A multicentre randomised controlled trial comparing safety, efficacy, and cost-effectiveness of the Surgisis anal fistula plug versus surgeon's preference for transsphincteric fistula-in-ano

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MINI-ABSTRACT

The FIAT trial randomised 340 participants with transsphincteric anal fistulas to either the fistula plug or surgeon's preference. Faecal incontinence quality of life was similar in both groups and complications and re-interventions were common. Higher costs associated with the fistula plug mean that the fistula plug may not be cost-effective.

STRUCTURED ABSTRACT

Objective: To undertake a randomised 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 randomised to the fistula plug with surgeon's preference (advancement flap, cutting seton, fistulotomy, LIFT procedure). The primary outcome was faecal incontinence quality of life (FIQoL) at 12-months. Secondary outcomes were fistula healing, incontinence rates, and complication and re-intervention rates.

Results: Between May 2011 and March 2016, 304 participants were randomised to fistula plug or surgeon's preference. No differences were seen in FIQoL between the two 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. Faecal incontinence rates improved marginally in both groups. Complications and re-interventions 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 £2,738 (s.d. £1,151) for the fistula plug and £2,308 (s.d. £1,228) for the surgeon's preference group (mean difference +£430, p=0.0174). The average total QALYs gained was marginally higher in the fistula plug group. The fistula plug was 35% - 45% likely to be cost-effective across a willingness to pay threshold of £20,000-£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.

A multicentre randomised 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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INTRODUCTION

Fistula-in-ano affects 1-2 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 LIFT (Ligation of the Intersphincteric Fistula Tract) procedure has reported fistula healing in 47% - 95% of patients with minimal morbidity and incontinence.[11-16]

An alternative approach to treating anal fistulas is the bioprosthetic 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, Indiana, USA) 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.[17-19] Importantly, there is an additional cost for the plug, which might impact on its cost effectiveness and clinical adoption.

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

METHODS

Study design

The FIAT trial was a pragmatic, phase III, multi-centre, randomised 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 anaesthesia prior to randomisation. The fistula had to have a single internal opening and a tract at least 2cm in length. All patients had to be treated with a draining seton for a minimum of 6-weeks prior to randomisation. Participants were excluded if there was more than one 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 MRI scan.

All patients had to undergo MRI scan 6-months prior to randomisation. 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 5mm.

Surgical workshops were held to standardise fistula plug insertion and all surgeons were proctored for the first 3 fistula plug cases. Fistulotomy, cutting seton, advancement flap, and LIFT procedure were undertaken according to surgeons' usual practice. All participating radiologists attended a FIAT radiology workshop.

Randomisation and masking

Randomisation was performed using a secure 24-hour internet-based randomisation service or by telephone call immediately prior to fistula surgery. Participants were randomised in a one-to-one ratio to either fistula plug or surgeon's preference, minimised 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 standardised fistula plug procedure included removal of draining seton, gentle curettage of the tract, and insertion of either a 4mm or 7mm 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 randomised 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).[19] The FIQoL questionnaire comprises 29 multiple choice questions grouped into four domains – lifestyle, coping/behaviour, 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's incontinence score [20]; re-intervention rates at 6- and 12-months; complication rates and generic QoL at 6-weeks, 6- and 12-months, measured using EQ-5D-3L [21]; 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 i.e. medical treatment (e.g. antibiotics) or need for re-intervention (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% non-compliance 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 summarised 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 four domains of the FIQoL questionnaire. Further models were fitted, which included a time by treatment interaction term. EQ-5D-3L was analysed in a similar manner. Other continuous outcomes were presented as mean differences analysed using a t-test. Binary outcomes were presented as risk ratios (RRs) and time-to-event data was presented as hazard ratios (HRs). No corrections for multiple testing were made and two-sided tests were considered significant if $p<0{\cdot}05$. 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 non-adherence to the randomised allocation.

Pre-specified subgroup analyses were performed for the minimisation variables – age at randomisation (<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 four domains of the primary outcome, fistula healing, faecal 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 re-interventions over time.

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

Economic evaluation

The economic evaluation was performed using a UK NHS and Personal Social Service (PSS) 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,[22] NHS Reference Costs,[23] and the British National Formulary[24] (Supplemental data – HE1-HE3). Health related quality of life (HRQoL) was estimated from the EQ-5D-3L with differences between treatment groups assessed using two 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.[25] 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 four 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 three time points. Incremental cost effectiveness ratios (ICERs) were calculated to allow interpretation of results in terms of the NICE £20,000 - £30,000 per QALY willingness to pay threshold. Data interpretation Probabilistic sensitivity analysis was used to assess uncertainty and the results analysed using a cost effectiveness acceptability curve.

RESULTS

Between May 2011 and March 2016, 340 patients were randomised equally between fistula plug and surgeon's preference (Figure 1). Participants were recruited from 45 centres with recruitment varying from 1 to 32 participants by site.

The baseline characteristics, overall and by randomisation group, are shown in Table 1 (see Supplemental Table 1 for full details). The majority of participants were ASA grade 1 (77%), aged between 30 and 60 years (mean age 45.1 years), with more males than females (55% vs. 45%). There was no difference in co-morbidity 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 two 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 EUA, where data was available to confirm. The morphology of the fistulas at baseline EUA was similar between the groups. Baseline MRI scan characterised the fistula morphology as transsphincteric in 132 (87%) in the fistula plug and 138 (91%) in the surgeon's preference groups.

No significant differences were seen in any of the four FIQoL domains between the fistula plug and surgeon's preference groups (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 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 are shown in Table 4. The best performing procedure at 12-months in the surgeon's preference group was fistulotomy (12/16, 75%), and the worse performing was the LIFT procedure (21/50, 42%). No further sub-analysis 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 -1.66-0.79, p=0.48) at 12-months (Table 3).

Overall postoperative complications were low and similar in both groups; fistula plug 4/147 (3%) and surgeon's preference 2/144 (1%). Table 3 shows overall complication rates and rates of re-intervention (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% of reported complications). 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 re-intervention 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 re-interventions were still common in both groups (Table 3). No significant differences were seen between the treatment groups for time to first re-intervention and time to first surgical re-intervention.

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 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 pre-specified subgroups for the four 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 (£2,738 vs. £2,308; p=0.0174), due to higher surgery related costs (£2,306 vs. £1,728, p<0.001). The mean costs due to readmissions were higher for the fistula plug group (£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 non-imputed data showed that the fistula plug was associated with an Incremental Cost Effectiveness Ratio (ICER) of £10,993 with an overall net benefit of £352 over a 12-month time horizon (Supplemental data – Tables HE4-HE7). 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 to the non-imputed data. The ICER was £17,279 / QALY and the net benefit was £71. However, adjusting for the difference in baseline EQ-5D-3L values 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) showed that the probability of the fistula plug being cost-effective across the NICE acceptance threshold of £20,000 - £30,000 / QALY was approximately 35% to 45%.

DISCUSSION

The FIAT trial provides important data on the Surgisis® 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 whilst 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 non-transsphincteric 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.[26]

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 previous literature. Although Adamina *et al* reported a more marked improvement in QoL, this was in a small prospective cohort study and using the SF-36v2 questionnaire.[27] Bondi *et al*, in a randomised trial comparing the fistula plug to advancement flap, showed an improvement in QoL at 3 months follow-up, but no difference between the two techniques.[28]

The fistula healing rates reported in FIAT might be viewed as disappointing. Overall, only around one-third of fistulas healed by 6-weeks and just over a half healed by 12-months. However, the results of FIAT are in keeping with other randomised trials, which have reported healing rates of 66% and 71% for the fistula plug and 38% and 52% for advancement flap.[28,29] Several systematic reviews and meta-analyses have been published, documenting healing rates with the fistula plug varying between 35% - 87%.[17,18,30]

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% - 80% of cases.[15,31,32]

Although the healing rates following fistula surgery are poor and re-interventions 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.[33]

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 to 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 to 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[34-36], as data becomes available, modelling 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 as 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% - 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 aetiology 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 two groups, it is unlikely that achieving the original sample size of 400 patients would have altered the results.

Non-masking 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 whilst others did not. Masking of data collectors would have hindered the collection of treatment specific information. It is unlikely that non-masking affected the primary outcome.

CONTRIBUTORS

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The following institutions, surgeons, and radiologists participated in the trial:
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DGJ, JS, DT, RG, AS, CTH, MK, KH, and LM designed the study and were involved in study coordination. DGJ and JS were responsible for surgeon training in fistula plug insertion. DT was responsible for radiology training and centralised MRI review. CAH performed the statistical analysis with senior oversight by KH. AS and CTH designed the economic

evaluation and undertook the analysis. All authors contributed to data interpretation and the writing and review of the manuscript.

DECLARATION OF INTERESTS

We declare no competing interests.

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DATA SHARING

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

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Table 1: Baseline characteristics of recruited patients

			Surgisis Anal Fistula Plug (N=152)	Surgeon's Preference (N=152)	All Participants (N=304)
Minimisation 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 randomisation (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[1]			19/107 (18%)	17/105 (16%)	36/212 (17%)
Patient Characteristics					
Age at randomisation (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					
St Mark's Incontinence Score[2]	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			17 (11%)	19 (13%)	36 (12%)
Supralevator 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%)
		Supralevator	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	17/41 (41%)	19/35 (54%)	36/76 (47%)
		Ischioanal fossa	24/41 (60%)	18/35 (51%)	42/76 (56%)
		Supralevator	6/41 (15%)	2/35 (6%)	8/76 (11%)

[1]Secondary Extensions at Baseline EUA was not added to the minimisation procedure until 10/7/2012, version 2.2 of the randomisation notepad.

[2]St Marks Incontinence scores range from 0 to 24 where lower scores are better. When a total score was not computable from the individual St Marks domains the score provided at randomisation was used. The one participant with a missing St Marks score had a colostomy.

[3]First/Recurrent fistula was deemed unknown when both first and recurrent were answered yes, or both were answered no.

Table 2: Primary outcome FIQoL

	Surgisis Anal Fistula Plug (N =152)	**Surgeon's Preference** (N =152)	**Mean Difference[1]** (95% CI)	**p-value**
FIQoL Lifestyle[2]				
Baseline	3.46 (0.75, 138)	3.34 (0.83, 131)	0.03 (-0.10, 0.15)	**0.67**
6 weeks	3.49 (0.76, 127)	3.42 (0.82, 126)		
6 months	3.57 (0.73, 124)	3.50 (0.77, 128)		
12 months	3.60 (0.70, 125)	3.54 (0.75, 128)		
FIQoL Coping/Behaviour[2]				
Baseline	3.30 (0.75, 138)	3.14 (0.88 131)	0.11 (-0.03, 0.24)	**0.11**
6 weeks	3.39 (0.76, 127)	3.18 (0.89, 126)		
6 months	3.44 (0.79, 124)	3.31 (0.90, 128)		
12 months	3.43 (0.83, 124)	3.33 (0.85, 128)		
FIQoL Depression/Self-perception[2]				
Baseline	3.04 (0.77, 132)	2.99 (0.81, 120)	0.09 (-0.06, 0.24)	**0.22**
6 weeks	3.13 (0.78, 115)	3.03 (0.85, 118)		
6 months	3.23 (0.76, 114)	3.16 (0.91, 117)		
12 months	3.29 (0.85, 115)	3.20 (0.85, 118)		
FIQoL Embarrassment[2]				
Baseline	3.26 (0.82, 132)	3.08 (0.87, 120)	0.12 (-0.05, 0.29)	**0.18**
6 weeks	3.34 (0.84, 115)	3.09 (0.92, 117)		
6 months	3.34 (0.85, 114)	3.29 (0.89, 118)		
12 months	3.35 (0.89, 116)	3.25 (0.95, 118)		

[1]Mean difference. Values >0 favour fistula plug.
[2]FIQoL scores range from 1 to 4 where higher scores are better.

Table 3: Secondary outcomes

	Surgisis Anal Fistula Plug (N =152)	Surgeon's Preference (N =152)	Estimate (95% CI)	p-value
Clinical fistula healing				
6 weeks	42/141 (30%)	45/137 (33%)	0.91 (0.64, 1.29)[1]	0.58
6 months	50/127 (39%)	62/128 (48%)	0.81 (0.61, 1.08)[1]	0.14
12 months	66/122 (54%)	66/119 (55%)	0.98 (0.78, 1.23)[1]	0.83
St Marks Incontinence score[5]				
6 weeks	3.72 (4.22, 134)	3.87 (4.97, 132)	-0.15 (-1.26, 0.96)[2]	0.79
6 months	3.06 (4.44, 120)	3.61 (4.55, 117)	-0.55 (-1.70, 0.60)[2]	0.35
12 months	3.22 (4.54, 120)	3.65 (4.91, 112)	-0.44 (-1.66, 0.79)[2]	0.48
Complications				
Post-operative[8]	4/147 (3%)	2/144 (1%)	1.96 (0.36, 10.53)[3]	0.42
6 weeks	49/142 (35%)	25/137 (18%)	1.89 (1.24, 2.88)[3]	0.002
6 months	27/129 (21%)	27/129 (21%)	1.00 (0.62, 1.61)[3]	1.00
12 months	28/124 (23%)	24/121 (20%)	1.14 (0.70, 1.85)[3]	0.60
Re-interventions				
Post-operative[8]	2/147 (1%)	1/144 (1%)	1.96 (0.18, 21.37)[3]	0.57
6 weeks	30/142 (21%)	16/137 (12%)	1.81 (1.03, 3.17)[3]	0.03
6 months	25/129 (19%)	30/129 (23%)	0.83 (0.52, 1.34)[3]	0.45
12 months	28/124 (23%)	27/121 (22%)	1.01 (0.64, 1.61)[3]	0.96
EQ5D3L visual analogue scale[6]				
Baseline	73.30 (18.67, 139)	74.61 (17.75, 131)	1.66 (-1.45, 4.77)[4]	0.29
6 weeks	75.88 (18.44, 128)	75.99 (18.22, 125)		
6 months	80.14 (15.63, 124)	77.64 (20.67, 129)		
12 months	79.62 (19.04, 125)	79.47 (15.62, 125)		
EQ5D3L health status score[7]				
Baseline	0.77 (0.27, 136)	0.76 (0.25, 130)	0.01 (-0.04, 0.05)[4]	0.76
6 weeks	0.78 (0.24, 121)	0.77 (0.25, 125)		
6 months	0.83 (0.21, 121)	0.79 (0.27, 129)		
12 months	0.85 (0.21, 121)	0.82 (0.24, 126)		

[1]Risk ratio. Values >1 favour fistula plug.
[2]Mean difference. Values <0 favour fistula plug.
[3]Risk ratio. Values <1 favour fistula plug.
[4]Mean difference. Values >0 favour fistula plug.
[5]St Marks incontinence scores range from 0 to 24 where lower scores indicate greater incontinence.
[6]EQ5D3L visual analogue scale scores range from 0 to 100 where higher scores indicate better health.
[7]EQ5D3L health status scores range from -0.594 to 1 where higher scores indicate better health.
[8]Postoperative refers to complication or re-intervention 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 Weeks	41/136 (30%)	7/48 (15%)	11/17 (65%)	11/21 (52%)	16/55 (29%)
6 Months	51/123 (41%)	20/40 (50%)	14/17 (82%)	10/19 (53%)	17/55 (31%)
12 Months	63/115 (55%)	27/42 (64%)	12/16 (75%)	9/17 (53%)	21/50 (42%)

Table 5: General complications by randomised group at different time points

	Surgisis® Anal Fistula Plug (N =152)	**Surgeon's Preference** (N =152)	Risk Ratio[1] (95% CI)	**p-value**
Post-operative				
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 Weeks				
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 Months				
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 Months				
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%)		

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	£2,297 (118)		0.800 (0.021)			
Fistula plug	£2,750 (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

Figure 1

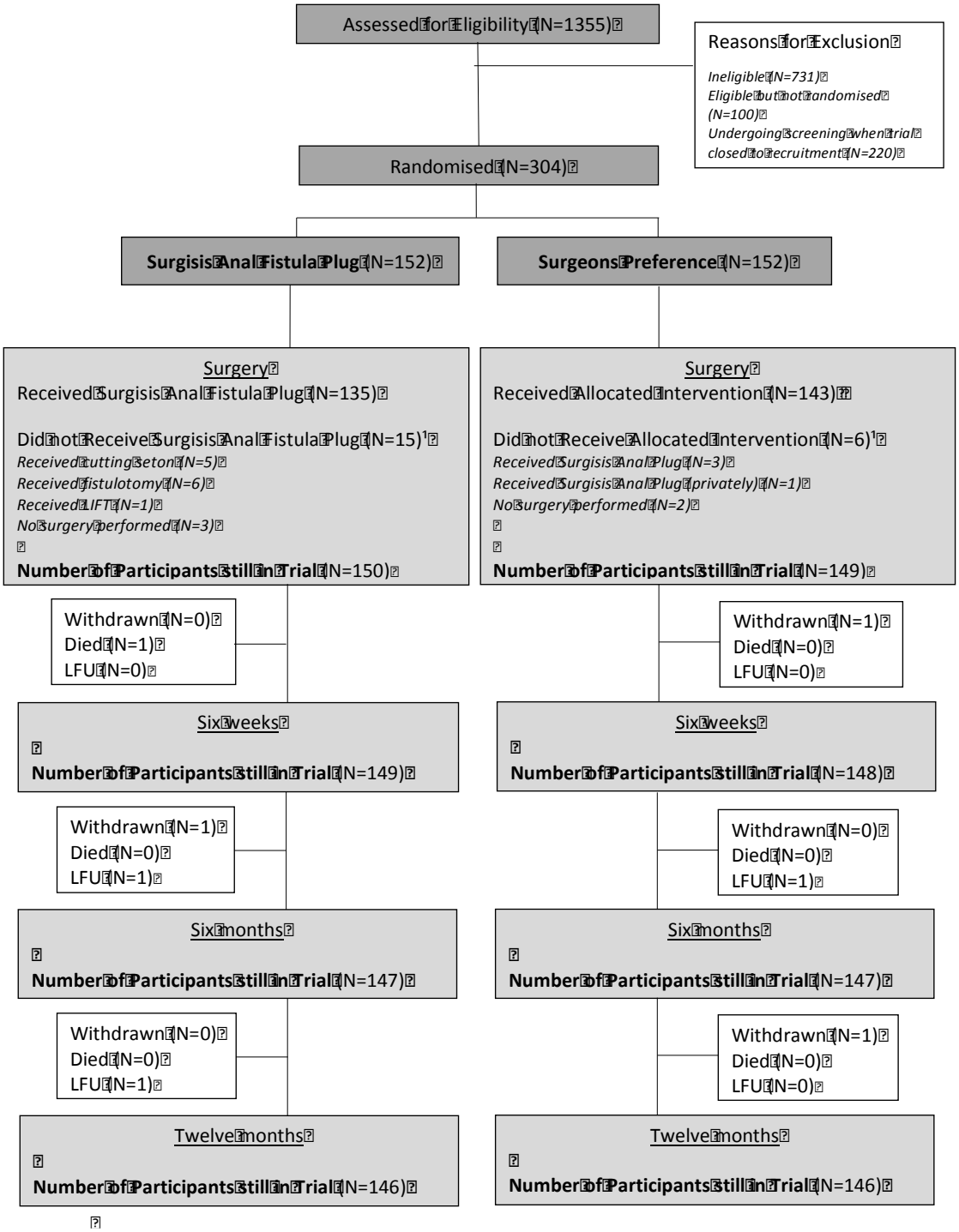
Assessed for Eligibility (N=1355)
Reasons for Exclusion
Ineligible (N=731)
Eligible but not randomised (N=100)
Undergoing screening when trial closed to recruitment (N=220)
Randomised (N=304)
Surgisis Anal Fistula Plug (N=152)
Surgeons Preference (N=152)
Surgery
Received Surgisis Anal Fistula Plug (N=135)
Did not Receive Surgisis Anal Fistula Plug (N=15)1
Received cutting seton (N=5)
Received fistulotomy (N=6)
Received LIFT (N=1)
No surgery performed (N=3)
Number of Participants still in Trial (N=150)
Surgery
Received Allocated Intervention (N=143)
Did not Receive Allocated Intervention (N=6)1
Received Surgisis Anal Plug (N=3)
Received Surgisis Anal Plug (privately) (N=1)
No surgery performed (N=2)
Number of Participants still in Trial (N=149)
Withdrawn (N=0)
Died (N=1)
LFU (N=0)
Withdrawn (N=1)
Died (N=0)
LFU (N=0)
Six weeks
Number of Participants still in Trial (N=149)
Six weeks
Number of Participants still in Trial (N=148)
Withdrawn (N=1)
Died (N=0)
LFU (N=1)
Withdrawn (N=0)
Died (N=0)
LFU (N=1)
Six months
Number of Participants still in Trial (N=147)
Six months
Number of Participants still in Trial (N=147)
Withdrawn (N=0)
Died (N=0)
LFU (N=1)
Withdrawn (N=1)
Died (N=0)
LFU (N=0)
Twelve months
Number of Participants still in Trial (N=146)
Twelve months
Number of Participants still in Trial (N=146)

FIGURE LEGENDS

Figure 1: Trial profile.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Structured Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	3
	4b	Settings and locations where the data were collected	3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	3
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	3
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	6
	13b	For each group, losses and exclusions after randomisation, together with reasons	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6&7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6&7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	6&7
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	9
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

FIAT: Consort flowchart