

A Multicenter Randomized Controlled Trial Comparing Safety, Efficacy, and Cost-effectiveness of the Surgisis Anal Fistula Plug Versus Surgeon's Preference for Transsphincteric Fistula-in-Ano

The FIAT Trial

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Objective: To undertake a randomized comparison of the Biodesign Surgisis anal fistula plug against surgeon's preference in treating cryptoglandular transsphincteric fistula-in-ano.

Summary Background Data: The efficacy of the Biodesign Surgisis anal fistula plug in healing anal fistulae is uncertain.

Methods: Participants were randomized to the fistula plug with surgeon's preference (advancement flap, cutting seton, fistulotomy, Ligation of the Intersphincteric Fistula Tract procedure). The primary outcome was faecal incontinence quality of life (FIQoL) at 12-months. Secondary outcomes were fistula healing, incontinence rates, and complication and reintervention rates.

Results: Between May 2011 and March 2016, 304 participants were randomized to fistula plug or surgeon's preference. No differences were seen in FIQoL between the 2 groups at 12 months. Clinical fistula healing was reported in 66/122 (54%) of the fistula plug and 66/119 (55%) of the surgeon's preference groups at 12 months. Fecal incontinence rates improved marginally in both the groups. Complications and reinterventions were frequent, with significantly more complications in the fistula plug group at 6-weeks (49/142, 35% vs 25/137, 18%; $P=0.002$). The mean total costs were £2738 (s.d. £1151) for the fistula plug and £2308 (s.d. £1228) for the surgeon's preference group (mean difference +£430, $P=0.0174$). The average total quality adjusted life

years (QALYs) gained was marginally higher in the fistula plug group. The fistula plug was 35% to 45% likely to be cost-effective across a willingness to pay threshold of £20,000 to £30,000/QALY.

Conclusions: The Biodesign Surgisis anal fistula plug is associated with similar FIQoL and healing rates to surgeon's preference at 12 months. Higher costs and highly uncertain gains in QALYs mean that the fistula plug may not be considered as a cost-effective treatment in the UK NHS.

Keywords: anal fistula, complications, cost effectiveness, fistula plug, quality of life, surgery

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Fistula-in-ano affects 1 to 2 in 10,000 of Western populations and causes significant morbidity and financial costs.^{1,2} The majority of fistulas are low and can be treated by simple fistulotomy with reasonable chance of cure and little risk of incontinence. The remaining high fistulas, of which transsphincteric fistulae are the most common, are more challenging to treat.

Many surgical techniques have been proposed to treat transsphincteric anal fistulas, but the results are generally disappointing with high rates of recurrence and frequent compromise of anal sphincter function. Fistulotomy is associated with low recurrence rates between 2% and 9%,^{3,4} but with change in continence in up to 50% of patients.⁵ Placement of a cutting seton is associated with recurrence rates between 0% and 8%, minor incontinence in 34% to 63%, and major incontinence in 2% to 26% of patients.^{6–8} Advancement flaps preserve the external anal sphincter, however, recurrence rates of 25% to 54% are reported with a change in continence in 30% to 35% of patients.^{9,10} More recently, the Ligation of the Intersphincteric Fistula Tract (LIFT) procedure has reported fistula healing in 47% to 95% of patients with minimal morbidity and incontinence.^{11–16}

An alternative approach to treating anal fistulas is the bio-prosthetic fistula plug, which is inserted into the fistula tract to act as a scaffold to encourage tissue in-growth and healing. Initial reports with the BioDesign Surgisis plug (Cook Medical, Bloomington, IN) showed excellent healing rates, but subsequent results have been less encouraging with healing rates ranging widely from 35% to 87%, although no study reported an increased risk of incontinence.^{17–20} Importantly, there is an additional cost for the plug, which might impact its cost effectiveness and clinical adoption.

The Fistula-in-ano trial (FIAT) trial was commissioned in 2009 to undertake a randomized evaluation of the fistula plug against other surgical techniques for transsphincteric fistulas with the primary outcome being faecal incontinence quality of life.

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D.G.J., J.S., D.T., R.G., A.S., C.T.H., M.K., K.H., and L.M. designed the study and were involved in study coordination. D.G.J. and J.S. were responsible for surgeon training in fistula plug insertion. D.T. was responsible for radiology training and centralized MRI review. C.A.H. performed the statistical analysis with senior oversight by K.H. A.S. and C.T.H. designed the economic evaluation and undertook the analysis. All authors contributed to data interpretation and the writing and review of the manuscript.

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METHODS

Study Design

The FIAT trial was a pragmatic, phase III, multicenter, randomized controlled trial comparing the Biodesign Surgisis, anal fistula plug with other surgical treatments (surgeon's preference) for transsphincteric anal fistulae (ISRCTN 78352529). Surgeon's preference included advancement flap, cutting seton, fistulotomy, and LIFT procedure. Ethical committee approval was obtained (10/H0405/29). The trial was overseen by an independent Trial Steering Committee and Data Monitoring and Ethics Committee. Trial related information, including the protocol, is available at <http://www.birmingham.ac.uk/fiat>

Participants

Patients were eligible for FIAT if they were 18 years of age or older with a clinical diagnosis of cryptoglandular transsphincteric fistula—defined as involving 1/3 or more of the external anal sphincter at examination under anesthesia prior to randomization. The fistula had to have a single internal opening and a tract at least 2 cm in length. All patients had to be treated with a draining seton for a minimum of 6-weeks prior to randomization. Participants were excluded if there was more than 1 internal fistula opening (multiple external openings, secondary tracts, and horse-shoe extensions were allowed), there was clinical or radiological evidence of active infection (purulent discharge), the fistula had previously been treated with fistula plug (previous treatment by any other means was allowed), there was a cultural or religious objection to the use of pig tissue, or an absolute contraindication to magnetic resonance imaging (MRI) scan.

All patients had to undergo MRI scan 6 months prior to randomization. All MRI scans were performed in a minimum of 2 planes, which included axial and coronal orientations with the imaging plane inclined to the anal canal, using either a STIR or fat saturated T2 sequence with a maximum slice thickness of 5 mm.

Surgical workshops were held to standardize fistula plug insertion and all surgeons must have inserted at least 3 fistula plugs prior to participation. Fistulotomy, cutting seton, advancement flap, and LIFT procedure were undertaken according to surgeons' usual practice. All participating radiologists attended a FIAT radiology workshop.

Randomization and Masking

Randomization was performed using a secure 24-hour Internet-based randomization service or by telephone call immediately prior to fistula surgery. Participants were randomized in a one-to-one ratio to either fistula plug or surgeon's preference, minimized for age, ASA grade, planned type of surgery, and presence or absence of fistula tract extensions.

No masking of participants, surgeons, or data collectors was undertaken.

Procedures

The standardized fistula plug procedure included removal of draining seton, gentle curettage of the tract, and insertion of either a 4 or 7 mm rehydrated plug into the internal opening. The button of the plug was secured by suture, with a mucosal flap used at the surgeon's discretion. The tip of the plug was cut flush with the external opening, which was enlarged if necessary. Participants randomized to the surgeon's preference group underwent the chosen procedure in accordance with the surgeon's usual technique.

Outcomes

The primary outcome measure was the Faecal Incontinence Quality of Life (FIQoL).²⁰ The FIQoL questionnaire comprises 29 multiple choice questions grouped into 4 domains—lifestyle, coping/

behavior, depression/self-perception, and embarrassment and was assessed at baseline, 6-weeks, and 6- and 12-months post randomisation. The secondary outcome measures were: clinical and radiological fistula healing rate at 12-months; incontinence, measured using the St Mark incontinence score²¹; reintervention rates at 6- and 12-months; complication rates and generic QoL at 6-weeks, 6- and 12-months, measured using EQ-5D-3L²²; and cost-effectiveness at 12-months. Complications included expected and unexpected adverse events in the postoperative period. Severity of complications was not graded using a scoring system, but in terms of remedial treatment, that is, medical treatment (eg, antibiotics) or need for reintervention (radiological, endoscopic, surgical). Infective complications included wound dehiscence, cellulitis, or purulent discharge. Clinical evidence of fistula healing was defined as no visible external opening and no ongoing infection (purulent discharge).

Statistical Analysis

It was estimated that a total of 400 patients (200 in each group) would be needed to detect a small to moderate treatment effect for the primary endpoint. To allow for a 20% noncompliance rate, the aim was to recruit a total of 500 patients. In January 2015, the sample size was reduced to 300 patients due to slow recruitment, giving a 69% power to detect a small to moderate (0.3 s.d.) or 98% power to detect a moderate (0.5 s.d.) treatment effect (with $\alpha=0.05$).

Demographic factors and baseline clinical characteristics were summarized with numbers and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, or medians and interquartile ranges for non-normal continuous variables.

The primary analysis was a comparison between the allocated treatments, using an unadjusted, intention-to-treat analysis. The FIQoL was presented using mean differences produced from a repeated measures model incorporating the 6-week, 6-month, and 12-month time-points with the baseline score included as a covariate. Separate models were constructed for each of the 4 domains of the FIQoL questionnaire. Further models were fitted, which included a time by treatment interaction term. EQ-5D-3L was analyzed in a similar manner. Other continuous outcomes were presented as mean differences analyzed using a *t* test. Binary outcomes were presented as risk ratios (RRs) and time-to-event data was presented as hazard ratios. No corrections for multiple testing were made and 2-sided tests were considered significant if $P<0.05$. All results were reported as point estimates and 95% confidence intervals with corresponding *P* values. A per-protocol analysis was undertaken for the primary outcome only as a sensitivity analysis to explore the potential effect of nonadherence to the randomized allocation.

Prespecified subgroup analyses were performed for the minimization variables—age at randomization (<30, 30–39, 40–49, 50–59, 60–69, ≥ 70), ASA grade (I–IV), planned type of surgery (advancement flap, cutting seton, LIFT procedure, fistulotomy), and presence of fistula extensions (yes, no), which were limited to the 4 domains of the primary outcome, fistula healing, fecal incontinence, and EQ-5D-3L. The treatment effect within these subgroups was examined by adding the subgroup by treatment group interaction parameter to the model.

Post hoc analyses were undertaken to assess the healing rates associated with the different interventions in the surgeon's preference group, and the frequency of reinterventions over time.

All analyses were done in SAS version 9.4 (Cary, NC) or Stata 14 (StataCorp LLC, Texas, USA).

Economic Evaluation

The economic evaluation was performed using a UK NHS and Personal Social Service perspective. Resource use data collected

from patients at 6 weeks, 6 months, and 12 months were combined with data collected within the trial. Unit costs to estimate the total health resource cost for each participant were informed from national sources such as the PSSRU Unit Costs of Health and Social Care,²³ NHS Reference Costs,²⁴ and the British National Formulary²⁵ (Supplemental data—HE1-HE3, <http://links.lww.com/SLA/C180>). Health related quality of life was estimated from the EQ-5D-3L with differences between treatment groups assessed using 2 sample *t* tests. The primary health-related outcome measure was the quality adjusted life year (QALY), derived by converting responses to the EQ-5D-3L questionnaire to utilities using standard UK tariff values.²⁶ QALYs were calculated by multiplying these values with the time spent in each state, with quality of life linearly interpolated for the periods between the 4 observations provided in the trial data. Average QALYs between adjacent time points were calculated to generate smoothed estimates between the time points. Patient-level analysis on complete cases was conducted. Multiple imputations by chained equations were used to impute missing EQ-5D-3L data and individual components of total costs at all 3 time points. Incremental cost effectiveness ratios (ICERs) were calculated to allow interpretation of results in terms of the National Institute for Health and Clinical Excellence £20,000 to £30,000 per QALY willingness to pay threshold. Data interpretation probabilistic sensitivity analysis was used to assess uncertainty and the results analyzed using a cost effectiveness acceptability curve.

RESULTS

Between May 2011 and March 2016, 304 patients were randomized in a 1:1 ratio between fistula plug and surgeon's preference (Fig. 1). Participants were recruited from 45 centers with recruitment varying from 1 to 32 participants by site.

The baseline characteristics, overall and by randomization group, are shown in Table 1 (see Supplemental Table 1 for full details, <http://links.lww.com/SLA/C181>). The majority of participants were ASA grade 1 (77%), aged between 30 and 60 years (mean age 45.1 yrs), with more males than females (55% vs 45%). There was no difference in comorbidity between the groups, with smokers making up 23% and 25% of the fistula plug and surgeon's preference groups, respectively. Incontinence scores at baseline were low and similar between the 2 groups. Sixty-four (42%) participants in the fistula plug arm and 73 (48%) participants in the surgeon's preference arm had undergone previous fistula surgery. All fistulae were deemed to be transsphincteric at Examination under Anaesthesia, where data was available to confirm. The morphology of the fistulas at baseline Examination under Anaesthesia was similar between the groups. Baseline MRI scan characterized the fistula morphology as transsphincteric in 132 (87%) in the fistula plug and 138 (90%) in the surgeon's preference groups.

There were no differences in the findings for the per-protocol sensitivity analysis, except the FiQoL coping/behaviour domain, which was shown to be borderline statistically significant (RR 0.15, 95%CI 0.01-0.28) (Table 2). Models including the treatment by time interaction term were also non-significant. Similarly, there were no statistically significant differences in the findings for the per-protocol sensitivity analysis. A marginal improvement in FIQoL scores was observed in all domains at 6 weeks following surgery and was maintained until 12 months.

One-third of participants had clinical evidence of a healed fistula at the 6-week time-point, which was similar in both the groups (Table 3). At 6 months, in the surgeon's preference arm, 62 (48%) of 128 fistulas were reported as healed compared with 50 (39%) of 127 in the fistula plug arm ($P=0.14$). However, this difference was not sustained at 12 months where 54% of fistulas in the fistula plug arm and 55% in the surgeon's preference arm were regarded as clinically healed ($P=0.83$).

The post hoc analysis of clinical fistula healing rates by received procedure and at the various follow-up time points is shown in Table 4. The best performing procedure at 12 months in the surgeon's preference group was fistulotomy (12/16, 75%), and the worst performing was the LIFT procedure (21/50, 42%). No further subanalysis was done as the study was not powered to detect differences between individual procedures; only between the fistula plug and surgeon's preference groups.

A follow-up MRI was performed in 110 (72%) of 152 participants in the fistula plug group and 112 (74%) of 152 participants in the surgeon's preference group. Overall, 192 (86%) patients underwent 12-month MRI imaging, with 31 (14%) undergoing MRI imaging for clinical relapse prior to the 12-month time-point. There was no statistical difference in fistula healing as judged by MRI: 54 (49%) participants in the fistula plug arm compared with 63 (57%) participants in surgeon's preference group.

No significant differences were observed in the St. Mark's incontinence scores between treatment groups (mean difference -0.44 , 95% CI -1.66 to 0.79 , $P=0.48$) at 12 months (Table 3).

Overall postoperative complications were low and similar in both the groups; fistula plug 4/147 (3%) and surgeon's preference 2/144 (1%). Table 3 shows overall complication rates and rates of reintervention (radiological, endoscopic, surgical) by treatment group. Complications were most prevalent at 6-weeks follow-up with 49 (35%) of 142 participants reporting complications in the fistula plug arm compared with 25 (18%) of 137 in the surgeon's preference arm (RR 1.89, 95% CI 1.24–2.88; $P=0.002$) (Table 5). This was largely driven by a greater proportion of participants in the fistula plug group experiencing unexplained pain (65% vs 36%). Infective complications were reported in 50% of participants in the fistula plug arm and 38% of the surgeon's preference arm in those participants who underwent clinical follow-up at 12 months.

Plug extrusion was reported in 20/126 (16%) of the fistula plug group, with persistent discharge in 47/104 (45%) at 6 months and 40/101 (40%) at 12 months. Wound-related problems were similar for the fistulotomy and LIFT procedures, reported in 2/14 (14%) and 8/44 (18%) respectively at 12 months. Complications related to the advancement flap occurred in 4/22 (18%) at 6 weeks and persisted in 2/16 (13%) at 12-month follow-up.

At 6-weeks follow-up, 30 (21%) of 142 participants in the fistula plug arm had a reintervention compared with 16 (12%) of 137 participants in the surgeon's preference group (RR 1.81 95% CI 1.03–3.17; $P=0.03$). This difference was not seen at 6- and 12-months follow-up, where reinterventions were still common in both the groups (Table 3). No significant differences were seen between the treatment groups for time to first reintervention and time to first surgical reintervention.

Analysis of the EQ-5D-3L data showed a marginal improvement in both the health-related quality of life and the visual analogue score between baseline and 12-months in both the groups (Table 3). No significant differences were seen for either the health status score or the visual analogue score between the fistula plug and surgeon's preference groups.

Subgroup analyses found no evidence that the treatment effect differed between the prespecified subgroups for the 4 domains of the primary outcome, fistula healing, faecal incontinence, and EQ-5D-3L.

Complete health resource use and QALY data were available for 177 participants with 87 participants in the fistula plug and 90 participants in the surgeon's preference group. The mean total resource use costs throughout the whole period of follow-up were significantly higher for the fistula plug (£2738 vs £2308; $P=0.0174$), due to higher surgery-related costs (£2306 vs £1728, $P<0.001$). The mean costs due to readmissions were higher for the fistula plug group

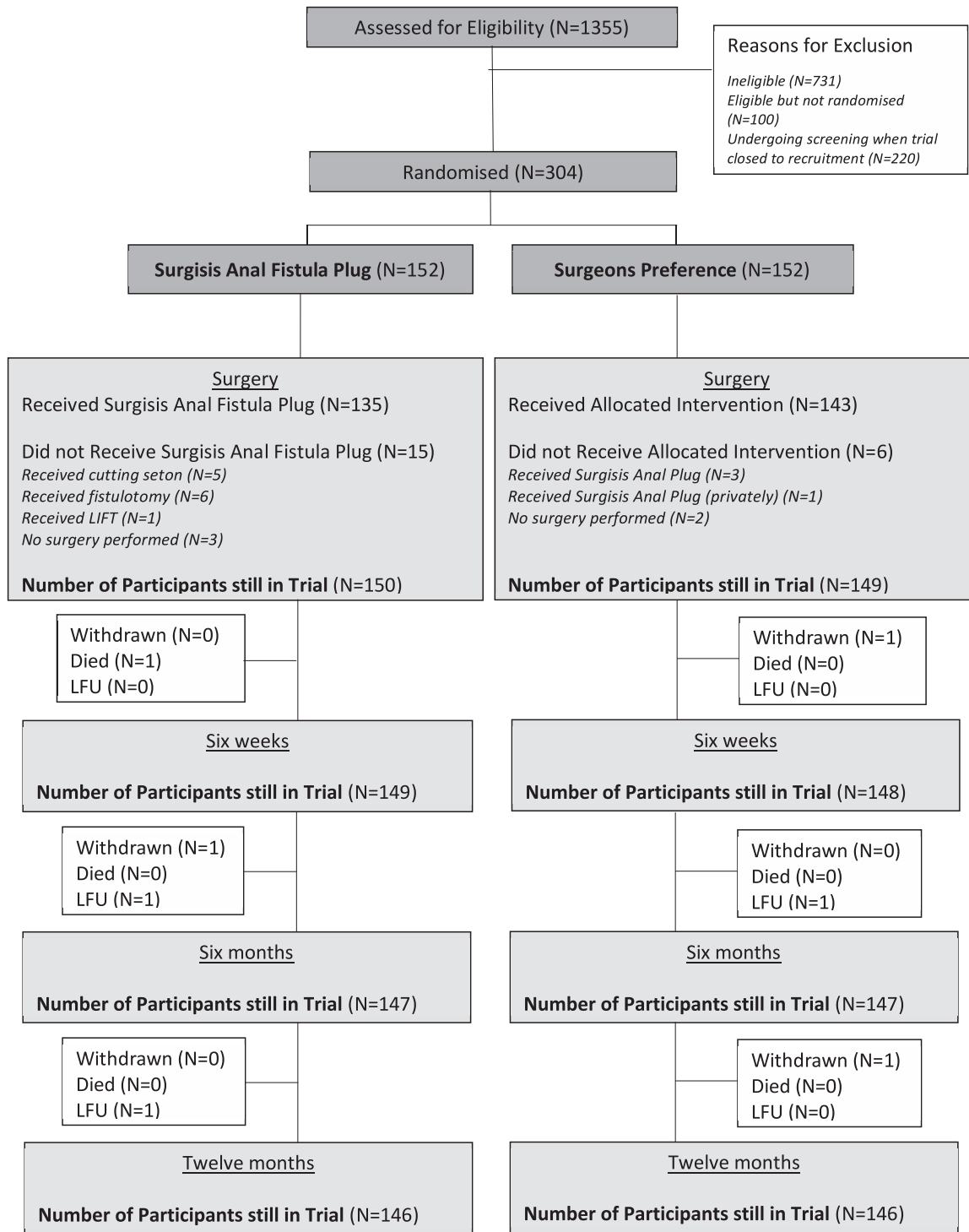


FIGURE 1. Trial profile.

(£159 vs £89, $P=0.233$), but the mean costs due to health and social services use outside hospital were higher for the surgeon's preference group (£484 vs. £267, $P=0.109$). The probabilistic cost-effectiveness analysis for the nonimputed data showed that the fistula plug was associated with an ICER of £10,993 with an overall net benefit of £352 over a 12-month time horizon (Supplemental data –

Tables HE4-HE7, <http://links.lww.com/SLA/C180>). Considering the probabilistic cost-effectiveness analysis for the imputed data, there were only minor differences in the mean costs and mean QALYs for both treatment groups compared with the nonimputed data. The ICER was £17,279/QALY and the net benefit was £71. However, adjusting for the difference in baseline EQ-5D-3L values

TABLE 1. Baseline Characteristics of Recruited Patients

	Surgis Anal Fistula Plug (n=152)	Surgeon's Preference (n=152)	All Participants (n=304)
Minimization variables			
ASA grade			
P1 normal healthy patient	118 (78%)	117 (77%)	235 (77%)
P2 mild systemic disease	31 (20%)	30 (20%)	61 (20%)
P3 severe systemic disease	3 (2%)	5 (3%)	8 (3%)
Age at randomization (years)			
<30	23 (15%)	22 (15%)	45 (15%)
30–39	39 (26%)	36 (24%)	75 (25%)
40–49	35 (23%)	45 (30%)	80 (26%)
50–59	33 (22%)	29 (19%)	62 (21%)
60–69	12 (8%)	10 (6%)	22 (7%)
≥70	10 (6%)	10 (6%)	20 (6%)
Type of surgery			
Advancement flap	32 (21%)	34 (22%)	66 (22%)
Fistulotomy	6 (3%)	2 (1%)	8 (2%)
Cutting seton	57 (38%)	57 (38%)	114 (38%)
LIFT procedure	57 (38%)	59 (39%)	116 (38%)
Secondary extensions at baseline EUA*	19/107 (18%)	17/105 (16%)	36/212 (17%)
Patient Characteristics			
Age at randomization (years)			
Mean (SD, n)	45.2 (14.1, 152)	44.9 (13.7, 152)	45.1 (13.9, 304)
Sex			
Male	86 (57%)	81 (53%)	167 (55%)
Female	66 (43%)	71 (47%)	137 (45%)
Smoker	35 (23%)	38 (25%)	73 (24%)
St Mark's Incontinence score†			
Median [IQR, n]	4 [1–6, 151]	4 [2–8, 152]	4 [2–7, 303]
Fistula history			
Previous fistula surgery	64 (42%)	73 (48%)	137 (45%)
EUA			
Length of primary tract (cm)			
Median [IQR, n]	3.5 [3.0–4.0, 148]	3.0 [2.5–4.0, 145]	3.0 [3.0–4.0, 293]
Internal opening relative to dentate line:			
Below	12 (8%)	21 (14%)	33 (11%)
At	96 (64%)	99 (66%)	195 (65%)
Above	43 (28%)	30 (20%)	73 (24%)
Extent of external sphincter involvement			
<1/3	18 (12%)	20 (13%)	38 (12%)
1/3	5 (3%)	3 (2%)	8 (3%)
>1/3	127 (85%)	127 (85%)	254 (85%)
Secondary tracts			
Supraleator extension	4 (3%)	4 (3%)	8 (3%)
Horse-shoe extensions	10 (7%)	6 (4%)	16 (5%)
Active infection/abscess	27 (18%)	26 (17%)	53 (18%)
Seton inserted	149 (99%)	149 (99%)	298 (99%)
Radiology MRI			
Fistula type			
Superficial	3 (2%)	1 (1%)	4 (1%)
Intersphincteric	14 (9%)	12 (8%)	26 (9%)
Transsphincteric	132 (87%)	138 (90%)	270 (89%)
Supraleator	0 (–)	1 (1%)	1 (<1%)
Extrasphincteric	1 (1%)	0 (–)	1 (<1%)
Blind Sinus	1 (1%)	0 (–)	1 (<1%)
Missing	1	0	1
Extensions present	41 (27%)	35 (23%)	76 (25%)
Number of extensions			
Median [IQR, n]	1.0 [1.0–1.0, 41]	1.0 [1.0–1.0, 35]	1.0 [1.0–1.0, 76]
Location of extensions			
Intersphincteric	17/40 (41%)	19/35 (54%)	36/75 (47%)
Ischioanal fossa	24/40 (60%)	18/35 (51%)	42/75 (56%)
Supraleator	6/40 (15%)	2/35 (6%)	8/75 (11%)

*Secondary extensions at baseline EUA was not added to the minimization procedure until 10/7/2012, version 2.2 of the randomization notepad.

†St Mark's Incontinence scores range from 0 to 24 where lower scores are better. When a total score was not computable from the individual St Mark's domains the score provided at randomization was used. The 1 participant with a missing St Mark's score had a colostomy.

TABLE 2. Primary Outcome FIQoL

	Surgis Anal Fistula Plug (n=152)	Surgeon's Preference (n=152)	Mean Difference* (95% CI)	P Value
FIQoL Lifestyle [†]				
Baseline	3.46 (0.75, 138)	3.34 (0.83, 131)	0.03 (−0.10, 0.15)	0.67
6 wks	3.49 (0.76, 127)	3.42 (0.82, 126)		
6 mo	3.57 (0.73, 124)	3.50 (0.77, 128)		
12 mo	3.60 (0.70, 125)	3.54 (0.75, 128)		
FIQoL Coping/behavior [†]				
Baseline	3.30 (0.75, 138)	3.14 (0.88, 131)	0.11 (−0.03, 0.24)	0.11
6 wks	3.39 (0.76, 127)	3.18 (0.89, 126)		
6 mo	3.44 (0.79, 124)	3.31 (0.90, 128)		
12 mo	3.43 (0.83, 124)	3.33 (0.85, 128)		
FIQoL Depression/self-perception [†]				
Baseline	3.04 (0.77, 132)	2.99 (0.81, 120)	0.09 (−0.06, 0.24)	0.22
6 wks	3.13 (0.78, 115)	3.03 (0.85, 118)		
6 mo	3.23 (0.76, 114)	3.16 (0.91, 117)		
12 mo	3.29 (0.85, 115)	3.20 (0.85, 118)		
FIQoL Embarrassment [†]				
Baseline	3.26 (0.82, 132)	3.08 (0.87, 120)	0.12 (−0.05, 0.29)	0.18
6 wks	3.34 (0.84, 115)	3.09 (0.92, 117)		
6 mo	3.34 (0.85, 114)	3.29 (0.89, 118)		
12 mo	3.35 (0.89, 116)	3.25 (0.95, 118)		

*Mean difference. Values >0 favor fistula plug.

[†]FIQoL scores range from 1 to 4 where higher scores are better.**TABLE 3.** Secondary Outcomes

	Surgis Anal Fistula Plug (n=152)	Surgeon's Preference (n=152)	Estimate (95% CI)	P Value
Clinical fistula healing				
6 wks	42/141 (30%)	45/137 (33%)	0.91 (0.64, 1.29)*	0.58
6 mo	50/127 (39%)	62/128 (48%)	0.81 (0.61, 1.08)*	0.14
12 mo	66/122 (54%)	66/119 (55%)	0.98 (0.78, 1.23)*	0.83
St Marks Incontinence score [¶]				
6 wks	3.72 (4.22, 134)	3.87 (4.97, 132)	−0.15 (−1.26, 0.96) [‡]	0.79
6 mo	3.06 (4.44, 120)	3.61 (4.55, 117)	−0.55 (−1.70, 0.60) [‡]	0.35
12 mo	3.22 (4.54, 120)	3.65 (4.91, 112)	−0.44 (−1.66, 0.79) [‡]	0.48
Complications				
Postoperative ^{††}	4/147 (3%)	2/144 (1%)	1.96 (0.36, 10.53) [‡]	0.42
6 wks	49/142 (35%)	25/137 (18%)	1.89 (1.24, 2.88) [‡]	0.002
6 mo	27/129 (21%)	27/129 (21%)	1.00 (0.62, 1.61) [‡]	1.00
12 mo	28/124 (23%)	24/121 (20%)	1.14 (0.70, 1.85) [‡]	0.60
Reinterventions				
Postoperative ^{††}	2/147 (1%)	1/144 (1%)	1.96 (0.18, 21.37) [‡]	0.57
6 wks	30/142 (21%)	16/137 (12%)	1.81 (1.03, 3.17) [‡]	0.03
6 mo	25/129 (19%)	30/129 (23%)	0.83 (0.52, 1.34) [‡]	0.45
12 mo	28/124 (23%)	27/121 (22%)	1.01 (0.64, 1.61) [‡]	0.96
EQ5D3L visual analogue scale				
Baseline	73.30 (18.67, 139)	74.61 (17.75, 131)	1.66 (−1.45, 4.77) [§]	0.29
6 wks	75.88 (18.44, 128)	75.99 (18.22, 125)		
6 mo	80.14 (15.63, 124)	77.64 (20.67, 129)		
12 mo	79.62 (19.04, 125)	79.47 (15.62, 125)		
EQ5D3L health status score ^{**}				
Baseline	0.77 (0.27, 136)	0.76 (0.25, 130)	0.01 (−0.04, 0.05) [§]	0.76
6 wks	0.78 (0.24, 121)	0.77 (0.25, 125)		
6 mo	0.83 (0.21, 121)	0.79 (0.27, 129)		
12 mo	0.85 (0.21, 121)	0.82 (0.24, 126)		

*Risk ratio. Values >1 favor fistula plug.

[†]Mean difference. Values <0 favor fistula plug.[‡]Risk ratio. Values <1 favor fistula plug.[§]Mean difference. Values >0 favor fistula plug.[¶]St Marks incontinence scores range from 0 to 24 where higher scores indicate greater incontinence.^{||}EQ5D3L visual analogue scale scores range from 0 to 100 where higher scores indicate better health.^{**}EQ5D3L health status scores range from −0.594 to 1 where higher scores indicate better health.^{††}Postoperative refers to complication or reintervention prior to discharge following initial fistula surgery.

TABLE 4. Fistula Healing Rates Per Received Procedure at Each Follow-up Time-point

	Treatment Received				
	Fistula Plug	Cutting Seton	Fistulotomy	Advancement Flap	LIFT Procedure
6 wks	41/136 (30%)	7/48 (15%)	11/17 (65%)	11/21 (52%)	16/55 (29%)
6 mo	51/123 (41%)	20/40 (50%)	14/17 (82%)	10/19 (53%)	17/55 (31%)
12 mo	63/115 (55%)	27/42 (64%)	12/16 (75%)	9/17 (53%)	21/50 (42%)

TABLE 5. General Complications by Randomized Group at Different Time Points

	Surgis Anal Fistula Plug (n=152)	Surgeon's Preference (n=152)	Risk Ratio ¹ (95% CI)	P Value
Postoperative				
Complication data available	147	144		
Complications	4 (3%)	2 (1%)	1.96 (0.36, 10.53)	0.42
Bleeding	2/4 (50%)	0/2 (—)		
Urinary retention	0/4 (—)	1/2 (50%)		
Unexplained pain	2/4 (50%)	1/2 (50%)		
Septic event	0/4 (—)	0/2 (—)		
6 wks				
Complication data available	142	137		
Complications	49 (35%)	25 (18%)	1.89 (1.24, 2.88)	0.002
Bleeding	9/49 (18%)	5/25 (20%)		
Unexplained pain	32/49 (65%)	9/25 (36%)		
Septic event	15/49 (31%)	11/25 (44%)		
6 mo				
Complication data available	129	129		
Complications	27 (21%)	27 (21%)	1.00 (0.62, 1.61)	1.00
Bleeding	5/27 (19%)	4/27 (15%)		
Unexplained pain	14/27 (52%)	7/27 (26%)		
Septic event	5/27 (19%)	11/27 (41%)		
12 mo				
Complication data available	124	121		
Complications	28 (23%)	24 (20%)	1.14 (0.70, 1.85)	0.60
Bleeding	6/28 (21%)	4/24 (17%)		
Unexplained pain	10/28 (36%)	8/24 (33%)		
Septic event	14/28 (50%)	9/24 (38%)		

1 values < 1 favour Surgis and fistula plug

between the fistula plug and surgeon's preference groups, the ICER increased to £32,400 (Table 6). The cost-effectiveness acceptability curve (Supplemental data—Figure HE1, <http://links.lww.com/SLA/C180>) showed that the probability of the fistula plug being cost-effective across the National Institute for Health and Clinical Excellence acceptance threshold of £20,000 to £30,000/QALY was approximately 35% to 45%.

DISCUSSION

The FIAT trial provides important data on the Surgis anal fistula plug, and other common procedures, to treat transsphincteric anal fistulas.

Trial recruitment was slower than expected, meaning that a revised target of 300 patients was adopted while retaining reasonable power to detect a small to moderate treatment effect for the primary end-point. The main reason for slow recruitment was ineligibility due

to fistula classification—76% of screened participants were excluded with nontranssphincteric fistulas as judged by a combination of clinical and MRI assessment. The compulsory use of baseline MRI ensures that our cohort is a homogeneous population of transsphincteric fistulae and highlights the difficulty of fistula classification based on clinical examination alone.²⁷

The marginal improvement in FIQoL at 12-month's follow-up, in both the fistula plug and surgeon's preference groups, is in keeping with the previous literature. Although Adamina et al²⁸ reported a more marked improvement in QoL, this was in a small prospective cohort study and using the SF-36v2 questionnaire. Bondi et al²⁹, in a randomized trial comparing the fistula plug to advancement flap, showed an improvement in QoL at 3 months follow-up, but no difference between the 2 techniques.

The fistula healing rates reported in FIAT might be viewed as disappointing. Overall, only around one-third of fistulas healed by

TABLE 6. Cost-effectiveness Results (NHS and PSS Perspective, Probabilistic) (Imputed)

Strategy	Total Cost Mean (SD)	Incremental Cost Mean (SD)	QALY Mean (SD)	Incremental QALY Mean (SD)	ICER Mean (SD)	Inc. Net Benefit Mean (SD)
Surgeon's preference	£2297 (118)		0.800 (0.021)			
Fistula plug	£2750 (112)	£453 (163)	0.826 (0.018)	0.026 (0.027)	£17,279 (1,168,154)	£71 (578)
Adjusted –baseline EQ-5D					£32,400	–£168

6 weeks and just over a half healed by 12 months. However, the results of FIAT are in keeping with other randomized trials, which have reported healing rates of 66% and 71% for the fistula plug and 38% and 52% for advancement flap.^{29,30} Several systematic reviews and meta-analyses have been published, documenting healing rates with the fistula plug varying between 35% and 87%.^{17–19,31}

Although care has to be taken when drawing conclusions about fistula healing by procedure undertaken, because of the low numbers, it is notable that the LIFT procedure performed worst, with only 42% healed at 12 months. This contrasts to the literature, which documents healing following the LIFT procedure in 70% to 80% of cases.^{15,32,33}

Although the healing rates following fistula surgery are poor and reinterventions are common, the surgical procedures themselves impart a low risk of morbidity. The main complication related to any type of fistula surgery appears to be protracted pain, with septic complications becoming more problematic on longer follow-up and probably reflecting fistula recurrence. The higher rate of unexpected pain with the fistula plug might due to sphincter spasm secondary to suturing the plug to the internal anal sphincter, or a lower threshold for reporting pain with a technique perceived to be a minimally invasive. Despite our best efforts to standardise fistula plug insertion, the plug extrusion rate remained at 16%, similar to previous reports.³⁴

Preservation of continence is of paramount importance when contemplating fistula surgery and it is reassuring that incontinence scores improved over time in both groups. It is perhaps surprising that the surgeon's preference group did not perform worse than the fistula plug group, given that it contained techniques known to injure the anal sphincter mechanism.

The cost-effectiveness analysis of the complete cases showed that the fistula plug group had a slightly higher QALY gain but the mean cost for the fistula plug was greater, driven by the additional cost of the plug. Applying probabilistic analysis to the complete data, the ICER was found to be £10,933/QALY, indicating that the fistula plug may be considered to be more cost-effective compared with surgeon's preference, although the standard deviation indicates the large uncertainty in this estimate. Using multiple imputation to increase the data set and probabilistic sensitivity analysis, the fistula plug was again found to be more costly but more effective compared with surgeon's preference. However, when adjustment was made for differences in EQ-5D-3L at baseline, the ICER increased to £32,400 suggesting the fistula plug is not cost effective at the current UK cost effectiveness threshold. Given the cost driver is the cost of the plug, if it were assumed that the EQ-5D-3L utility values collected at 12 months remained unchanged, then it might be concluded that the fistula plug would become increasingly cost-effective as time passes. Whilst there is currently little evidence beyond 12 months follow-up to justify this assumption,^{35–37} as data becomes available, modeling approaches could be implemented to provide further insights to inform the cost basis for wider adoption of fistula plug technology. Based on the current analysis, it is concluded that higher costs and highly uncertain gains in QALYs mean that the fistula plug may not be considered a cost-effective treatment in the UK NHS.

The FIAT study has highlighted the shortfalls in the surgical management of transsphincteric anal fistulas. Patients undergoing fistula surgery have only a 50% to 60% chance of cure. They should be counselled appropriately and warned that multiple interventions may be necessary. Fortunately, the risk of incontinence following fistula surgery is low and patients can expect an improvement in symptom-specific quality of life. Further research and better understanding of the etiology underlying cryptoglandular anal fistula is required if surgical outcomes are going to improve.

Limitations

Lowering the sample size to 300 participants reduced the power of the study, but was offset by a low rate (2%) of participants lost to follow-up and excellent compliance with follow-up data. Given the lack of any convincing difference in FIQoL between the 2 groups, it is unlikely that achieving the original sample size of 400 patients would have altered the results.

Nonmasking of surgeons, participants, or data collectors to treatment allocation might have introduced an element of bias. It would have been difficult to mask participants, given that some had an anodermal wound while others did not. Masking of data collectors would have hindered the collection of treatment-specific information. It is unlikely that nonmasking affected the primary outcome.

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DATA SHARING

All data requests should be submitted to the corresponding author for consideration. Access to available anonymized data may be granted following review.

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