= **114** patients with complex high trans-sphincteric anal fistula with a single tract
Age and sex	Median 39 years; 77% (88/114) male; median BMI 24 kg/m^2
Patient selection criteria	Inclusion criteria: high trans-sphincteric fistula (involving more than 30% of the external anal sphincter) or female patient with an anterior trans-sphincteric fistula. Exclusion criteria: multiple fistula tracts, fistulas that did not involve the external sphincter, or fistulas related to Crohn's disease.
Technique	A single dose of a broad-spectrum intravenous (IV) antibiotic was given 30 minutes before surgery. A conical biologic plug was fashioned from a 3 X 5-cm sheet of human acellular dermal matrix (Ruinuo, Qingyuanweiye Bio-Tissue Engineering Ltd). All patients were told to follow a clear liquid diet for 48 hours and to avoid any strenuous activity. Broad-spectrum IV antibiotics and metronidazole were given for 1 day after the procedure. Strenuous activity, sexual activity, exercise, and lifting weights were discouraged for the first 4 postoperative weeks.
Follow-up	**Median 19.5 months (range 11 to 46 months)**
Conflict of interest/source of funding	This work was supported by the Program for Outstanding Medical Academic Leader, Beijing, People's Republic of China, the New Century National Hundred, Thousand, and Ten Thousand Talent Project, Republic of China, the National Natural Science Foundation of China, the Basic and Clinical Cooperation Project of Capital Medical University and the Youth Foundation of Beijing Chaoyang Hospital.

Analysis

Follow-up issues: Data were collected at regular outpatient department visits scheduled to take place 4 weeks, 3 months, and 6 months after surgery. In addition, data from the last available follow-up visit were included in the analyses.

Study design issues:

- The main outcome measures were fistula closure rate and postoperative incontinence (Wexner scores).

- If the initial ADM plug failed, patients chose whether to be treated with another ADM plug or with a cutting seton. Faecal incontinence was assessed with the Cleveland Clinic Florida (Wexner) incontinence scale at the 6-month postoperative visit. For patients who received a cutting seton after failure of the initial ADM plug, a Wexner score obtained just before the cutting seton operation was used for this analysis. A Wexner score was obtained again at the 6-month visit after placement of the cutting seton.

Study population issues:

- No patient had received a draining seton before the ADM plug procedure.

- In all patients, the surgery was done by a colorectal surgeon. However, for 18 patients the surgeon was an expert in the technique for placement of the ADM plug, and for 96 patients the surgeons were 2 attending physicians who were not experts in this technique.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **114** **Overall success rate at 6 months**: 54% (62/114) -Success was defined as the absence of fistula drainage at 6 months of follow-up, with closure of the internal opening shown on anoscopy, closure of the external opening shown on perineal examination, and no observation of abscess formation at any time during follow-up. **Overall plug failure rate**: 46% (54/114) -Most plug failures occurred within 30 days, with only 1 plug failure occurring 6 months after surgery. -On multiple logistic regression analysis, smoking (p<0.001), long distance between external opening (p<0.001), and performance of the operation by a non-expert surgeon (p=0.018) were statistically significantly associated with plug failure. **Re-operation** -Of 40 patients who had a cutting seton placement after plug failure, 33 (82.5%) reported a successful outcome. -12 patients refused further surgery.	No mortality or major complications were observed. **Plug extrusion**: 10% (11/114) [All plug extrusions occurred within the first 2 postoperative weeks (days 2–14).] **Sepsis**: 8% (9/114) [8 cases occurred between day 10 and day 24 and 1 case 120 days after the operation.] **Incontinence rate 6 months after the procedure (or just before placement of cutting seton)** -Overall study population: 2% (2/114) -Subgroup of patients who had seton placement after ADM failed: 75% (30/40) **Wexner score** (median [range]) -ADM: 0 (0 to 4) -Seton placement: 5 (0 to 20)
Abbreviations used: ADM, acellular dermal matrix; BMI, body mass index;	

Study 8 Adamina M (2014)

Details

Study type	**Prospective case series**
Country	Canada (3 centres) and Switzerland (1 centre)
Recruitment period	2007 to 2009
Study population and number	n= **46** consecutive patients with a complex anal fistula
Age and sex	Median 46 years; 65% (30/46) male Median BMI: 27
Patient selection criteria	Inclusion criteria: complex anal fistula not amenable to simple fistulotomy, defined as high trans-sphincteric fistula: anterior trans-sphincteric fistula in a woman; previous fistulotomy; fistula presenting with multiple fistula openings (including horseshoe fistula); and diminished continence. Exclusion criteria: uncomplicated fistula curable by simple fistulotomy; rectovaginal fistula; local sepsis; pregnancy; human immunodeficiency virus positivity; and inflammatory bowel disease.
Technique	The BFP (anal fistula plug Surgisis; Cook Biotech) was used. Patients had a draining seton for at least 6 weeks before placement of the BFP. No antibiotic prophylaxis was needed. The patient was instructed to restrict physical and sexual activity for 2 weeks postoperatively. Stool softener, paracetamol and sitz baths were advised.
Follow-up	**Median 68 months**
Conflict of interest/source of funding	Not reported

Analysis
Follow-up issues: Clinical evaluation was performed at 10 days, 6 weeks and 6 months after surgery, and was completed by telephone interviews.
Study design issues:

- The primary end-points were clinical success rate, anal continence and quality of life at 6-month follow up.
- Clinical success was defined as the absence of drainage, pain and fistula openings on physical examination at 6 months of follow up, and as the absence of abscess formation or discharge at any time during further follow-up examinations.
- Anal continence and quality of life were measured pre- and postoperatively using the validated Faecal Incontinence Score Index (FISI) and Short Form-36 Health Survey, version 2 (SF- 36 v2) questionnaires.
- The FISI is a 4-item score measuring the severity of anal incontinence to gas, mucus, and liquid and solid stools. FISI scores of more than 30 predict a detrimental effect on quality of life after anal fistula surgery.
- The study was powered to detect a meaningful difference in quality of life upon treatment of complex anal fistula. A difference of 3–5 points in SF-36 v2 norm-based scores for both the summary component scores and individual scale scores was deemed clinically meaningful. For a two-tailed paired t-test with $\alpha = 0.050$, inclusion of 45 patients yielded a power of 90% to detect a difference of five points at 6-month follow-up.

Study population issues:

- 61% (28/46) of patients had more than 3 previous fistula surgeries.
- 41% (19/26) of patients had complicated anal fistulae presenting with a branched fistula tract or multiple fistula openings.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **46**

Healing rate (overall): 43% (20/46)

Recurrence rate (overall) : 57% (26/46)

Median time to recurrence: 24.8 (95% CI 9.4 to 73.8) months

Recurrence rate at 6 months: 30.7% (95% CI 15.9 to 42.8%)

Recurrence rate at 1 year: 40.2% (95% CI 23.9 to 53.1%)

Recurrence rate at 2 years: 48.0% (95% CI 30.6 to 61.1%)

The risk of recurrence for complicated fistulae increased by 234% in univariate Cox regression (hazard ratio = 3.34; 95% CI 0.95 to 11.70). No other patient characteristics, including sex, location of the internal opening, body mass index and tobacco use, significantly influenced the recurrence rate.

Re-operation

- 11% (5/46) of patients had a repeat BFP procedure
- 1 of these patients had 2 repeat procedures.

Quality of life (SF-36 v2)

	Before surgery (n=45)	6 weeks (n=38)	6 months (n=35)
Physical component summary (1–81)* (median [IQR])	47.2 (39.8 to 53.1)	48.6 (43.4 to 55.6)	56.2 (50.4 to 59.3)
Range	27.9 to 64.2	27.9 to 64.2	34.1 to 64.0
p value (compared with before surgery)		0.051	**<0.001**
Mental component summary (-9 to 82)* (median [IQR])	48.5 (36.0 to 55.0)	50.6 (42.6 to 55.1)	55.3 (44.9 to 56.7)
Range	17.4 to 64.4	17.4 to 64.4	24.3 to 62.6
p value (compared with before surgery)		0.547	**0.013**

*Possible range of values; the highest score equals the best possible condition.

SF-36 v2 health transition

Self-perceived health status	Before surgery (n=45)	6 weeks (n=38)	6 months (n=35)
Much worse	0%	0%	0%
Somewhat worse	22% (10/45)	5% (2/38)	11% (4/35)
Equal	58% (26/45)	37% (14/38)	31% (11/35)
Somewhat better	13% (6/45)	26% (10/38)	14% (5/35)
Much better	9% (4/45)	32% (12/38)	43% (15/35)
p-value (compared with before surgery)		**0.004**	**0.005**

Safety

Extrusion of BFP: 7% (3/46) within 4 days of the procedure.

2/3 patients had a successful repeat BFP procedure; the third patient declined to have a repeat BFP.

Abscess: none

Anal continence

	Before surgery (n=45)	6 weeks (n=38)	6 months (n=35)
FISI severity (median [IQR])	19 (0.0 to 31.0)	20 (4.0 to 36.0)	12 (4.0 to 31.0)
Range	0 to 54	0 to 61	0 to 46
p value (compared with before surgery)		0.929	**0.008**
Urgency			
Twice or more daily	22% (10/45)	5% (2/38)	9% (3/35)
Once a day	11% (5/45)	21% (8/38)	14% (5/35)
Twice or more weekly	7% (3/45)	13% (5/38)	11% (4/35)
Once a week	2% (1/45)	8% (3/38)	3% (1/35)
One to three times a month	16% (7/45)	13% (5/38)	17% (6/35)
Never	42% (19/45)	39% (15/38)	46% (16/35)
p value (compared with before surgery)		0.566	0.256

Abbreviations used: BFP, bioprosthetic fistula plug; BMI, body mass index; CI, confidence interval; FISI, faecal incontinence score index; IQR, interquartile range; SF-36 v2, short form-36 health survey, version 2

Study 9 NIHR funded FIAT Fistula-in-ano trial comparing Surgisis® anal fistula plug versus surgeon's preference (advancement flap, fistulotomy, cutting seton) for transsphincteric fistula-in-ano (Unpublished NIHR Health Technology Assessment Report at 21st March 2019).

[Academic in confidence]

Data have been redacted.

Study 10 Lin H (2019)

Details

Study type	**Systematic review and meta-analysis**
Country	Systematic review and meta-analysis: China Studies included: USA (3), UK (1), Canada (1), China (1), Germany (1), Netherlands (1), Spain (!), Switzerland (1) and Norway and Sweden (1).
Study period	Date of search not reported Publication years for the included studies: 2007 to 2017
Study population and number	**n=810 (327 AFP and 483 RAF) p**atients with complex cryptoglandular anal fistulas from 11 studies
Age and sex	Means 32 years to 53.1 years; sex not reported clearly
Patient selection criteria	Inclusion criteria: Original research from non-RCTs or RCTs among adults; the interventions of interest were AFP and RAF; the participants of interest were patients who were diagnosed with complex cryptoglandular anal fistulas; the primary outcomes of interest were the healing and recurrence rate; the OR with 95% CI of the risk of the healing or recurrence rate was either provided or could be calculated; the most recent and complete study was included if data from the same population had been published more than once; articles were published without language restriction from their inception to October 2017. Exclusion criteria: Participants were non-human, children, pregnant women or HIV-positive; participants with anal fistulas associated with Crohn's disease, radiation, malignancy, pre-existing faecal incontinence or chronic diarrhoea; absence of primary and secondary outcome data; the publication type was case reports, conference abstracts or a review.
Technique	AFPs were used but made from different materials.
Follow-up	**Mean 3 months to 27.3 months**
Conflict of interest/source of funding	None

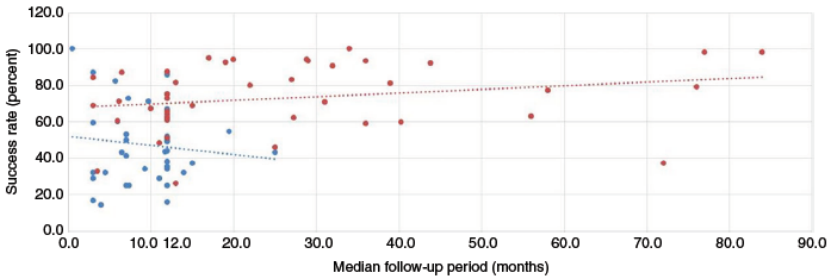
Analysis
Follow-up issues: Losses to follow-up were not discussed in the review.
Study design issues:

- This study compared the efficacy of AFP with RAF for complex cryptoglandular anal fistulas which were defined as high transsphincteric fistulas or transsphincteric fistulas that involved greater than 30% of the external sphincter, suprasphincteric, extrasphincteric or horseshoe fistulas.
- A subgroup analysis of studies with long-term follow-up was conducted to discover the actual healing and recurrence rates with the AFP and RAF.
- Recurrence was defined as the presence of an abscess arising in the area or obvious evidence of fistulation.
- A suitable search strategy was used to search the following databases: Embase, PubMed and the Cochrane Library databases.
- Two investigators independently searched and reviewed the identified studies, extracted the data and assessed the quality of the relevant articles, using the Jadad scoring system (1 to 7 points) for RCTs and the Newcastle-Ottawa scale (1 to 9 points) for non-RCTs. The risk of bias in the RCTs was assessed using a quality checklist recommended by the Cochrane Handbook for Systemic Reviews.

Study population issues:

- The included 11 studies consisted of 5 RCTs (1 RCT was conference abstract) and 6 non-RCTs. The sample size of all included studies ranged from 24 to 123.
- Of the 5 RCTs, 2 were designed as double-blind multicentre RCTs, 1 as a single-blind and single-centre RCT, and 1 as single-centre RCT.
- Only 4 RCTs and 1 non-RCT provided long-term (12 months) follow-up, and the follow-up time was no more than 10 months in the remaining studies.
- There was a lack of high-level evidence: 4 RCTs (quality score of each RCT were 4, 5, 6 and 6) and 6 non-RCTs (4 studies with a score of 6 and 2 studies with a score of 8).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **810** (327 AFP versus 483 RAF from 11 studies) **Healing rate between AFP and RAF:** - 5 RCTs: OR: 0.46, 95% CI 0.16 to 1.34, I^2=79%, p=0.16 - 4 non-RCTs: OR: 0.64, 95% CI 0.25 to 1.64, I^2=66%, p=0.35 **At a median follow-up of 11 months, healing rate between AFP and RAF:** - 4 RCTs: OR: 0.32, 95% CI 0.13 to 0.78, I^2=60%, p=0.01 **Recurrence rate between AFP (n=245) and RAF (n=404):** - 4 RCTs: OR: 2.10, 95% CI 0.38 to 11.74, I^2=86%, p=0.40 - 4 non-RCTs: OR: 2.75, 95% CI 0.46 to 16.43, I^2=81%, p=0.27 **At a median follow-up of 11 months, recurrence rate between AFP and RAF:** - 3 RCTs: OR: 4.45, 95% CI 1.45 to 13.65, I^2=60%, p=0.009 **Success rate at a median of 12 months**: 39 AFP- and 43 RAF-related original research focused on the treatment of complex cryptoglandular anal fistulas were extracted and analysed.  At a median follow-up of 12 months, the healing rate was less than 60% in the AFP group and more than 60% in the RAF group.	**Fistula complications between AFP and RAF:** - 3 RCTs: OR: 1.16, 95% CI 0.34 to 3.94, I^2=0%, p=0.81 - 4 non-RCTs: OR: 1.61, 95% CI 0.17 to 15.14, I^2=64%, p=0.68 **At a median follow-up of 11 months, fistula complications between AFP and RAF:** - 2 non-RCTs: OR: 0.47, 95% CI 0.08 to 2.74, I^2=0%, p=0.40
Abbreviations used: AFP, anal fistula plug; CI, confidence interval; OR, odds ratio; RAF, rectal advancement flap.	

Study 11 Nasseri Y (2016)

Details

Study type	**Systematic review**
Country	Systematic review: US Not reported for individual studies
Recruitment period	Date of search not reported Publication years for the included studies: 2006 to 2013
Study population and number	**n=84 p**atients with Crohn's disease from 12 studies
Age and sex	Median 45 years; sex not reported for all studies
Patient selection criteria	Inclusion criteria: Articles described the use of AFPs for fistula-in-ano in Crohn's disease patients with clinical healing of the fistula as the primary outcome. Randomised/nonrandomised, controlled/uncontrolled clinical trials, prospective observational studies and retrospective case studies were included. Exclusion criteria: Abstracts, case reports, letters, comments, conference proceedings and studies not published in the English language were excluded. Patients receiving additional procedures such as fibrin glue and/or flap advancement were excluded. Studies including patients with rectovaginal or rectovesical fistula were excluded unless it contained the largest group of Crohn's disease patients with fistula-in-ano.
Technique	AFP
Follow-up	**Median 9 months**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues:

- The follow-up time was mostly short and highly variable, with as little as 3 months in some cases.
- Losses to follow-up were not discussed.

Study design issues:

- This study reviewed and analysed the findings of studies investigating the efficacy of AFP for the treatment of anal fistula in patients with Crohn's disease, with the primary outcome being success rate. A literature search was conducted via Pubmed, Embase, Medline, Scopus and the Cochrane Library for the period 1995 to 2014 using a suitable search strategy.
- Two authors independently reviewed the publications and then extracted and analysed the data, and any disagreements were resolved by the primary author. Quality assessment of the studies was not reported.
- This review was presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews and meta-analyses
- Due to the heterogeneity of the included studies, it was not possible to perform a weighted analysis to obtain a summary estimate of the efficacy of the procedure. Statistical significance could not be achieved due to the low sample sizes (Type II error).
-

Study population issues:

- Of the 12 included studies, 8 were non-randomised prospective and 4 retrospective studies; and 2 studies reported the number of patients having previous fistula surgery.
- In terms of the plug type, 11 studies used Surgisis® and 1 applied GORE® BIO-A®.
- Sixty-four per cent of the patients included were involved in studies that had major affiliations with the AFP industry.

Key efficacy and safety findings

Efficacy
Number of patients analysed: **n=84 (12 studies)** **Successful fistula closure rate:** - The total success rate in all studies: 58.3% (49/84, 95% CI 47 to 69) - The success rate in patients with a recurrent anal fistula from previous treatment: 40% (2/5, 95% CI 5 to 85) - The overall success rate of Surgisis® brand plug: 60% (48/80, 95% CI 48 to 71) - The overall success rate of GORE® BIO-A® brand plug: 25% (1/4, 95% CI 1 to 81) - The success rate of studies using preoperative medication: inferior success rates in CD patients who received preoperative medication than those who did not (study 1, 14.3% [1/7] versus 42.9% [3/7]; study 2, 50% [2/4] versus 87.5% [14/16]) - The success rate of the 4 studies affiliated with the AFP industry: 59.2% (32/54) - The success rate of the 8 studies unaffiliated with the AFP industry: 56.6% (17/30) **Recurrence rate**: 13.6% (3/22 in 5 studies)
Abbreviations used: AFP, anal fistula plug; CD, Crohn's disease; CI, confidence interval.

Study 12 Dozois EJ (2019)

Details

Study type	**Case series**
Country	US
Study period	Not reported
Study population and number	n=15 patients with a single tract transsphincteric cryptoglandular fistula
Age and sex	Mean 39.8 years; 53% (8/15) female
Patient selection criteria	Inclusion criteria: Adults 18 to 65 years with new or previously treated unhealed single tract cryptoglandular fistulas Exclusion criteria: Patients were excluded if they had IBD, clinically significant comorbidities, a history of cancer, hepatitis, or HIV, or they were pregnant or lactating.
Technique	MSC-MATRIX: mesenchymal stem cells – coated Gore Bio-A fistula plug
Follow-up	**6 months**
Conflict of interest/source of funding	This work was supported by the Mayo Clinic Discovery Translation Award. One author is a Consultant and on the Advisory Board for AbbVie, a consultant for Boehringer Ingelheim Pharma and Celgene, Consultant and Advisory Board member for Janssen, and a consultant for Robarts, Takeda, and MediBeacon. One author is a consultant for Takeda. One author is a consultant for Medtronics and received a grant to institution from Siemens Healthineers. Two authors are inventors of technology used as a tool in this research; the technology has been licensed to a commercial entity (PLTMax; Mill Creek LifeScienes). These authors and the Mayo Clinic have equity in the company and have contractual rights to receive royalties from the licensing of this technology.

Analysis

Follow-up issues:

- Patients were observed for 6 hours postoperatively for acute adverse events before discharge from the hospital, and then followed up at day 1, week 2, and months 1, 2, 3, and 6 after the procedure.
- One patient withdrew from study and travelled internationally for treatment.

Study design issues:

- This open-label, phase I prospective clinical trial aimed to determine safety, feasibility and efficacy of using an autologous mesenchymal stem cell-coated fistula plug in patients with transsphincteric cryptoglandular fistulas.
- Clinical healing was defined as healed (cessation of drainage with reepithelization of external opening), improved (decrease in drainage), or no change.
- A single experienced radiologist comparing the pre- and post-intervention scans was blinded to the patient's clinical response.

Study population issues:

- The median duration of disease at the time of study enrolment was 30 years (range 1 year to 13 years).
- The median number of surgical procedures including incision and drainage and attempt at repair before placement of the MSC-MATRIX was 3.5 (range 1 to 20).
- Previous surgical interventions to close the fistula had failed in 12 of 15 patients, with numbers of previous failed repairs ranging from 1 to 5.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **15** **Clinical healing rates at 6-month follow-up:** • Complete clinical healing rate: 20% (3/15) • Partial healing rate: 53% (8/15) • No clinical improvement: 27% (4/15) **Radiographical improvement at 6-month follow-up:** 73% (11/15)	**Short-term (within 30 days postintervention) adverse events:** • Abdominal wall seroma: n=1 (no intervention was required, and the seroma resolved without complications) • Perianal abscess: n=2 One patient developed an abscess on postoperative day 10 that required surgical drainage and seton placement. The plug was not removed. This patient's sepsis resolved without complications. The fistula continued to drain and a seton remained in place up to 6 months. One patient claimed the plug fell out on postoperative day 6 and this patient later developed an abscess that required drainage.
Abbreviations used:	

Validity and generalisability of the studies

- Two RCTs[3, 5] were included in a systematic review and meta-analysis[10], but the total sample of 2,455 derived from removing duplications.
- The evidence includes heterogeneous populations both within and between studies. Seven studies excluded patients with Crohn's disease[1, 3-6, 10, 12].
- One or several plugs were used during the procedures.
- A draining seton was placed before the procedures for some patients.
- Various AFPs were used, such as acellular dermal matrix plug[7], mesenchymal stem cells – coated AFP[12] and Biodesign AFP[1-6, 8, 9].
- In most of the studies included, patients had a history of fistula procedures.
- Enrolment in study 4 was stopped early due to difficulties in patient recruitment.
- A study noted that plug extrusion may be the result of a learning curve issue.
- In study 2, the patients had ano-perineal fistulas.

Existing assessments of this procedure

- The German S3 guidelines: anal abscess and fistula (second revised version)[10] were published in 2017. They stated:

  "*New technical developments*

  Surgisis® AFP™ anal fistula plug

  […] To sum up, plugging has added a new option for the treatment of high anal fistula, but the healing rates are quite low.

  Evidence level: 1b
  Recommendation grade: B
  Consensus strength: strong consensus"

- The Association of Coloproctology of Great Britain and Ireland published a position statement on the treatment of anal fistula[11] in 2018. It says:

"Recommendations

Accepting that rates of healing are variable, an anal fistula plug is an option for treating transsphincteric fistulas, especially where surgical options are considered to have a significant risk of jeopardizing continence. The additional cost of the plug should be taken into account when considering this surgical treatment. (Grade C)"

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Radially emitting laser fibre treatment of an anal fistula. NICE interventional procedures guidance 644 (2019). Available from http://www.nice.org.uk/guidance/ipg644

Technology appraisals

- Darvadstrocel for treating complex perianal fistulas in Crohn's disease. NICE technology appraisal 556 (2019). Available from http://www.nice.org.uk/guidance/TA556

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for bioprosthetic plug insertion for anal fistula were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing studies:

- The FIAT trial The Fistula-In-Ano Trial comparing Surgisis® anal fistula plug versus surgeon's preference (advancement flap, fistulotomy, cutting seton) for transsphincteric fistula-in-ano. RCT. n=306. Results were expected to be published in 2018.UK (47 centres).
- NCT03381365 A Pilot Study to Assess the Efficacy of an Anorectal Fistula Plug With Sealing of the Internal Opening (Curaseal AF) as a Treatment for Perianal Fistula. Case series. Estimated enrolment=15. Recruiting. UK. Estimated Primary Completion Date: 31/12/2017.
- NCT03321266 Retrospective Review of the Cook Biodesign® Fistula Plug to Treat Anorectal Fistulas. Retrospective case series. Estimated enrolment: 73. Recruiting. Germany, United States. Estimated Study Completion Date: December 2018.

References

1. Xu Y, and Tang W (2016) Comparison of an anal fistula plug and mucosa advancement flap for complex anal fistulas: a meta-analysis. ANZ Journal of Surgery 86(12), 978-982
2. Senejoux A, Siproudhis L, Abramowitz L et al. (2016) Fistula Plug in Fistulising Ano-Perineal Crohn's Disease: a Randomised Controlled Trial. Journal of Crohn's & colitis 10(2), 141-8
3. Bondi J, Avdagic J, Karlbom U et al. (2017) Randomized clinical trial comparing collagen plug and advancement flap for trans-sphincteric anal fistula. The British journal of surgery 104(9), 1160-1166
4. Schwandner T, Thieme A, Scherer R et al. (2018) Randomized clinical trial comparing a small intestinal submucosa anal fistula plug to advancement flap for the repair of complex anal fistulas. International journal of surgery open 15, 25-31.
5. Koperen Pj, Bemelman Wa, Gerhards Mf et al. (2011) The anal fistula plug treatment compared with the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistula: a double-blinded multicenter randomized trial. Diseases of the colon and rectum 54(4), 387-393
6. Blom J, Husberg-Sellberg B, Lindelius A et al. (2014) Results of collagen plug occlusion of anal fistula: a multicentre study of 126 patients. Colorectal Disease 16(8), 626-30
7. Han J G, Wang Z J, Zhao B C et al. (2011) Long-term outcomes of human acellular dermal matrix plug in closure of complex anal fistulas with a single tract. Diseases of the Colon & Rectum 54(11), 1412-8
8. Adamina M, Ross T, Guenin M O et al. (2014) Anal fistula plug: a prospective evaluation of success, continence and quality of life in the treatment of complex fistulae. Colorectal Disease 16(7), 547-54
9. Unpublished data from the NIHR funded FIAT Fistula-in-ano trial comparing Surgisis® anal fistula plug versus surgeon's preference (advancement flap, fistulotomy, cutting seton) for transsphincteric fistula-in-ano
10. Lin H, Jin Z, Zhu Y et al. (2019) Anal fistula plug vs rectal advancement flap for the treatment of complex cryptoglandular anal fistulas: a systematic review and meta-analysis of studies with long-term follow-up. Colorectal disease, 21(5): 502-515
11. Nasseri Y, Cassella L, Berns M et al. (2016) The anal fistula plug in Crohn’s disease patients with fistula-in-ano: a systematic review. Colorectal disease, 18(4): 351-356
12. Dozois EJ, Lightner AL, Mathis KL et al. (2019) Early results of a phase I trial using an adipose-derived mesenchymal stem cell-coated fistula plug for

the treatment of transsphincteric cryptoglandular fistulas. Diseases of the colon & rectum, 62(5): 615-622

13. Ommer A, Herold A, Berg E et al. (2017) German S3 guidelines: anal abscess and fistula (second revised version). Langenbeck's Archives of Surgery 402(2), 191-201

14. Williams G, Williams A, Tozer P et al. (2018) The treatment of anal fistula: second ACPGBI Position Statement - 2018. Colorectal Disease 20 Suppl 3:5-31

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	20/05/19	Issue 5 of 12, May 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	20/05/19	Issue 5 of 12, May 2019
HTA database (CRD website)	20/05/19	-
MEDLINE (Ovid)	20/05/19	1946 to May 17, 2019
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	20/05/19	1946 to May 17, 2019
EMBASE (Ovid)	20/05/19	1974 to 2019 Week 20

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 rectal fistula/ or rectovaginal fistula/
2 Fistula/
3 Anal Canal/
4 fistul*.tw.
5 (anal* or anus* or rectal* or rectum* or anorect* or ano* or intersphinct* or transsphinct* or perineal* or perianal*).tw.
6 3 or 5
7 2 or 4
8 6 and 7
9 (recto?vag* adj3 fistul*).tw.
10 1 or 8 or 9
11 Biocompatible Materials/
12 "Prostheses and Implants"/
13 (plug* or implant* or block*).tw.
14 surgisis*.tw.
15 AFP.tw.
16 Gore Bio-A.tw.
17 or/11-16
18 10 and 17
19 limit 18 to yr="2006 -Current"
20 animals/ not humans/
21 19 not 20
22 limit 21 to ed=20180901-20190531

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abbas M A, Jackson C H, and Haigh P I (2011) Predictors of outcome for anal fistula surgery. Archives of Surgery 146(9), 1011-6	Retrospective case series n=12 plug Follow-up=6 months	Fistulotomy is the preferred operation for anal fistula. Plugging is associated with the highest operative failure and septic complication rates. Incontinence was influenced more by fistula type and age rather than procedure.	Larger studies are included
Adamina M, Hoch JS, Burnstein MJ. (2010)To plug or not to plug: a cost-effectiveness analysis for complex anal fistula. Surgery 147: 72–8.	Non-randomised comparative study n = 24 (12 vs 12) Follow-up = 7 months	*Complex anal fistulae* Success rate: • Fistula plug = 50% (6/12) • Endoanal advancement flap = 33% (4/12), p = 0.68	Larger studies are included
Almeida Isuru S, Wickramasinghe Dakshitha, Weerakkody Pragathi, and Samarasekera Dharmabandhu N (2018) Treatment of fistula in-ano with fistula plug: experience of a tertiary care centre in South Asia and comparison of results with the West. BMC research notes 11(1), 513	Retrospective case series n=51 Follow-up= 12 months	Twenty-three (56.1%) patients had complete healing while 18 (43.9%) patients failed the fistula plug procedure during the follow up period of 12 months. Logistical regression failed to identify any statistical significant association with demographic or disease factors and healing. Healing was 1.5 times less likely for every failed procedure prior to AFP insertion.	Larger studies are included
Ba-bai-ke-re A, Wen H, Huang H-G et al. (2010) Randomized controlled trial of minimally invasive surgery using acellular dermal matrix for complex anorectal fistula. World Journal of Gastroenterology 16: 3279–86.	RCT n = 90 (45 fistula plug vs 45 endorectal advancement flap) Median follow-up: 6 months	Success rate: • Fistula plug = 82.2% (37/45) • Endorectal advancement flap = 64.4% (29/45), p<0.05 Fistula recurrence: • Fistula plug = 4.4% (2/45) • Endorectal advancement flap = 28.9% (13/45), p = 0.0047 Early extrusion of the plug occurred in 4 patients and late extrusion in 1 patient. Quality of life scores: (assessed using the Fecal Incontinence Quality of Life Scale; higher scores indicate better quality of life)	Was included in previous overview.

		• Fistula plug = 85.9 ± 5.3 • Endorectal advancement flap = 65.3 ± 8.9 p < 0.0001	
Bobkiewicz A, Krokowicz L, Borejsza-Wysocki M, and Banasiewicz T (2017) A novel model of acellular dermal matrix plug for anal fistula treatment. Report of a case and surgical consideration based on first utility in Poland. Polski Przeglad Chirurgiczny 89(4), 52-55	Case report n=1 Follow-up = 2 months	In the authors' opinion, the method is simple, safe and reproducible. Innovative shape of the plug minimizes the risk of its migration and rotation. It also perfectly blends with and adapts to the course and shape of the fistula canal, allowing it to become incorporated and overgrown with tissue in the fistula canal. The relatively short operation time, minor postoperative pain and faster convalescence are with no doubt additional advantages of the method.	Larger studies are included.
Buchberg B, Masoomi H, Choi J et al. (2010) A tale of two (anal fistula) plugs: is there a difference in short-term outcomes? The American Surgeon 76(10):1150-3	Retrospective comparative case series n=22 (12 bioprosthetic plug [Cook] versus 10 synthetic plug [Gore]) Follow-up=95 days	The overall procedural success rate in the Gore group was 54.5 per cent (6 of 11) versus 12.5 per cent (2 of 16) in the Cook group. The reasons for failure were unknown in the majority of patients and plug dislodgement in two patients.	Larger studies are included.
Champagne BJ, O'Connor LM, Ferguson M et al. (2006) Efficacy of anal fistula plug in closure of cryptoglandular fistulas: long-term follow-up. Diseases of the Colon & Rectum 49: 1817–21.	Case series n = 46 Follow-up = 12 m	*High cryptoglandular anorectal fistulae* Success rate = 83%	Larger studies are included. *Included in original overview.* *Included in systematic review.*
Chan S, McCullough J, Schizas A et al. Williams A, and Cohen C R (2012) Initial experience of treating anal fistula with the Surgisis anal fistula plug. Techniques in Coloproctology 16(3), 201-6	Prospective case series n=44 FU=mean 10.5 months	Successful healing rate: 50% (22/44) of patients Overall success rate: 35% (23/62) of plugs 19/ 29 patients healed following first-time plug placement, whereas repeated plug placement was successful in 3/15 patients (20%; p = 0.0097). There was a statistically significant difference in the healing rate between patients who had 1 or less operations before plug insertion compared with patients who needed multiple operations (18/24 patients vs. 4/20 patients; p = 0.0007).	Larger studies included with more outcomes reported.

Christoforidis D, Pieh MC, Madoff RD et al. (2009) Treatment of transsphincteric anal fistulas by endorectal advancement flap or collagen fistula plug: a comparative study. Diseases of the Colon & Rectum 52: 18–22.	Non-randomised comparative study n = 80 (37 fistula plug vs 43 endorectal advancement flap) Mean follow-up (months): 14 (plug), 56 (flap) (p < 0.0001)	Success rate: • Fistula plug = 32.4% (12/37) • Endorectal advancement flap = 62.8% (27/43), p = 0.008 Early extrusion of the plug occurred in 7 patients. Fistula recurrence: • Fistula plug = 13.5% (5/37) • Endorectal advancement flap = 7.0% (3/43)	Was included in previous overview.
Christoforidis D, Etzioni DA, Goldberg SM et al. (2008) Treatment of complex anal fistulas with the collagen fistula plug. Diseases of the Colon & Rectum 51: 1482–7.	Case series n = 47 Follow-up = 6.5 months	*Complex anal fistulae* Success rate = 31% per procedure (43% per patient) An increased amount of external sphincter involvement was associated with a higher failure rate (p<0.05)	Larger studies are included.
Chung W, Ko D, Sun C et al. (2010) Outcomes of anal fistula surgery in patients with inflammatory bowel disease. American Journal of Surgery 199: 609–13.	Non-randomised comparative study n = 51 (4 fistula plug) Follow-up = 12 weeks	*Patients with inflammatory bowel disease* Healing rates at 12 weeks: • Fistula plug = 75% • Fibrin glue = 0% • Flap advancement = 20% • Seton drain = 28% Continence scores were not altered.	Larger studies are included.
Chung W, Kazemi P, Ko D et al. (2009) Anal fistula plug and fibrin glue versus conventional treatment in repair of complex anal fistulas. American Journal of Surgery 197: 604–8.	Non-randomised comparative study n = 232 (27 fistula plug, 23 fibrin glue, 86 seton drain, 96 flap advancement) Follow-up: 12 weeks	Healing rates at week 12: • Fistula plug = 59.3% (16/27) • Fibrin glue = 39.1% (9/23) • Seton drain = 32.6% (28/86) • Flap advancement = 60.4% (58/96) p < 0.05 'between the treatment groups' Of the 11 fistula plug patients with persistent fistulae at 12 weeks, 3 had infection and 5 had plug extrusion (all occurring within 4 weeks).	Was included in previous overview.
Cintron J R, Abcarian H, Chaudhry V et al. (2013) Treatment of fistula-in-ano using a porcine small intestinal submucosa anal fistula plug. Techniques in Coloproctology 17(2), 187-91	Prospective case series n=73 Follow-up=1 year	Plug extrusion (fallout) rate: 9% (7/78). There was no difference in closure rates between primary and recurrent fistulas (primary = 20/53 = 38% and recurrent 8/20 = 40%). Overall patient success rate: 38% (28/73) Plug success rate when plug fallouts were eliminated: 39.5%.	Larger studies are included.

		The fistulas in 4/8 patients with Crohn's disease closed (50%). Postoperative abscesses: 5% (4/73)	
Cirocchi R, Trastulli S, Morelli U et al. (2013) The treatment of anal fistulas with biologically derived products: is innovation better than conventional surgical treatment? An update. Techniques in Coloproctology 17(3), 259-73	Systematic review and meta-analysis Search date until February 2012 Fibrin glue, fistula plug or acellular dermal matrix versus surgical treatment	The review shows that there are no significant advantages of the new techniques involving biologically derived products. Further randomized controlled trials are needed.	A more recent systematic review and meat-analysis is included.
Echenique I, Mella JR, Rosado F et al. (2008) Puerto Rico experience with plugs in the treatment of anal fistulas. Boletin - Asociacion Medica de Puerto Rico 100: 8–12.	Case series n = 23 Follow-up = not reported	*Anal fistulae (excluding patients with inflammatory bowel disease)* Success rate = 60% (14/23)	Larger studies are included.
El-Gazzaz G, Zutshi M, Hull T. (2010) A retrospective review of chronic anal fistulae treated by anal fistulae plug. Colorectal Disease 12: 442–7.	Case series n = 33 Follow-up = 222 days	*Complex anal fistulae (61% cryptoglandular, 39% Crohn's disease)* Success rate = 25% (8/32) Reasons for failure = sepsis (87%) and plug dislodgment (13%)	Larger studies are included
Ellis CN, Rostas JW, Greiner FG. (2010) Long-term outcomes with the use of bioprosthetic plugs for the management of complex anal fistulas. Diseases of the Colon & Rectum 53: 798–802.	Case series n=63 Follow-up: 12 months minimum	Success of initial plug = 76% (48/63) Types of failure: • Technical issues (plug extruded within 1 week of placement) = 1.6% (1/63) • Primary failure (plug not extruded but fistula failed to heal) = 15.9% (10/63) • Late failure (fistula healed but subsequently recurred during follow-up; median time to recurrence was 7 months) = 6.4% (4/63)	Was included in previous overview.
Ellis CN. (2007) Bioprosthetic plugs for complex anal fistulas: an early experience. Journal of Surgical Education 64: 36–40.	Non-randomised comparative study n = 113 (18 fistula plug) Follow-up = 6 months	*Complex anal fistulae* Fistula recurrence: • Fistula plug = 12% (2/18) • Advancement flap = 33% (31/95)	*Included in original overview*
Fang X, Miao C, Hu Y et al. (2018) Clinical efficacy of anal fistula plug treatment regimens in anal fistula patients. Biomedical Research (India) 29(3), 617-622	Retrospective comparative study n=52 (25 plug versus 27 incision-thread-drawing) Follow-up=3 months	The results showed that there were significant differences on postoperative pain between the two groups ($p<0.001$). Further, the healing time in patients with AFP treatment was remarkably lower than those	Larger studies are included

		with incision-thread-drawing treatment (p<0.05), whereas the anal scar area and the functional score of anal sphincter in patients with AFP treatment was markedly higher than those with incision-thread-drawing treatment (p<0.001). Nevertheless, the cure rates were not obviously different between the 2 groups.	
Fisher O M, Raptis D A, Vetter D et al. (2015) An outcome and cost analysis of anal fistula plug insertion vs endorectal advancement flap for complex anal fistulae. Colorectal Disease 17(7), 619-26	Prospective comparative case series n=71 (31 plug versus 40 advancement flap) Follow-up=median 6 months for the plug and 4 months for the advancement flap	Twelve (39%) recurrences occurred in the AFP and 17 (43%) in the ERAF group (p = 1.00). The median length of stay was 1.23 and 2.0 days (p < 0.001), respectively.	This study is included in the systematic review and meta-analysis included in Table 2.
Garg P, Song J, Bhatia A et al. (2010) The efficacy of anal fistula plug in fistula-in-ano: a systematic review. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 12(10), 965-970	Systematic review Search date: 2009 n=317 (12 studies) No RCTs were founds Follow-up=2.5 to 12 months	Overall success rate (patient cure rate): 24–92% Overall tract closure rate: 61–90% Plug extrusion rate: 4–41% (43/232) Abscess formation (sepsis / suppuration) = 4–29% (11/108)	Was included in previous overview. A more recent systematic review and meta-analysis is included.
Garg P. (2009) To determine the efficacy of anal fistula plug in the treatment of high fistula-in-ano: an initial experience. Colorectal Disease 11: 588–91.	Case series n = 23 Follow-up = 292 days	*High cryptoglandular anal fistulae* Success rate = 71% (15/21)	Larger studies are included.
Hall J F, Bordeianou L, Hyman N, Read et al. (2014) Outcomes after operations for anal fistula: results of a prospective, multicenter, regional study. Diseases of the Colon & Rectum 57(11), 1304-8	Registry n=10 plug Follow-up = 3 months	Healing rates of fistula plugs at 3 months: 20% (95% CI 5 to 50). Hospital site was the only variable associated with healing (p < 0.05).	Larger studies are included.
Hansen MS, Kjær ML and Andersen J (2019) Efficacy of plug treatment for complex anorectal fistulae: Long-term Danish results. Annals of Coloproctology.	Case series n=36 patients who underwent plug (Cook-Surgisis or Gore) insertion Median follow-up: 18 months	Of 36 patients, the fistulae of 52.8% of the patients healed. The plug failure rate was 44.4% and the fistula recurrence rate was 26.3%. the overall success rate for plug treatment was 39% when adjusted for recurrence. The use of bioprosthetic plugs to treat patients with complex	This study includes a small sample.

		anal fistulae seems to be a safe, viable option for complex fistula repair when other surgical attempts have failed. However, it should not be the treatment of choice.	
Hyman N, O'Brien S, Osler T. (2009) Outcomes after fistulotomy: results of a prospective, multicenter regional study. Diseases of the Colon & Rectum 52: 2022–7.	Non-randomised comparative study (registry data) n = 245 (43 fistula plug, 120 fistulotomy, 36 staged fistulotomy, 21 draining seton only, 13 cutting seton, 5 fibrin glue, 4 advancement flap, 1 other, 1 unrecorded) Follow-up: 3 months	Number of fistulae healed at 3 months: • Fistula plug = 32% (14/43), p<0.001 • Fistulotomy = 87% (104/120) • Staged fistulotomy = 50% (18/36), p = 0.005 • Draining seton only = 5% (1/21), p<0.001 • Cutting seton = 69% (9/13), p = 0.019 • Fibrin glue = 80% (4/5), p = 0.451 • Advancement flap = 75% (3/4), p = 0.236	Was included in previous overview.
Johnson EK, Gaw JU, Armstrong DN. (2006) Efficacy of anal fistula plug vs. fibrin glue in closure of anorectal fistulas. Diseases of the Colon & Rectum 49: 371–6.	Non-randomised comparative study n = 25 (15 vs 10) Follow-up = 3 months	*High transsphincteric fistulae or deeper (excluding Crohn's disease)* Persistence of fistula: • Fistula plug = 13% (2/15) • Fibrin glue = 60% (6/10) p < 0.05	Larger, more recent studies are included. *Included in original overview*
Köckerling F, Rosen von T, acob D (2014) Modified plug repair with limited sphincter sparing fistulectomy in the treatment of complex anal fistulas. Frontiers in surgery 1:17. doi:10.3389/fsurg.2014.0001	Prospective case series n=40 Follow-up=mean 19 months	90% (36/40) of patients had their complex anal fistulas or rectovaginal fistulas completely healed without any sign of recurrence. None of these patients complained about continence problems.	Larger studies are included,
Kouchi K, Takenouchi A, Matsuoka A et al. (2017) Efficacy of an anal fistula plug for fistulas-in-Ano in children. Journal of Pediatric Surgery 52(8), 1280-1282	Prospective case series n=8 Follow-up = 9 years	Eight of 11 fistulas (73%) were successfully treated. Three fistulas recurred, and fistulectomies were performed. No sequelae were observed after AFP treatment.	Larger studies are included,
Ky AJ, Sylla P, Steinhagen R et al. (2008) Collagen fistula plug for the treatment of anal fistulas. Diseases of the Colon & Rectum 51: 838–43.	Case series n = 45 Follow-up = 6.5 m	*Simple and complex anal fistulae* Healing rate: • 3 – 8 weeks = 84% • 12 weeks = 62% • 6.5 months = 55% Closure rate was significantly higher in patients with simple versus complex fistulae (71% vs 35%, p<0.02) and with	Larger studies with longer follow-up are included.

		non-Crohn's disease versus Crohn's disease (67% vs 27%, p<0.02). Postoperative complications = perianal abscess in 5 patients.	
Lawes DA, Efron JE, Abbas M et al. (2008) Early experience with the bioabsorbable anal fistula plug. World Journal of Surgery 32: 1157–9.	Case series n = 17 Follow-up = 7 m	*Cryptoglandular anal fistulae* Successful closure = 24% (4/17) Acute postoperative sepsis = 29% (5/17)	Larger studies are included.
Leng Q, and Jin H Y (2012) Anal fistula plug vs mucosa advancement flap in complex fistula-in-ano: A meta-analysis. World Journal of Gastrointestinal Surgery 4(11), 256-61	Systematic review and meta-analysis Search up until April 2011 n=6 studies (408 patients) 167 Plug versus 241 flap	Overall success rate: risk difference (RD) = -0.12, 95%CI: -0.39 to 0.14 Incidence of fistula recurrence: RD = 0.13; 95% CI: -0.18 to 0.43 Postoperative impaired continence : RD = -0.08, 95% CI: -0.15 to -0.02 Incidence of other complications: RD = -0.06, 95%CI: -0.11 to -0.00 The postoperative quality of life, for patients treated using the AFP was better to that of the MAF patients. Patients treated with the AFP had less persistent pain of a shorter duration and the healing time of the fistula and hospital stay were also reduced.	A more recent systematic review and meta-analysis comparing the AFP with the flap is already included.
McGee MF, Champagne BJ, Stulberg JJ et al. (2010) Tract length predicts successful closure with anal fistula plug in cryptoglandular fistulas. Diseases of the Colon & Rectum 53: 1116–20.	Case series n=41 (42 fistula tracts) Mean follow-up=24.5 months	Successful closure = 43% (18/42) 20 patients had initial success at 6 months but 2 of these experienced failure at 9 and 12 months respectively.	Was included in previous overview.
Muhlmann M D, Hayes J L, Merrie A E et al. (2011) Complex anal fistulas: plug or flap?.ANZ Journal of Surgery 81(10), 720-4	Retrospective comparative stuy n=55 (22 plug versus 48 flap) Follow-up=mean 5 months	The results of treatment of complex anal fistulas are disappointing. The choice of operation of either a RMAF or a FP did not alter the poor healing rates of about one third of patients in each group.	Larger studies are included.
O'Connor L, Champagne BJ, Ferguson MA et al. (2006) Efficacy of anal fistula plug in closure of Crohn's anorectal fistulas. Diseases of the Colon & Rectum 49: 1569–73.	Case series n = 20	*Crohn's anorectal fistulae* Success rate = 80% (16/20)	Larger studies are included. *Included in original overview.*

O'Riordan JM, Datta I, Johnston C, et al. (2012) A systematic review of the anal fistula plug for patients with Crohn's and non-Crohn's related fistula-in-ano. Dis Colon Rectum, 55, 351–358.	Systematic review n=20 studies with 530 patients	The plug extrusion rate was 8.7% (46 patients). The proportion of patients achieving fistula closure varied widely between studies for non-Crohn's, ranging from 0.2 (95% CI 0.04–0.48) to 0.86 (95% CI 0.64–0.97). The pooled proportion of patients achieving fistula closure in patients with non-Crohn's fistula-in-ano was 0.54 (95% CI 0.50-0.59). The proportion achieving closure in patients with Crohn's disease was similar (0.55, 95% CI 0.39–0.70).	More recent systematic review has been included in table 2.
Ortiz H, Marzo J, Ciga MA et al. (2009) Randomized clinical trial of anal fistula plug versus endorectal advancement flap for the treatment of high cryptoglandular fistula in ano. British Journal of Surgery 96: 608–12.	RCT n = 43 (21 fistula plug vs 22 endorectal anal flap) Follow-up: 1 year	Fistula recurrence (1-year follow-up): • Fistula plug = 80% (12/15) • Endorectal anal flap = 12.5% (2/16) RR 6.40, 95% CI 1.7 to 24.0, p <0.001	Was included in previous overview.
Owen G, Keshava A, Stewart P et al. (2010) Plugs unplugged. Anal fistula plug: the Concord experience. ANZ Journal of Surgery 80: 341–3.	Case series n = 32 Follow-up = 15 months	*Complex anal fistulae* Success rate = 37%	Larger studies are included.
Ozturk E (2015) Treatment of recurrent anal fistula using an autologous cartilage plug: a pilot study. Techniques in Coloproctology 19(5), 301-7	Case series n=10 Median follow-up=24 months	The cartilage plug seems to be a promising alternative for anal fistula treatment.	Larger studies are included.
Pu Y W, Xing C G, Khan I et al. (2012) Fistula plug versus conventional surgical treatment for anal fistulas. A system review and meta-analysis. Saudi Medical Journal 33(9), 962-6	Systematic review and meta-analysis Search up until 30/112011 n=428 from 5 studies (plug versus surgical treatment)	The recurrence rate was higher in patients who accept fistula plug treatment (62% versus 47%) (p=0.004). Anal fistula plug has a moderate probability of success with little risk of incontinence, but the recurrence rate is significantly higher than the conventional surgical treatment. This meta-analysis failed to find a statistically significant difference in incontinence rate between conservative treatment and conventional surgical treatment.	Another, more recent systematic review and meta-analysis is included.
Ratto C, Litta F, Donisi L et al. (2016) Prospective evaluation of a new device	Case series n=10	The technical procedure is simple and has low risk of perioperative morbidity. The	Larger studies are included.

for the treatment of anal fistulas. World Journal of Gastroenterology 22(30), 6936-43	Follow=up=6 months	pre- and post-operative continence status did not change in any of the patients. The initial results at the 6-mo follow up seem to be promising. However, a longer follow-up period and a larger sample size are needed to confirm these preliminary results.	
Saba R B, Tizmaghz A, Ajeka S et al. (2016) Treating anal fistula with the anal fistula plug: case series report of 12 patients. Electronic Physician [Electronic Resource] 8(4), 2304-7	Case series n=12 Median follow-up=23 months	Fistula plugs are effective for the long-term closure of complex anal fistulas. Success of treatment with the fistula plug depends on the eradication of sepsis prior to plug placement.	Larger studies are included.
Safar B, Jobanputra S, Sands D et al. (2009) Anal fistula plug: initial experience and outcomes. Diseases of the Colon & Rectum 52: 248–52.	Case series n = 36 procedures Follow-up = 126 days	*Complex anal fistulae* Success rate = 14% (5/36) Reasons for failure: infection requiring drainage and seton placement (n = 8), plug dislodgement (n = 3), persistent drainage/tract and need for other procedures (n = 20).	Larger studies are included.
Schwandner O, Stadler F, Dietl O et al. (2008) Initial experience on efficacy in closure of cryptoglandular and Crohn's transsphincteric fistulas by the use of the anal fistula plug. International Journal of Colorectal Disease 23: 319-324.	Case series n = 19 Follow-up = 279 days	*Transsphincteric anorectal fistulae (12 cryptoglandular, 7 Crohn's disease)* Success rate at 9 months = 61% (11/18) No deterioration of continence was documented. There were significant improvements in quality of life factors.	Larger studies are included.
Schwandner T, Roblick MH, Kierer W et al. (2009) Surgical treatment of complex anal fistulas with the anal fistula plug: a prospective, multicenter study. Diseases of the Colon & Rectum 52: 1578–83.	Case series n = 60 Follow-up = 12 m	*Single transsphincteric fistulae* Success rate at 12 months = 62% The success rate was significantly lower in smokers and diabetics.	Larger studies or studies with longer follow-up are included.
Song WL, Wang ZJ, Zheng Y et al. (2008) An anorectal fistula treatment with acellular extracellular matrix: a new technique. World Journal of Gastroenterology 14: 4791–4.	Case series n = 30 Follow-up = 14 days	*Low anorectal fistulae* Success rate = 100%	Larger studies with longer follow-up are included.
Tan K K, Kaur G, Byrne C et al. (2013) Long-term outcome of the anal fistula plug for anal fistula of cryptoglandular origin.	Case series n=26 Median follow=up=59 weeks	Recurrence rate: 87% (26/30) The role of the fistula plug in the management of anal fistula of cryptoglandular	Larger studies with longer follow-up are included.

Colorectal Disease 15(12), 1510-1514		origin remains debatable and warrants further evaluation.	
Thekkinkattil DK, Botterill I, Ambrose NS et al. (2009) Efficacy of the anal fistula plug in complex anorectal fistulae. Colorectal Disease 11: 584–7.	Case series n = 43 Follow-up = 47 weeks	*Complex anorectal, rectovaginal and pouch vaginal fistulae* Success rate = 44%	Larger studies are included.
van Koperen PJ, D'Hoore A, Wolthuis AM et al. (2007) Anal fistula plug for closure of difficult anorectal fistula: a prospective study. Diseases of the Colon & Rectum 50: 2168–72.	Case series n = 17 Follow-up = 7 months	*Complex high anorectal fistulae (therapy-resistant)* Healing rate = 41% (7/17)	Larger studies are included
Wang JY, Garcia-Aguilar J, Sternberg JA et al. (2009) Treatment of transsphincteric anal fistulas: are fistula plugs an acceptable alternative? Diseases of the Colon & Rectum 52: 692–7.	Non-randomised comparative study n = 55 (29 vs 26) Follow-up = 279 days (plug)	*Transsphincteric, cryptoglandular anal fistulae* Successful outcome: • Fistula plug = 34% (10/29) • Advancement flap (62% (16/26) p = 0.045	Larger studies are included.
Zhao B, Wang Z, Han JG, et al (2019) Long-term outcomes of ligation of the inter-sphincteric fistula tract plus bioprosthetic anal fistula plug (LIFT-Plug) in the treatment of trans-sphincteric perianal fistula. Medical Science Monitor, 25, 1350-1354.	Case series n=78 patients who were treated with the LIFT-plug technique. Median follow-up: 30 months	Clinical healing of the anal fistula occurred in 75 patients (96.2%). Fistula recurred in 2 patients because of spontaneous expulsion of the plug at 7 days post-surgery; perianal abscess occurred in 1 patient. Two patients were identified to a rare complication of gas incontinence (Wexner score 1).	Studies with a larger sample are included in table 2.
Zubaidi A, Al-Obeed O. (2009) Anal fistula plug in high fistula-in-ano: an early Saudi experience. Diseases of the Colon & Rectum 52: 1584–8.	Case series n = 22 (23 tracts) Follow-up = 12 m	*High anorectal fistulae* Success rate = 83% (19/23)	Larger studies are included.