FIAT

The Fistula-In-Ano Trial comparing Surgisis® anal fistula plug versus surgeon's preference for transsphincteric fistula-in-ano.

Fistula-in-ano is a common condition, affecting an estimated 1-2 per 10,000 of the population and up to 50% of patients who present with a perianal abscess. The majority of cases are low fistulae amenable to simple fistulotomy. However, high fistulae involving a substantial proportion of the sphincter muscle present a difficult management problem. For these fistulae surgical treatment is tailored to achieve maximal rates of healing with minimal compromise of sphincter function. Fistulotomy, cutting seton, and advancement flap have all been advocated for complex fistulae, however none of the current techniques produce reliable healing rates and all of them are associated with varying degrees of incontinence.

Closure of anal fistulae using a suturable bioprosthetic plug made from lyophilized porcine intestinal submucosa has been recently reviewed by NICE. The conclusions were that while there are no safety concerns associated with the procedure, there "...is not adequate evidence on efficacy for it to be used without special arrangements for consent and for audit or research".

The use of the fiustula plug is currently on an ad hoc basis and has not yet been reliably assessed in a randomised controlled trial. **FIAT** (Fistula-in-ano trial) is a multi-centre randomised controlled trial designed to evaluate whether the fistula plug can produce better symptom-specific quality of life than standard surgical techniques for the treatment of high-transsphinteric fistula-in-ano.

Patients with a confirmed high transsphincteric fistula involving a significant proportion of the external sphincter complex are randomised to either insertion of the Surgisis® fistula plug or the "surgeon's preference" of advancement flap, fistulotomy or cutting seton. The primary outcome measures relate to quality of life (QoL), as measured by the faecal incontinence QoL scale and the EQ-5D (EuroQoL). **FIAT** aims to randomise 500 patients over three years, which would provide 90% power to detect a small to moderate treatment effect (0.3 s.d., difference of 0.10 on the EQ-5D scale) between the two arms of the trial.

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Trial Sponsor: University of Leeds**;** Tel: 0113 206 5218

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1. BACKGROUND

Fistula-In-Ano

Fistula-in-ano is a common condition, affecting an estimated 1-2 in 10,000 of the population[1,2], with the majority being in the 3rd to 5th decades of life. Whilst the majority are low fistulae amenable to simple fistulotomy, higher trans sphincteric fistulae involving a substantial proportion of the external muscle present a difficult management problem. For these fistulae surgical treatment is tailored to achieve maximal rates of healing with minimal compromise of sphincter function. Fistulotomy, cutting seton, and advancement flap have all been advocated for mid and high fistulae with varying degrees of success. Simple fistulotomy is associated with low recurrence rates, variously reported between 2% and 9%[3,4], but may be associated with a change in continence in up to 50% of patients[5]. The use of a cutting seton does appear to reduce the rate of incontinence but does not completely eliminate it. The recurrence rates for complex fistulae treated with a cutting seton are reported between 0% and 8%, with minor incontinence in 34% to 63% and major incontinence in 2% to 26%[6-12]. In addition, the use of a cutting seton is often a protracted process requiring repeated EUA and frequently a completion fistulotomy. Rectal and anal advancement flaps have been advocated as a means of closing mid and high fistulae with preservation of the external sphincter muscle. However, fistula recurrence rates of 25% to 54% have been reported with a change of continence in 30% to 35% of patients[13,14]. Thus, none of the current techniques for the treatment of high anal fistulae produce reliable healing rates and all are associated with varying degrees of incontinence.

Definitions

For the purposes of this study a high fistula is defined as one that on clinical grounds runs a significant risk of incontinence if treated with fistulotomy (i.e. potentially involves a significant portion of the external sphincter complex).

A low fistula is defined as one that can be treated with fistulotomy with minimal risk of long term incontinence (i.e. has minimal involvement of the external sphincter complex).

An extension/collection is defined as an area of sepsis branching away from the primary fistula track, and may include a horseshoe extension or blind sinus track.

The Surgisis® Anal Fistula Plug

More recently the use of a bioprosthetic plug, Surgisis® anal fistula plug, made from lyophilized porcine intestinal submucosa has been described.

To date, the evidence on the efficacy of the Surgisis® fistula plug is limited. A recent review of the literature has identified a total of 10 published manuscripts, 18 abstracts, and one case-report on the use of the fistula plug; no randomised trial has been reported. Of the 29 identified reports, 26 were retrospective reviews and three were comparative reviews (two comparing the fistula plug with advancement flap and one with fibrin glue). Most of the reports contained a heterogeneous patient cohort, with fistulae of mixed aetiology, variable fistula classification, and limited follow-up. Excluding duplicate publications, this cohort yielded a total of 556 patients treated with a Surgisis® fistula plug for cryptogenic fistula-in-ano, with a median follow-up of 211 days (range: 30 – 730 days). The overall healing rate was 56%, with a wide range observed between 15% and 85%[15-22]. The main reason for failure appeared to be dislodgement of the plug in 10% - 15% of cases, which may be a technical issue related to the learning curve for the procedure. Continence was preserved in all patients.

The need for FIAT – A Phase III trial of the anal fistula plug versus surgeon's preference for treatment of high transsphincteric fistula-in-ano.

Currently the Surgisis® anal fistula plug is being used on an ad hoc basis to treat a variety of fistulae based on limited scientific evidence for its efficacy. It costs more (approximately £495 + VAT/plug) than standard treatments and there are legitimate concerns regarding reported rates of healing and recurrence. Recently NICE has reviewed the evidence for the fistula plug and concluded "Current evidence suggests that there are no major safety concerns associated with the closure of anal fistula using a suturable bioprosthetic plug. However, evidence on the efficacy and cost-effectiveness of the procedure is not adequate for it to be used without special arrangements for consent and for audit or research"[23].

There is thus an urgent need for a randomised controlled trial to formally evaluate the role of the anal fistula plug in the treatment of these high anal fistulae and to determine whether its higher initial cost as compared to other current techniques is justified in terms of better patient outcomes.

The **FIAT** trial aims to address this knowledge gap by evaluating whether the fistula plug can produce relief of symptoms whilst maintaining anal sphincter function and preserving symptom-specific (incontinence) quality of life.

The information obtained by randomising 500 patients into **FIAT** will help guide the treatment of many thousands of future patients.

2. TRIAL DESIGN

The **FIAT** trial is a pragmatic, multi-centre, randomised controlled trial designed to provide reliable evidence on the value of the Surgisis® anal fistula plug in the treatment of high fistula-in-ano.

Objectives

FIAT is a pragmatic, Phase III multi-centre randomised controlled trial with the following objectives:

Primary objective:

To compare the Surgisis® anal fistula plug with standard treatments for high trans-sphincteric anal fistulae in terms of:

- symptom-specific quality of life.

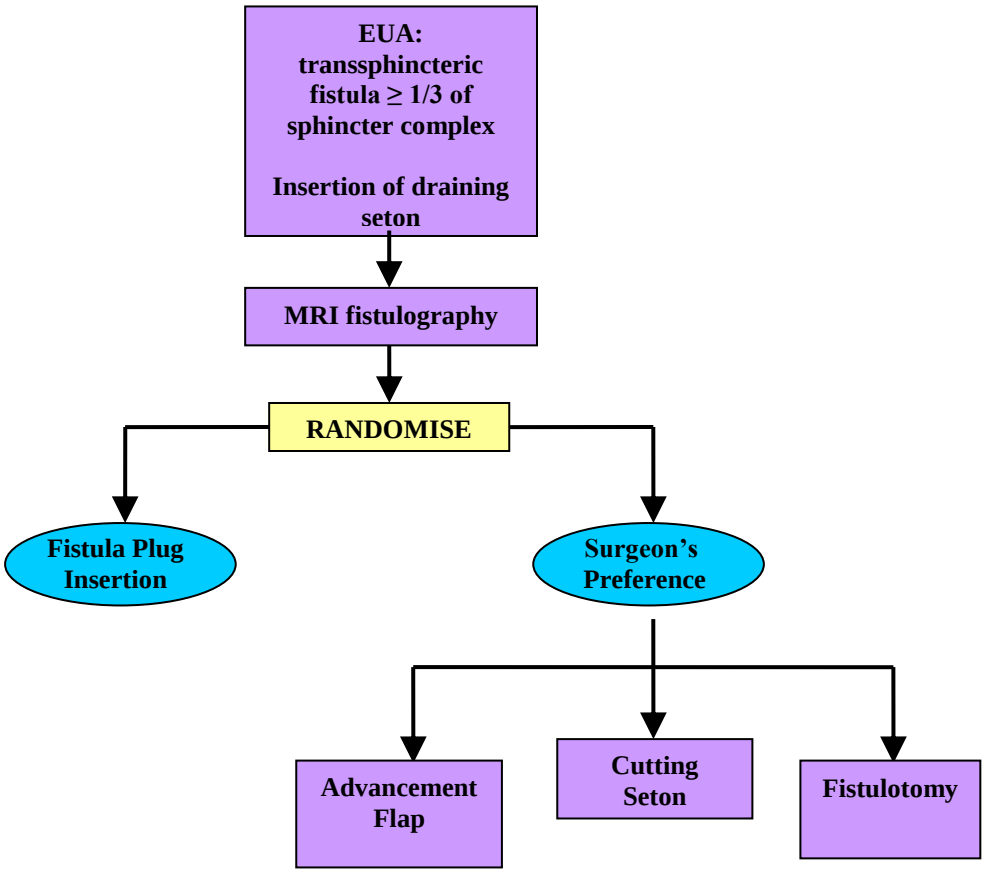
Secondary objectives:

To compare the Surgisis® anal fistula plug with standard techniques for high transsphincteric anal fistulae in terms of:

- fistula healing rates
- complication and re-intervention rates
- faecal incontinence rates
- cost-effectiveness
- health economic benefits.

Trial Design

Patients with a confirmed high transsphincteric fistula at risk of incontinence with fistulotomy (involving approximately 1/3 or more of the external sphincter complex), will be randomised between insertion of the Surgisis® fistula plug and the surgeon's preference of advancement flap, cutting seton and fistulotomy.



Outcome Measures

The primary outcome measures relate to quality of life and are assessed at baseline, 6 weeks, 6 and 12 months:

1. The Faecal Incontinence Quality of Life scale: this is a validated, symptom-specific quality of life questionnaire [24].
2. EQ-5D (EuroQoL). A validated generic quality of life questionnaire assessing five quality of life domains scored on a 3-point ordinal scale. The combination of answers will be transformed to give an overall quality of life utility score for each patient.

Symptom-specific quality of life has been chosen rather than fistula healing rates as it reflects the primary aim of fistula surgery: to produce symptom relief whilst maintaining anal sphincter function and preserving symptom-specific QoL.

The secondary outcome measures are:

1. Fistula healing rate at 12 months.

2. Faecal incontinence rates (St Marks Incontinence Score) at baseline, 6 and 12 months.
3. Complication rates at 6 weeks, 6 months and 12 months.
4. Rates of re-intervention at 6 and 12 months.
5. Generic quality of life assessed using EuroQoL EQ-5D and visual analogue scale scores at baseline, 6 weeks, 6 and 12 months.

Resource usage will be monitored throughout the trial for the economic analysis. NHS costs associated with each trial arm will be estimated from case report forms plus patient reported data at 6-weeks, 6, and 12 months. Resources used within the initial surgical hospitalisation will be assessed using the operative and post-operative forms, with resources incurred at outpatient clinics derived from the 6 week, 6, and 12 month forms. Resources used from adverse events will be assessed from the AE/SAE form. Out-patient clinic attendances, other than NHS contacts and prescribed items within the NHS will be identified using patient reported data.

Information regarding the patient's perceptions of recovery will also be collected.

3. PATIENT ENTRY

Centre eligibility

The entry criteria for a site to participate in the **FIAT** trial are that participating surgeons must have inserted at least 3 fistula plugs. In addition, a lead surgeon, or someone delegated by them, must have attended a **FIAT** surgical workshop. This surgeon must then take responsibility for dissemination of information at the site, standardisation of fistula plug insertion technique, and communication with the **FIAT** trial office at BCTU. A lead radiologist nominated by each site to supervise MRI fistula imaging should have also received training for the study by attendance at a workshop or use of electronic learning materials.

Patient eligibility and recruitment

The **FIAT** trial will recruit patients with cryptogenic transsphincteric anal fistulae. It is likely that suitable patients will be identified either in the out-patient clinic or following acute admission with perianal abscess/sepsis. Patients with recurrent fistulae, previously treated by any means other than a fistula plug, are eligible for participation

in the study. Patients in whom a second fistula plug is planned to treat recurrent fistulation are not eligible. As part of their routine investigation, patients will undergo examination under anaesthesia (EUA) to characterise the fistula in accordance with Parks' classification [25], to drain any accompanying sepsis, and to insert a draining seton. The seton should be left in situ for a minimum of 6 weeks, during which time an MRI scan should be performed to further characterise the fistula.

It is appreciated that, as part of their normal care, a proportion of patients will have had an MRI scan prior to EUA and seton insertion. This is acceptable, provided that a baseline MRI has been performed within 6 months of randomisation and that no treatment other than draining seton insertion has taken place (i.e. all patients entered into **FIAT** should have undergone MRI assessment within 6 months of randomisation). Based on the results of the EUA and MRI scan patient suitability for inclusion in the trial will be determined in accordance with the eligibility criteria.

For the purposes of this study a high fistula is defined as one that on clinical grounds runs a significant risk of incontinence if treated with fistulotomy (i.e. potentially involves a significant portion of the external sphincter complex). A low fistula is defined as one that can be treated with fistulotomy with minimal risk of long term incontinence (i.e. has minimal involvement of the external sphincter complex)

Eligibility Criteria

Inclusion criteria

1. Clinical diagnosis of high transsphincteric cryptoglandular fistula-in-ano.
2. Patients must have undergone a prior EUA to characterise the nature of the fistula.
3. The fistula tract should be ≥ 2cm in length.
4. Only a single internal fistula opening should be present at EUA, such that the fistula is suitable for treatment by insertion of a single fistula plug.
5. Patients must have been treated with a draining seton for a minimum period of 6 weeks prior to randomisation.
6. Patients must be 18 years or older and able to provide informed consent.
7. Fistulae must be cryptoglandular aetiology.

Exclusion criteria

1. Unable/unwilling to provide informed consent.
2. Contraindication to general anaesthesia.
3. Low transsphincteric fistulae.
4. Non-cryptoglandular fistulae e.g. Crohns, obstetric, irradiation, malignant etc.
5. Other perineal fistulae e.g. rectovaginal fistulae, pouch-vaginal fistulae etc.
6. Complex disease in which more than one internal fistula opening is present and requiring concurrent insertion of more than one fistula plug.
7. Clinical evidence of active perianal sepsis. In the event that there is disagreement between clinical and radiological assessment of active sepsis/collection, the clinical opinion will prevail.
8. Cultural or religious objection to the use of pig tissue.
9. Absolute contraindication to MRI scan e.g. cardiac pacemaker.
10. Patients with recurrent anal fistulae previously treated with a fistula plug.

It is not known how the presence of an extension or secondary track (defined as an area of sepsis branching away from the primary fistula track, and may include a horseshoe extension or blind sinus track) affects the healing rates of the fistula plug. For the purposes of the **FIAT** trial these findings on EUA or MRI scan should NOT be considered as exclusion criteria. However, there should be no evidence of undrained sepsis, either clinically or radiologically, prior to randomisation into the study.

If an undrained collection is identified, either at EUA or on MRI, then the collection should be drained and the patient re-evaluated after an appropriate interval by MRI to ensure that drainage is complete prior to entry into the study.

Complex fistula disease in which more than one fistula plug is inserted concurrently is not suitable for inclusion into **FIAT** since this scenario raises the possibility of a non-cryptoglandular aetiology.

MRI fistulography prior to randomisation

The purpose of the initial MRI scan is for the following:

1. To provide assessment for evidence of ongoing active perianal sepsis or undrained collection after seton insertion.

2. To provide baseline imaging for comparison with the scan either at 12 months for assessment of healing or sooner if there is treatment failure (recurrence).
3. To confirm the findings at EUA (i.e. consistent with a transsphincteric fistula of cryptoglandular origin involving approximately 1/3 or more of the external sphincter muscle).

The baseline MRI scan should be performed within 6 months of randomisation in all cases. It is anticipated that the majority will be performed in the period between initial EUA with seton insertion and randomisation. All MRI scans should be performed in a minimum of 2 planes, which must include 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. Whether a thinner slice thickness or additional sequences and imaging planes are selected may vary according to local radiologist preference, type of MRI scanner and patient factors. After completion of the scan, a reporting proforma should be completed to summarise the imaging findings in all cases (Appendix F).

Where undrained collections/extensions are identified on the initial MRI scan, a repeat MRI scan is required after surgical intervention to ensure resolution prior to randomisation. This should use the same MRI parameters described above and a further reporting proforma completed.

The completed MRI reporting proforma should be forwarded along with a copy of the baseline MRI on CD to the trials office.

MRI fistulography for follow up

MRI will be performed in all patients as part of follow up. This should occur at one of 2 points:

1. Where there is early failure of surgical treatment to evaluate fistula recurrence, **OR**

2. 12 months after randomised treatment, to assess for residual abnormality and confirm healing.

Where patients have suffered early treatment failure, a 12 month MRI scan is NOT required.

This MRI scan should use the same parameters used for baseline imaging. After completion of the scan a 'follow up' reporting proforma should be completed to summarise the imaging findings in all cases (Appendix N).

All follow up MRI scans are reimbursed at a rate of £250 per scan.

4. CONSENT & RANDOMISATION

Informed consent

The study will be conducted in compliance with the Research Governance Framework for Health and Social Care and ICH GCP.

It is envisaged that patients will be recruited from one of three main scenarios:

1. From the outpatient clinic, for patients presenting with *de novo* or recurrent perianal sepsis/ fistula in whom a high anal fistula is suspected or established. It is likely that this group will require an EUA with seton insertion and MRI assessment.
2. From the outpatient clinic, for patients referred specifically for treatment of complex anal fistulae. This group may already have undergone EUA, performed by the referring clinician, with or without seton insertion. In addition, an MRI assessment may have been performed. In such cases, there is no need to repeat the EUA or MRI scan provided it was performed within 6 months of randomisation and there was no undrained collection or surgical intervention.
3. Following acute admission for treatment of perianal sepsis. These patients are likely to have undergone an EUA and incision and drainage of an abscess/sepsis when a fistula was discovered and a draining seton inserted. It is likely that these patients will require MRI assessment.

Suitable patients will be approached for entry into **FIAT**, the rationale for the study explained along with the various treatment options, and a Patient Information Sheet provided (Appendix A). In scenarios 1 and 2 above this will likely be performed in the

outpatient setting, whilst in scenario 3 this may involve in-patient consultation. Initial discussion regarding participation in **FIAT** can take place whilst awaiting further investigation by EUA and MRI.

Once all investigations are complete (EUA, seton insertion, MRI assessment), the trial inclusion/exclusion criteria should be checked and, if suitable, the patient can be approached for consent to participate in **FIAT**. This may be in the outpatient clinic or following admission for surgery. Consent should be obtained in quadruplicate on the Consent Form provided (Appendix B), with one copy retained in the patients notes, one copy given to the patient, one copy kept in the local site file and one copy forwarded to BCTU. Once consent to participate has been obtained, patients can be randomised into the trial (see below). This may be in the outpatient clinic or following admission for surgery.

Randomisation by telephone & internet

Patients are entered in the trial by telephone call to the randomisation service (telephone number 0800 9530274, toll-free in the UK, or +44 (0) 121 415 9137 from elsewhere) or by internet on the website https://www.trials.bham.ac.uk/FIAT.

Telephone randomisation is available Monday-Friday 0900-1700 UK time. Randomisation out of these hours can be obtained by logging on to the **FIAT** website. Each centre and each randomiser will be provided with a unique log-in and password to do this. Randomisation notepads (Appendix D) are provided in the **FIAT** study folder and should be used to collate the necessary information prior to randomisation. After all the necessary details have been provided, the treatment allocation will be specified at the end of the telephone call. The patient's GP should be notified that they are in **FIAT**, and a specimen "Letter to GP" is provided for this purpose (Appendix C).

5. TREATMENT

Experimental Arm – Anal Fistula Plug Insertion

Patients will receive a preoperative phosphate enema as bowel preparation and a single dose of intravenous prophylactic antibiotics at induction of anaesthesia. The choice of antibiotic prophylaxis is at the surgeon’s discretion. The draining seton will be cut and a silk suture secured to one end and the seton removed, pulling the silk suture into the fistula tract. In turn, the silk suture is tied to the end of a Cook fistula

brush, which is used to gently but not vigorously debride the fistula tract. If desired, the fistula tract may be irrigated with saline or hydrogen peroxide. The Surgisis® anal fistula plug will be re-hydrated for 2 minutes in saline and secured to the silk suture. The plug will be pulled into the internal opening until resistance is met. The head of the plug will be secured to the internal opening and internal sphincter with a 2/0 vicryl or equivalent absorbable suture. Excess plug sitting above the mucosa should be trimmed flush. The mucosa of the internal opening may be closed as necessary. The tip of the plug will be cut flush with the external opening, and if necessary the external opening enlarged to facilitate drainage. Postoperatively, patients will be able to eat and drink as tolerated. No further antibiotics will be administered. Analgesics will be administered as necessary. The postoperative day of discharge will be recorded and patients advised to avoid all strenuous exertion for a period of 2 weeks.

Control Arm – Surgeon's Preference

For the purposes of the trial, the standard surgical techniques have been grouped together as a single comparator and termed "Surgeon's Preference". All surgical interventions will be performed according to standardised protocols. These are summarized below.

Advancement flap

Patients will receive a preoperative phosphate enema as bowel preparation and a single dose of intravenous prophylactic antibiotics at induction of anaesthesia. The choice of antibiotic prophylaxis is at the surgeon's discretion. The location of the internal opening will be identified and the draining seton removed. A vascularised flap of rectal tissue (rectal flap) or anoderm (anal flap) will be mobilised off the underlying internal sphincter or subcutaneous fat. The site of the internal opening on the flap will be excised. The fistula tract as it passes through the internal sphincter may be closed with an absorbable suture. The mobilised flap will be advanced over the site of the internal opening and sutured to the underlying internal sphincter with an absorbable suture. Postoperatively, patients will be able to eat and drink as tolerated. No further antibiotics will be administered. Stool softeners, bulking agents, and analgesics will be administered as necessary. The postoperative day of discharge will be recorded.

Fistulotomy

Patients will receive a preoperative phosphate enema as bowel preparation. No perioperative antibiotics will be administered unless there is a specific indication (e.g. prosthetic heart valve). The location of the internal opening will be identified and the draining seton removed. The course of the primary tract and any secondary tracts will be delineated with a fistula probe and the tract(s) laid open. The fistulotomy wound may be marsupialized as required. Postoperatively, patients will be able to eat and drink as tolerated. No further antibiotics will be administered. Stool softeners, bulking agents, and analgesics will be administered as necessary. The postoperative day of discharge will be recorded.

Cutting seton

Patients will receive a preoperative phosphate enema as bowel preparation. No perioperative antibiotics will be administered unless there is a specific indication (e.g. prosthetic heart valve). The location of the internal opening will be identified and the draining seton removed. The course of the fistula tract will be delineated with a fistula probe and a 1/0 Prolene or equivalent non-absorbable seton material passed through the external opening, primary tract, and internal opening. If necessary, the skin bridge between the external opening and the external sphincter may be divided. The seton will be tied firmly around the fistula tract and the contained sphincter muscle. Postoperatively, patients will be able to eat and drink as tolerated. Analgesics will be administered as necessary. No further antibiotics will be administered. The postoperative day of discharge will be recorded.

Compatibility with other studies

It is unlikely that patients suitable for inclusion in **FIAT** will also be involved in other colorectal clinical trials. In the unlikely event that a **FIAT** patient is also found to have a colorectal cancer, he/she may be withdrawn from the allocated fistula treatment as the cancer treatment will take priority and will influence the fistula management. A record of outcome for any such patients will be kept.

Data Collection & Clinical Follow-Up

Data will be collected at baseline, intraoperative, postoperative, and at 6-weeks and 6 and 12 months follow-up; this is summarised in the table overleaf:

	Baseline	Operative	Postoperative	6 weeks	6 months	12 months
Clinical examination	√			√	√	√
St Mark's Incontinence score	√				√	√
Faecal Incontinence QoL + EQ-5D	√		√		√	√
EUA	√					
MRI	√					√
Operative details		√				
Complications		√	√	√	√	√
Resource usage		√	√	√	√	√
Re-interventions			√	√	√	√

6. SAFETY MONITORING PROCEDURES

Serious adverse events (SAEs)

An SAE is an untoward event which:

- is fatal or life threatening
- requires or prolongs hospitalisation
- is significantly or permanently disabling or incapacitating
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

For the purposes of this study, adverse events include, but are not limited to:

- Unexpected events occurring during the surgical intervention e.g. excessive bleeding
- Significant postoperative bleeding, above that normally expected following the surgical intervention, and any bleeding requiring transfusion or surgical intervention for haemostasis
- Urinary retention requiring catheterisation
- Postoperative pain above that normally expected following the surgical intervention
- Perianal or perineal sepsis requiring hospitalisation or surgical intervention
- Faecal incontinence or defaecatory disturbance above that normally expected following the surgical intervention
- Complications related to the administration of the general anaesthetic or other medications e.g. allergic response to antibiotics
- Unexpected events related to MRI fistulography

Events NOT considered to be SAEs are hospitalisations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen
- admission to a hospital or other institution for general care, not associated with any deterioration in anorectal symptoms.
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Reporting AEs

From the first administration of trial treatment until the completion of the 12-month follow-up all adverse events related to the underlying high-anal fistula or its treatment, whether observed directly or reported by the patient, will be collected and recorded on the appropriate data collection forms (Appendix O). The Trials Unit will provide details of all adverse events to the Data Monitoring and Ethics Committee (DMEC) for their review, initially on a 6-monthly basis.

Reporting SAEs

SAEs will be collected for all patients in the study from the first trial treatment to the completion of 12-months follow-up. All SAEs must be recorded on the SAE Form (Appendix O) and faxed to the BCTU on +44 (0) 121 415 8871 within 24 hours of the research staff becoming aware of the event.

SAEs still present at the end of the study must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the end of the planned period of follow-up.

The BCTU will report all SAEs to the DMEC and Trial Steering Committee approximately 6-monthly and to the main REC annually. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform the main REC as this will be done by the BCTU as detailed above.

End of Trial

The end of the trial for regulatory purposes is defined as the date of the last visit of the last patient undergoing the protocol based treatment. Long-term follow-up, to at least one year after randomisation of the last patient, constitutes the non-interventional phase of the trial.

7. SIZE, STATISTICS & DATA MONITORING

The **FIAT** trial aims to randomise a minimum of 500 patients over three years (~15 patients per month). The aim is to recruit patients from 25 large centres contributing 125 patients per year, and from 25 smaller centres contributing 50 patients per year.

It is estimated that a total of 400 patients will need to be recruited in a 1:1 ratio (200 fistula plug: 200 surgeon's preference) to be able to detect a small to moderate treatment effect (0.3 s.d.) between the 2 arms of the study for the primary endpoint of QoL. To allow for a 20% non-compliance rate (non-acceptance, loss-to-follow-up, incomplete data), it is aimed to recruit a total of 500 patients.

The choice of the 0.3 s.d. treatment effect size is pragmatic. An effect size of 0.2 s.d. is considered small, 0.5 moderate, and 1.0 large (Cohen 1977). Randomisation of 500 patients in total would provide good statistical power (80% at $p<0.05$) to detect an effect size of 0.25 s.d., high power (82% at $p<0.01$) to detect a an effect size of 0.3 and very high power (97% at $p< 0.01$) to detect an effect size of 0.4 s.d. Using the observed standard deviation of 0.32 for the change from baseline in EuroQoL EQ-5D score at 1 year in the PROSPER trial of rectal surgery, an effect size of 0.3sd corresponds to an absolute difference between treatments of 0.10 on the EQ-5D utility scale.

Comparisons between groups over time will use repeated measures analyses, a statistically efficient approach that allows all of the follow-up data collated during the study to be used, which will further enhance statistical power. Quality of life scores at particular time points will be compared using standard two sample t-tests. Pre-specified sub group analyses will be by choice of surgical comparator in the standard treatment arm (advancement flap, fistulotomy, or cutting seton). Vigorous efforts will be made to minimise the amount of missing outcome data and, consequently, the potential for drop-out bias.

Health economic analysis

The cost-effectiveness of the Surgisis® fistula plug will be assessed within the trial period using collected data. Resource usage will be monitored throughout the trial as secondary outcomes. Costs will be assigned to these resources using NHS or PSSRU Reference Costs and the British National Formulary. Where costs cannot be assigned on this basis, information from hospital finance departments and/or expert judgement will be used instead. Quality of life will be assessed using EQ-5D scores, supplemented by patient provided information about recovery to obtain more precise estimates of quality of life. EQ-5D scores will be converted into health related quality of life figures anchored on dead (at 0) and full health (at 1) using the standard MVH algorithm based on 10 year time trade-off data. Quality-adjusted life years will be assessed on this basis within the 12 months of the trial. Comparisons will include both Surgisis® fistula plug versus randomised treatment on an ITT basis, and Surgisis® fistula plug versus treatment based on initial surgeon's preference. A probabilistic sensitivity analysis will be used to assess uncertainty.

The cost-effectiveness of the Surgisis® fistula plug beyond the trial period will be assessed through Markov modelling. These models allow outcomes to be extrapolated beyond the trial period, and a lifetime model will be used in this analysis. The Markov model will be formed using both the 12 month data from the trial in addition to the published literature on longer-term outcomes and expert judgement, as necessary. As in the within-trial period, comparisons will include both Surgisis® fistula plug versus randomised treatment on an ITT basis, and Surgisis® fistula plug versus treatment based on initial surgeon's preference.

A probabilistic sensitivity analysis will be used to assess uncertainty in both the trial-period and lifetime analyses, with Bayesian Value of Information analyses, net benefit calculations, and cost-effectiveness acceptability curves used to provide information about decision uncertainty in the model.

Data monitoring

During the period of intake in the study, interim analyses of safety and outcome data will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with any other analyses that the committee may request.

The DMEC will meet annually, or more frequently if considered appropriate, and will advise the chair of the trial's steering committee if, in their view, the randomised comparison in **FIAT** has provided both (a) "proof beyond reasonable doubt"[1] that for all, or for some types of patient, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in the main outcome measures, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results.

The steering committee can then decide whether to modify the study protocol. Unless this happens, however, the steering committee, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

If the clinical coordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the **FIAT** trial office to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8. ORGANISATION

To ensure the smooth running of **FIAT** and to minimise the overall procedural workload, it is proposed that each centre should designate individuals who would be chiefly responsible for local coordination of surgical, radiological and administrative aspects of **FIAT**. The **FIAT** Trial Office will provide as much assistance as they can to local co-ordinators and investigators in obtaining research ethics and Trust approval in each centre and helping resolve any local problems that may be encountered.

As FIAT is funded by the NIHR HTA it will automatically be eligible for inclusion in the Comprehensive Local Research Networks (CLRNs) portfolio. This will have benefits in coordination of research effort, dissemination of trial information, and local support for investigators.

[1] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

Principal Investigator at each centre

Each **FIAT** site should nominate one person to act as the local Principal Investigator. This local PI will bear the responsibility for the conduct of the research at their centre. The responsibilities of the local Principal Investigator will be to ensure that trial recruitment, randomisation, and follow-up proceeds according to the Protocol. The local PI will also be responsible for ensuring standardisation of the fistula plug technique. The local PI should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

Chief Radiological Coordinator at each centre

High quality radiological imaging will be an essential component in **FIAT**. It is suggested that each centre should designate one person as Local Radiological Coordinator. This person will be encouraged to attend a trial training day and/or view an on-line presentation on MRI imaging requirements for the study. The radiological coordinator will be responsible for arranging submission of MRI data for centralised evaluation. This person will be sent updates and newsletters, and will be invited to **FIAT** progress and training meetings.

Central coordination: supply of all trial materials, 24-hour randomisation service and data collection and analysis

The **FIAT** Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing collaborating centres with the **FIAT** folders containing trial materials. Additional supplies of any printed material can be obtained on request and can be downloaded from the **FIAT** trial website www.FIAT.bham.ac.uk. The **FIAT** Study Office will assist the local Principal Investigators in obtaining Trust regulatory approval. Patient entry in a centre can start as soon as approval is given and the **FIAT** Study Office has confirmed that the site can open. The **FIAT** Study Office also provides the 24-hour randomisation service and is responsible for collection of data (including reports of serious adverse events thought to be due to trial treatment) and for data analyses.

Clinical Queries

During office hours, the clinical coordinators (see inside front cover for contact details) provide an on-call service for any **clinical** queries about the trial.

Finance

FIAT is funded by the NIHR Health Technology Assessment programme and organised by the Department of Health funded University of Birmingham Clinical Trials Unit. The general structure of the study was designed by the Research and Audit Committee of the Association of Coloproctology of Great Britain and Ireland, and the Birmingham Clinical Trials Unit.

Cost Implications

The **FIAT** trial can offer some financial support to the collaborating hospitals.

Fistula plug supply:

Surgisis® plugs to be used within the trial will be supplied free of charge. Only one fistula plug per patient will be supplied free of charge. The cost of multiple plugs, for example to treat fistula recurrence, will be borne by the participating institution. Immediately prior to site opening, the BCTU will initiate delivery of a small supply of plugs. When plug insertion has been confirmed in a patient allocated to receive the fistula plug, BCTU will arrange for resupply. It is the responsibility of the local PI to ensure that plugs are only used for **FIAT** trial patients.

MRI scans:

Hospitals will be reimbursed for follow-up MRI scans performed either at 12-months or for imaging recurrence after the randomised treatment at the rate of £250 per scan. Reimbursement will be by invoice to the **FIAT** Study Office. Reimbursement will not be available for preoperative scans, which are deemed to be part of routine assessment for patients with transsphincteric fistulae.

Inclusion of patients into **FIAT** should not therefore incur any additional costs for participating hospitals. No additional follow-up visits or investigations are needed other than those that would normally be required for standard patient care.

Indemnity

FIAT was developed by the Research and Audit Committee of the Association of Coloproctology of Great Britain and Ireland and is funded by the Health Technology Assessment programme; the trial is sponsored by the University of Leeds. As it is not an industry-sponsored trial, ABPI guidelines on indemnity do not apply and there are no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity

liability arrangements for clinician initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.

Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of **FIAT** depends on the collaboration of surgeons, radiologists and nurses. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study.

Appendix A – Patient Information Sheet.

Delete this line and then print on Trust headed paper

FIAT – Fistula-In-Ano Trial to compare Surgisis® anal fistula plug versus surgeon's preference for transsphincteric fistula-in-ano.

Patient information Sheet
Version 2.0 24th May 2010

Summary of an Invitation to take part in a research study called FIAT.

- You have an anal fistula (an opening between the back passage and the skin) that needs to be treated with surgery.
- This hospital is taking part in a national research study called **FIAT**, which aims to find out which of several different ways of treating patients with anal fistula is best.
- One group of patients in **FIAT** receive standard surgery, which is one of 3 options: i) the insertion of a special stitch to slowly cut the fistula open ii) an operation to create a flap in the back passage to seal the fistula iii) cutting open the fistula to allow it to grow back with healthy tissue.
- The other group of patients have a new procedure where a "plug" is inserted into the fistula. The plug is made from pig collagen tissue and is believed to help fistulas heal.
- People are allocated to the two groups at random (like tossing a coin) to make sure the two groups are comparable.
- We are inviting you to take part in **FIAT** but you do not have to and if you decide not to this will not affect the quality of your care.
- Please take your time to think about whether you want to take part in the **FIAT** study. More details are provided below and your medical team will be happy to answer any questions.

FIAT – Fistula-In-Ano Trial to compare Surgisis® anal fistula plug versus surgeon's preference for transsphincteric fistula-in-ano.

Patient information Sheet
Version 2.0 24th May 2010

An invitation to take part in a research study called FIAT.

We would like to invite you to take part in a research study called FIAT. Before you decide whether or not you wish to take part in the FIAT study, you need to understand why the research is being done and what it would involve for you.

Part 1 below tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives more detailed information about the conduct of the study.

Please take your time to think about whether you want to take part in the FIAT study, talk to others about the study if you wish and ask us if there is anything that is not clear or if you would like more information.

PART 1

What is an anal fistula?

An anal fistula is an opening next to the back passage, which connects with the anal canal. It may cause an abscess, pain, or discharge from the opening. If left untreated, the symptoms are likely to continue and the fistula may get worse and painful with time.

What are the treatments for anal fistula?

The standard treatment for anal fistula is surgery. Depending on what your surgeon believes is most appropriate for you, standard surgery could be: 1) cutting the fistula open to allow it to grow back with healthy tissue (fistulotomy), 2) closing the fistula by creating a flap of tissue in the back passage which covers the opening to the fistula (advancement flap), or 3) placing a stitch into the fistula to slowly cut through it (cutting seton). Another possibility is to use a fistula plug, which is a relatively new treatment for anal fistula that involves the insertion of a biological material, made from pig collagen, into the fistula to encourage it to heal.

What are the advantages and disadvantages of each treatment?

None of the above operations is a guaranteed cure for your fistula and each may be associated with complications. Current success rates with standard surgery vary between 50 – 80%. If the surgery involves cutting open the fistula (fistulotomy), this will leave an open wound which may take several weeks to heal. If a cutting stitch is used (seton), then further minor operations may be required to

tighten the stitch as it cuts through the fistula. If a flap is used to close the fistula (advancement flap) then there will be a wound inside the back passage that may cause discomfort while it is healing. The main risk with standard surgery for anal fistula is that it can result in a change in continence (leakage or inappropriate passage of faeces from the back passage). This is usually minor in nature, although more serious problems with continence do sometimes occur.

The fistula plug is a simple operation to perform but does require a general anaesthetic. Unlike the standard surgical treatments there is no cutting of the muscle which controls continence, and therefore no risk to continence. However, the fistula plugs are expensive and their ability to heal fistulas is not accurately known. The current success rate is thought to be around 50% to 60%, and may be less than the standard treatments. If the plug fails to heal the fistula, it is likely that standard surgery would then be required. As the fistula plug is made from pig collagen, you should make your doctor aware if you have any cultural or religious objections to the use of pig material. If you are treated with a fistula plug you may experience a slight discharge from the fistula for a few weeks following insertion; this is normal and to be expected whilst the fistula is healing. As the plug is made from a natural collagen material it will dissolve, but this corresponds to the time taken for the fistula to heal, therefore the plug does not need to be removed once it has been put in place. There is a risk of further abscess formation following treatment, but this is the same as that following any treatment for an anal fistula. Some patients develop an allergic reaction to the plug. This can cause a skin rash which does settle on its own. Your healthcare team is trained to detect and treat any reactions that might happen. It is important that you let your surgeon know if you have any allergies or if you have reacted to any drugs or tests in the past.

What is the purpose of the FIAT study?

In order to find out whether, on balance, the fistula plug is better than standard treatments, we are comparing patients treated with the plug with similar patients who have been treated with standard surgery (fistulotomy, advancement flap, cutting seton). We will be assessing the ability of the plug to heal the fistula, any change in continence following treatment, and any change in quality of life as a result of treatment.

Why have I been invited to take part in FIAT?

Your surgeon will have invited you to take part in **FIAT** because you have an anal fistula that requires treatment to improve your symptoms. The **FIAT** study is trying to find out if treatment with the fistula plug is any better than the current standard surgical treatments. The **FIAT** study aims to include at least 500 people like you with anal fistula from hospitals throughout the UK.

Which treatment would I receive if I took part in the FIAT study?

So that we can find out which treatment is best, each person is put into a treatment group randomly (like a lottery). You have an equal chance of being allocated to the fistula plug or surgery groups. Neither you nor your doctor can choose which treatment you will receive. This is essential so that a fair comparison can be made between the different treatment groups. Dividing people into treatment groups in this way is what is called a 'randomised clinical trial' and it is the standard and most reliable way of comparing different treatments.

Do I have to take part?

No. Taking part in research is always voluntary. If you decide to take part you will be still free to withdraw at any time and without giving a reason. If you decide not to take part, then you don't have to give a reason why. Your specialist will be happy to talk through alternative options.

What will happen to me if I decide to take part in FIAT?

Most of the treatment you receive will be the same as you would have received even if you were not in a study. There are no extra clinic visits, blood tests, or operations required beyond your normal care. There is however some additional information that we would need to collect about your treatment and its effects. You will be required to undergo an MRI (magnetic resonance imaging) scan and an examination under anaesthesia (EUA) to assess your fistula; both of these are routine for patients with this type of anal fistula so you would have them whether you were participating in **FIAT** or not. If your fistula is suitable for treatment with a fistula plug, you will be asked to participate in the study and will need to sign a Consent Form if you agree to take part. Your details will then be passed to the **FIAT** Study Office at the University of Birmingham.

You will then have your fistula treated by either standard surgery or insertion of a fistula plug. If you are allocated to standard treatment, it will be a matter for you and your doctor to decide which of the three types of surgery (fistulotomy, advancement flap or cutting seton) is best for you. Once you have had your treatment we will need to collect information about any complications, whether the fistula has healed, any change in continence, and we will ask you to complete a short questionnaire on your quality of life. Most of this information will be collected at routine out-patient appointments, although some information may be collect by means of questionnaires sent by post. All information collected will be strictly confidential in the same way as your other medical records. As part of the study we will ask you to undergo a second MRI scan one year after your operation.

The second MRI scan is not part of routine care and will be performed to determine whether or not the fistula has healed. After that, your progress would be followed-up once a year.

What care will I need after the operation?

You may be referred to your Practice Nurse or a District Nurse following your discharge from hospital. You may require simple pain killers for a few days following your operation. You may be provided with laxatives to help your bowels. If you are treated with a fistula plug you will be asked to refrain from physical exertion for 2 weeks following your operation to avoid accidentally dislodging the plug.

What are the possible benefits from taking part in FIAT?

We cannot promise the study will help you but your participation in the study will provide valuable information on the treatment of anal fistula and this will be used for the benefit of future patients.

There are no direct benefits from participating in the study. It is not clear whether fistula plugs heal fistulas better or worse than conventional treatment; it is one of the aims of the study to find this out. A potential benefit of the fistula plug is that it is not associated with any change in continence.

PART 2

What if new relevant information becomes available?

Sometimes we get new information about the treatments being studied. If this happens, your surgeon will discuss how this affects your care and your participation in the **FIAT** study. Your research doctor might consider you should continue in the study or withdraw. Either way, he/she will explain the reasons and arrange for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form. If the study is stopped for any other reason, your doctor would, again, tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You can decide not to continue with the study follow-up at any time but, if you do, we would still like your data to remain on file and be included in the final study analysis unless you request that they should not be.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If the harm is due to someone's negligence, then you may have grounds for a legal action but you may have to pay for this. Whether or not you take part in the study, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated

during the course of this study, the normal National Health Service complaints mechanisms would be available to you. Taking part in the study would not affect your legal rights.

Will my taking part in the study be kept confidential?

If you decide to take part in **FIAT**, all information collected about you during the course of the trial will be kept strictly confidential in the same way as all of your other medical records. Information about you, your disease and progress will be sent by your doctors to the **FIAT** Study Office at the University of Birmingham Clinical Trials Unit (BCTU), on paper and electronically, where it will be securely stored under the provisions of the 1998 Data Protection Act. This will include a signed copy of your consent form. Your name and address will also be given to dedicated staff at the BCTU when you first enter the study, so that they can send Quality of Life questionnaires to your home address. Your GP, and the other doctors involved in your clinical care, will be notified of your participation in the **FIAT** trial and kept informed of your progress. We may use national records to track your progress, but otherwise all information about you and your treatment will remain confidential.

As we may also contact you by post or telephone to ask you to complete questionnaires asking about your progress, we will ask you to give us your permission to do so. With your permission, your relevant medical records may be inspected by authorised individuals from the BCTU and by the Department of Health (who are funding the study). They may also be looked at by regulatory authorities. The purpose of this is to check that the study is being carried out correctly.

What will happen to the results of the study?

Once the trial has finished we will publish the results in a medical journal so that others can benefit. We will also publicise the results on the trial's website www.FIAT.bham.ac.uk . No individual patients will be identified in any publications. A copy of the published results of the trial will be sent to all patients who have participated in **FIAT**. In line with clinical trial guidelines, at the end of the study, the data will need to be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

Who is organising and funding the research?

The **FIAT** study was developed by the Research and Audit Committee of the Association of Coloproctology of Great Britain and Ireland and is funded by the Heath Technology Assessment programme which is a part of the National Institute for Health Research (NIHR). The study is coordinated by the Clinical Trials Unit at the University of Birmingham and is sponsored by the University of Leeds. The research has been reviewed and approved by all of these organisations. There is no involvement of any companies other than providing the fistula plugs free of charge.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Trent Research Ethics Committee.

Where can I get further information?

If you have any further questions about anal fistula or clinical trials, please discuss them with your doctor or contact the **FIAT** study office at the University of Birmingham Clinical Trials Unit.

The **FIAT** study office is located at the University of Birmingham Clinical Trials Unit, Robert Aitken Institute, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Web address: www.bctu.bham.ac.uk; e-mail: FIAT@contacts.bham.ac.uk.

For any queries about the study or for further information please contact your responsible surgeon:

Name: ……

Tel No: ……

Position: ……

Thank you for your time in considering this study.

Appendix B: Consent Form

Delete this line and then print on Trust headed paper

FIAT trial Number | | | | |

Patient Consent Form

FIAT – Fistula In Ano Trial

Version 2.0 24th May 2010

Please **initial** each box to indicate your consent

1. I confirm that I have read and understood the information sheet for the **FIAT** study (Version 2.0, 24th May 2010) and have had the opportunity to ask questions. ☐
2. I understand that my participation in this study is voluntary and that I may withdraw at any time, without giving a reason, and without my medical and legal rights being affected. ☐
3. I understand that information about me and my progress will be supplied in confidence to the study coordinators at the University of Birmingham Clinical Trials Unit by my own doctors and by central registries for use in the **FIAT** study. ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Clinical Trials Unit at the University of Birmingham, or from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I understand that the study researchers may contact me by telephone, post or email to remind me to complete the questionnaires or to ask me the questions over the telephone and that my address will be passed to the Birmingham CTU for the sole purpose of issuing the trial questionnaires . ☐
6. I understand that my GP will be informed of my participation in the study and may be contacted to provide information about my progress, in confidence, to the central organisers. ☐
7. I understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status. ☐
8. I agree to a copy of my consent form being sent to the central organisers of the **FIAT** study at the Birmingham Clinical Trials Unit. ☐
9. I agree to take part in the above study. ☐

Name of Participant:……..

Signature:…….. Date: Day…..…/Month……../Year……

Name of Clinician:……

Signature:…… Date: Day..……/Month…..…/Year……

Appendix C: GP Letter

Delete this line and then print on Trust headed paper

Dear Dr ……..

Name..... D.o.B..... NHS No.....

Your patient, named above, has been diagnosed with transsphincteric fistula-in-ano. In your patient the fistula involves a substantial proportion of the sphincter which presents a difficult management problem. The current surgical treatments; simple fistulotomy, advancement flap and cutting seton, are tailored to achieve maximal healing rates with minimal compromise of sphincter function but each technique is associated with varying degrees of incontinence.

Recently a bioprosthetic plug made from lyophilized porcine intestinal submucosa has been used as treatment. However, although the plug has been shown to be safe, the evidence on its efficacy and rates of recurrence and healing is limited.

Your patient is suitable for entry to **FIAT**, a UK multi-centre clinical trial to evaluate if the fistula plug can produce relief of symptoms whilst maintaining anal sphincteric function and preserving symptom-specific (incontinence) quality of life. Patients are randomised between the fistula plug and the surgeon's surgery of choice (fistulotomy, advancement flap and cutting seton) termed "surgeon's preference".

FIAT was developed by the Association of Coloproctology of Great Britain & Northern Ireland, it is funded by the Health Technology Assessment programme, which is part of the NIHR, and is coordinated by the University of Birmingham Clinical Trials Unit (addess below) The trial has been approved by Trent Research Ethics Committee.

Your patient has kindly consented to take part in the **FIAT** Trial and has been randomly allocated to:

Anal fistula plug ☐

Surgeon's preference ☐ Type of surgery:_____

I, or another member of the multi-disciplinary team responsible for your patient, will be updating you regularly on progress. If you have any queries about the patient's management, please feel free to contact me. If you require any further information about the study, it can be obtained from the **FIAT** study office (see address below). Please file this letter in the patient's notes. I would appreciate being notified if they are no longer one of your patients.

Yours sincerely

<Consultant Name> ……

FIAT Study Office, University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Edgbaston, Birmingham, B15 2TT

Appendix D: Randomisation Notepad

FIAT – Randomisation notepad. Complete this form then telephone the Randomisation service: **0800 953 0274**
or use the online randomisation at: https://www.trials.bham.ac.uk/FIAT

Part A – Identifying Details

Date of Randomisation Day……/Month……/Year……

Randomising centre:..... Randomising clinician: ……

Patient's full name:……..... Date of Birth: Day……/Month……/Year……

NHS No: ……..... Hospital number:……

Part B – Pre-randomisation investigations

1. Has the patient had a baseline MRI scan within the last 6 months? Yes ☐ No ■
2. a. Has the patient had an EUA? Yes ☐ No ■
   b. Has a draining seton been inserted? Yes ☐ No ■
   c. Date of insertion of draining seton (must be more than 6 weeks) Day……/Month……/Year……
3. Does the patient have a high transsphincteric fistula? Yes ☐ No ■

Part C – Eligibility checklist

4. Is the fistula ≥ 2cm in length? Yes ☐ No ■
5. Does the fistula have a cryptoglandular aetiology? Yes ☐ No ■
6. Would surgery with fistulotomy carry a significant risk of incontinence (i.e. involving 1/3 or more of the external anal sphincter?) Yes ☐ No ■
7. Does the patient have any contraindications to general anaesthesia? Yes ■ No ☐
8. Is there evidence of active perianal sepsis? Yes ■ No ☐
9. Any other perineal fistulae present, e.g. pouch-vaginal, rectovaginal? Yes ■ No ☐
10. Does the patient have any objection to the use of pig tissue? Yes ■ No ☐
11. Does the patient have an absolute contraindication to MRI? Yes ■ No ☐

*If shaded boxes are ticked, patient **not eligible** for* **FIAT**

12. What is the patient's ASA grade?
    - ☐ P1 Normal healthy patient
    - ☐ P2 Mild systemic disease
    - ☐ P3 Severe systemic disease
    - ☐ P4 Severe life-threatening systemic disease
    - ■ P5 Not expected to survive without the operation
13. What is the patient's St Mark's incontinence score (from 0 to 24)? _____
    (Guidance to work out score will be on reverse of randomisation notepad)
15. Has the patient given written informed consent? Yes ☐ No ■
16. Which version of the consent form was used? _____
17. Name of the **clinician** taking written informed consent? _____

Part D – Randomisation – Treatment allocation

18. If allocated surgery which would be performed?
    - Advancement flap ☐
    - Fistulotomy ☐
    - Cutting seton ☐
19. The patient has been randomised to receive:
    - Surgery ☐
    - Surgisis® anal fistula plug insertion ☐

FIAT trial number |_|_|_|_|

Please return this form within 1 week of entry into the trial to: **FIAT** Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Version 1.0 15th April 2010

The FIAT Trial
BASELINE DATA FORM

Part A – Patient Demographics

Forename:……		Surname: ……
Date of Birth: ……/……/19……		NHS Number :……
Sex: (please circle) Male / Female	Height:……	Weight:……
Patient Address: …… ……		

Part B – Baseline Data

COMORBIDITY

Does the patient have diabetes? Yes ☐ No ☐ Is the patient a smoker? Yes ☐ No ☐

Does the patient have renal failure? Yes ☐ No ☐

Does the patient take steroids/immunosuppressant medication? Yes ☐ No ☐

If yes, please provide details:……

FISTULA HISTORY - PRESENTATION

Acute sepsis/Absess: Yes ☐ No ☐ Chronic sepsis/fistula: Yes ☐ No ☐

Other? Yes ☐ No ☐ If yes, please provide details:……

FISTULA HISTORY - PREVIOUS PERIANAL SEPSIS FISTULA

Is this the first perianal abscess/fistula? Yes ☐ No ☐

Is it a recurrent perianal abscess/fistula? Yes ☐ No ☐

Has the patient had previous fistula surgery? Yes ☐ No ☐ Number of previous interventions ……

If yes, please choose from the following options: a/ Previous seton? Yes ☐ No ☐

b/ Previous fistulotomy? Yes ☐ No ☐ c/ Previous advancement flap? Yes ☐ No ☐

d/ Previous fistula plug? Yes ☐ No ☐ e/ Other previous fistula surgery? Yes ☐ No ☐

If other, please provide details:……

Previous anorectal surgery? Yes ☐ No ☐ If yes, please provide details:……

……

ST MARKS INCONTINENCE SCORE

Incontinence for solid stools?	Never	Yes ☐ (score 0)	Rarely	Yes ☐ (score 1)
	Sometimes	Yes ☐ (score 2)	Weekly	Yes ☐ (score 3)
	Daily	Yes ☐ (score 4)		
Incontinence for liquid stools?	Never	Yes ☐ (score 0)	Rarely	Yes ☐ (score 1)
	Sometimes	Yes ☐ (score 2)	Weekly	Yes ☐ (score 3)
	Daily	Yes ☐ (score 0)		
Incontinence for gas?	Never	Yes ☐ (score 0)	Rarely	Yes ☐ (score 1)
	Sometimes	Yes ☐ (score 2)	Weekly	Yes ☐ (score 3)
	Daily	Yes ☐ (score 0)		

Appendix E: Baseline Data Form

Alternation in lifestyle?	Never	Yes ☐(score 0)	Rarely	Yes ☐(score 1)
	Sometimes	Yes ☐(score 2)	Weekly	Yes ☐(score 3)
	Daily	Yes ☐(score 0)		
Need to wear a pad or plug?		No ☐(score 0)		Yes ☐(score 2)
Taking constipation medicine?		No ☐(score 0)		Yes ☐(score 2)
Lack of ability to defer defecation for 15 mins?		No ☐(score 0)		Yes ☐(score 2)

TOTAL SCORE (sum): ……..

Part C – Baseline EUA

Date of EUA:……../……/20…….

Fistula classification according to Parks:

Transsphincteric? Yes ☐ No ☐

Site of internal opening (according to position on a clockface): ……..

Site of external opening (according to position on a clockface): ……..

Length of primary tract: ……..cm

Level of internal opening in relation to dentate line: Below ☐ At ☐ Above ☐

Extent of external sphincter involvement: <1/3 Yes ☐ >1/3 Yes ☐

Secondary tracts: Yes ☐ No ☐ If yes, number of secondary tracts: ……

Supralevator extensions? Yes ☐ No ☐ Horseshoe extensions? Yes ☐ No ☐

Active sepsis/abscess? Yes ☐ No ☐ If yes, please provide details:……

……

If yes, was drainage performed? Yes ☐ No ☐

Was a seton inserted? Yes ☐ No ☐ Seton material used:……

Please provide details:……

Additional procedures performed: Yes ☐ No ☐ If yes, please provide details:……

……

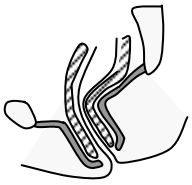
Any incidental findings? Yes ☐ No ☐ If yes, please provide details:……

……

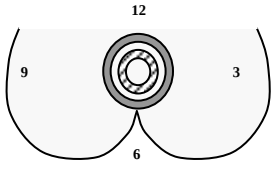
Any complications? Yes ☐ No ☐ If yes, please provide details:……

……

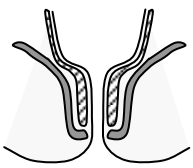
PART D – Diagrammatic Summary:



Sagittal Diagram.
Draw path of fistula and extensions.



External and Internal Opening(s).
Mark <u>each</u> with a <u>separate</u> cross.



Coronal.
Draw the path of the fistula with an unbroken black line.

Please return this form to: **FIAT** Study Office, The University of Birmingham, Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Appendix F: Baseline Radiology MRI Form

The FIAT Trial
BASELINE RADIOLOGY MRI FORM

Part A – Identifying Details

Patient Forename:…… **FIAT** Trial No:…… Hospital:……..

Patient Surname:…….. Hospital No:…….. Consultant Radiologist:……

D.O.B (dd-mon-yyyy) ……/……/19…….. NHS No:…… Consultant Surgeon:……

Radiology Reference Number……. Radiology Report Date ……/……/20……..

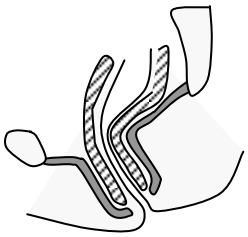
Part B - Fistula Location and Characterisation (define according to position on clock face)

Are findings from EUA known? Yes☐ No ☐

Number of fistula	**1**		
Internal opening (Clock position):			
External opening (Clock position):			
Seton present in track?	Yes☐	No☐	Cant identify ☐
Fistula type: Choose one from the following - is it? Superficial Intersphincteric Transsphincteric Supralevator Extrasphincteric Blind Sinus	☐ ☐ ☐ ☐ ☐ ☐		
Are extensions* present: *defined as an area of sepsis branching away from the primary fistula track (includes horseshoe extensions and blind ending sinus tracks)	Yes☐ No☐ If yes, total number of extensions:		
Location of extension:		Number	
Intersphincteric	☐		
Ischioanal fossa	☐		
Supralevator	☐		

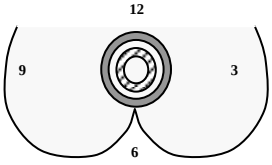
DIAGRAMMATIC SUMMARY:

Sagittal Diagram



Draw path of fistula and extensions.

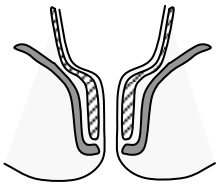
Position of external and internal openings



Mark each with a separate cross

Fistula tracks and collections

Coronal.



Draw the path of the fistula with an unbroken black line.

Version 1.0 15th April 2010

Appendix F: Baseline Radiology MRI Form

IMPORTANT INCIDENTAL FINDINGS:

_____

_____

_____

Is the MRI scan concordant with the EUA findings? Yes☐ No ☐ Don't know ☐
Does MRI depict additional findings vs. EUA? Yes☐ No ☐ Don't know ☐

Part C – MRI parameters

Imaging sequences acquired in axial and coronal plane: Yes☐ No ☐

Inclined to anal canal: Yes☐ No ☐

Additional plane(s) acquired: Yes☐ No ☐

MRI sequences performed: STIR ☐ Fat Suppressed T2 ☐
SPIR/SPARE ☐ Post Gad T1 ☐

Slice thickness (mm):……..

Part D – Confirmation of inclusion criteria

One discrete fistula is present Yes☐ No ■

MRI consistent with transsphicteric fistula involving >1/3 external anal sphincter muscle and fistula tract >2cms in length Yes☐ No ■

No undrained sepsis present (fluid in fistula or in extensions)? Yes☐ No ■

Consistent with cryptoglandular origin? Yes☐ No ■

If not consistent, what is it? Pilonidal ☐ Crohns ☐ Other ☐

If a shaded box is ticked discuss with surgeon regarding FIAT trial eligibility.

Please return this form to: **FIAT** Study Office, The University of Birmingham, Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Appendix G: 6-Week Cost Collection Form

The FIAT Trial
6-Week Cost Collection Form
(PLEASE ANSWER ALL QUESTIONS).

Patient Forename:…… **FIAT** Trial No:……

Patient Surname:…… D.O.B (dd-mon-yyyy) ……/……/19……

Please think about how your health has changed since your treatment began.

1. Your health since discharge (about 6 weeks ago).

Have you had to take any time off work because of your fistula (or complications) since your discharge from hospital? Y ☐ N ☐

→ If yes, how long were you off sick? **…….Days**

Do you feel your health is back to where it was before your operation? Yes ☐ No ☐

Do you feel you are able to enjoy your usual activities now? Yes ☐ No ☐

→ If yes, when were you first able to enjoy your usual activities after treatment? **…….Weeks**

Please think about your recent contact with the NHS.
If you are unsure about anything then please write in your best guess.

2. Who have you seen since discharge?

Other than at the fistula clinic, who else have you seen in the NHS about your fistula or any other complications resulting from your treatment:

			How many times since your discharge?
Your GP	Yes ☐	No ☐	_____
A nurse at the GP's surgery	Yes ☐	No ☐	_____
A district nurse at your house (to change dressings)	Yes ☐	No ☐	_____
A district nurse at your house (for any other reason)	Yes ☐	No ☐	_____
Walk in centres	Yes ☐	No ☐	_____
Accident and emergency	Yes ☐	No ☐	_____

If you have seen anyone else for your fistula who isn't listed above (e.g. a dietician), then please tell us about it below:

_____

_____

_____

_____

3. What treatments have you received since your discharge?

Since you were discharged from hospital, you may have received a prescription for your fistula or for any complications you have had after your treatment. This might be medication (such as antibiotics), could be something to help manage a problem with controlling your bowels (such as absorbent pads), or might be something else entirely.

Have you been given a prescription by the fistula clinic? Yes ☐ No ☐
(We won't ask anything more about this because we can ask the clinic about this.)

Have you been given a prescription by anyone else in the NHS? Yes ☐ No ☐

What were you prescribed?	How long did you use it for? How often?

Have you paid for anything else out of your own pocket? Yes ☐ No ☐

What did you buy?	How much did it cost you?

Thank-you for taking the time to complete this form.
Please return this form to your surgeon, who will send it on to:

FIAT Study Office, University of Birmingham Clinical Trials Unit,
FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Edgbaston,
Birmingham, B15 2TT

Appendix H: Intra-Operative Form

The FIAT Trial
INTRAOPERATIVE FORM

Part A – Identifying Details

Patient Forename:…….. **FIAT** Trial No:…… Hospital:……

Patient Surname:…… Hospital No:…… Consultant Radiologist:……

D.O.B (dd-mon-yyyy) ……/……/19……. NHS No:…… Consultant Surgeon:……

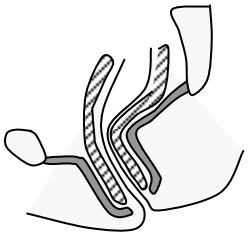
Date of Admission: ……/……/20……. Date of Surgery: ……/……/20…….

Part B - Fistula Classification

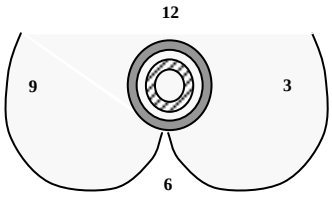
Is the seton still in situ? Y ☐ N ☐ Date seton **put in**: ……/……/20…….

Date seton **taken/came out**: ……/……/20……. (If applicable). Number of Fistulae:……

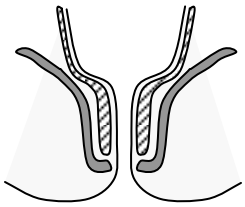
Classification according to Parks:	**FISTULA 1**		
Transphincteric	Yes ☐ No ☐		
Site of internal opening (position on clock face)			
Site of external opening (position on clock face)			
Length of primary tract	cm		
Level of internal opening in relation to dentate line	Below ☐	At ☐	Above ☐
Extent of external sphincter involvement	<1/3 ☐ >1/3 ☐		
Secondary tracts	Yes ☐ No ☐ If Yes, number:……..		
Supralevator extension	Yes ☐ No ☐		
Horse-shoe extensions	Yes ☐ No ☐		
Active sepsis/abscess If yes, please provide details:	Yes ☐ No ☐		
Drainage of abscess performed	Yes ☐ No ☐		
Incidental findings			
Coexistent pathology			



Saggital Diagram
Draw path of the fistula and extensions.



External and Internal Opening(s)
Mark each with a separate cross.



Coronal
Draw the path of the fistula with an unbroken black line.

Appendix H: Intra-Operative Form

Part C – For ALL surgery

Length of operation: ……..mins Intraoperative complications: Yes ☐ No ☐

If yes, details: ……

……

Was the baseline MRI scan useful as a guide to surgery? Very ☐ Somewhat ☐ Slightly ☐ Not at all ☐

Did the baseline MRI scan alter your surgical approach? Yes - major ☐ Yes - minor ☐ No ☐

Did you review the MRI report prior to surgery? Yes ☐ No ☐

Did you review the MRI images prior to surgery? Yes ☐ No ☐

Operation performed:

Fistula Plug	Yes ☐	No ☐	Please complete part D.
Cutting Seton	Yes ☐	No ☐	Please complete part E.
Fistulotomy	Yes ☐	No ☐	Please complete part F.
Advancement Flap	Yes ☐	No ☐	Please complete part G.

Part D – Fistula Plug

Perioperative antibiotics given: Yes ☐ No ☐

Bowel preparation given: Yes ☐ No ☐ → If Yes, what type: Enema Yes ☐ No ☐

Oral prep Yes ☐ No ☐

Type of fistula tract preparation:

Curetted with Cook fistula brush Yes ☐ No ☐

Tract irrigated Yes ☐ No ☐

If Tract irrigated: Saline Yes ☐ No ☐ Hydrogen Peroxide Yes ☐ No ☐

Other tract preparation: Yes ☐ No ☐ → Details:……

Length of fistula plug inserted: ……cm

Suture fixation at internal opening: Yes ☐ No ☐ External opening enlarged: Yes ☐ No ☐

Mucosal flap to cover internal opening/plug: Yes ☐ No ☐ Other procedure: Yes ☐ No ☐

If other procedure, details:……

Part E – Cutting Seton

Perioperative antibiotics given: Yes ☐ No ☐

Bowel preparation given: Yes ☐ No ☐ → If Yes, what type: Enema Yes ☐ No ☐

Oral prep Yes ☐ No ☐

Suture material used: ……

Cutaneous component laid open: Yes ☐ No ☐ Other procedure: Yes ☐ No ☐

If other procedure, details:……

Part F – Fistulotomy

Perioperative antibiotics given: Yes ☐ No ☐

Bowel preparation given: Yes ☐ No ☐ → If Yes, what type: Enema Yes ☐ No ☐

Oral prep Yes ☐ No ☐

Proportion of external sphincter divided: <1/2 ☐ >1/2 ☐ Wound marsupialised: Yes ☐ No ☐

Other procedure: Yes ☐ No ☐

If other procedure, details:……

Part G – Advancement Flap

Perioperative antibiotics given: Yes ☐ No ☐

Bowel preparation given: Yes ☐ No ☐ → If Yes, what type: Enema Yes ☐ No ☐

Oral prep Yes ☐ No ☐

Type of flap: Rectal mucosal flap Yes ☐ No ☐ Anodermal flap Yes ☐ No ☐

Internal opening sutured closed: Yes ☐ No ☐ External tract laid open Yes ☐ No ☐

Other procedure: Yes ☐ No ☐

If other procedure, details:……

Please return this form to: **FIAT** Study Office, The University of Birmingham, Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Appendix I: 6-Week Postoperative Form

The FIAT Trial
6- WEEK POSTOPERATIVE FORM

Part A – Identifying Details

Patient Forename:…….. **FIAT** Trial No:…… Hospital:……

Patient Surname:…… Hospital No:…… Consultant Radiologist:……

D.O.B (dd-mon-yyyy) ……/……/19……. NHS No:…… Consultant Surgeon:……

Date of follow-up visit: ……../……../…… (dd) (mon) (yyyy)

1. Evidence of fistula healing*: Is the patient symptom free? Yes ☐ No ☐

If No, please give details: ……..

Is there ongoing perianal sepsis/drainage Yes ☐ No ☐

Is the internal opening closed? Yes ☐ No ☐ Unable to assess ☐

Is the external opening closed? Yes ☐ No ☐

Has the fistula healed? Yes ☐ No ☐

(*Fistula healing defined as: No evidence of ongoing sepsis or discharge & closed internal and external openings).

2. General Complications: Were there any postoperative complications? Yes ☐ No ☐ If Yes, were they:

Bleeding: Yes ☐ No ☐

If Yes, was a transfusion required? Yes ☐ No ☐ → If Yes, no. of units transfused:……...

Was re-intervention required? Yes ☐ No ☐ → If Yes, please give details:……..

……

Unexplained pain: Yes ☐ No ☐

If Yes, was intervention required? Yes ☐ No ☐ → If Yes, please give details:……

……

Septic event: Yes ☐ No ☐ → If Yes, please give details:……

……..

Was re-intervention required for this? Yes ☐ No ☐ → If Yes, please give details:……

……

Other: Yes ☐ No ☐ → If Yes, please give details: ……

……

3. Specific Complications: Has the patient had:

Cutting Seton patients only: Seton extrusion? Yes ☐ No ☐

→ If yes, date of extrusion:……/……/20……..

Plug patients only: Fistula plug extrusion? Yes ☐ No ☐

→ If yes, date of extrusion:……/……/20……..

Fistulotomy patients only: Wound related problems? Yes ☐ No ☐

→ If yes, please give details:……

Advancement flap patients only. Flap dehiscence? Yes ☐ No ☐

→ If yes, please give details:……

Other specific complications? Yes ☐ No ☐

→ If yes, please give details:……

4. Other Re-Intervention Since Discharge: Has the patient had other interventions? Yes ☐ No ☐

→ If yes, please give details:……

Did the patient require a hospital stay? Yes ☐ No ☐ If yes, for how long? _____days

5. What is the patient's St Mark's incontinence score (from 0 to 24)? _____

Name of person completing form:……**Tel No**……

Date form completed: ……../……/20……

Please return this form to: **FIAT** Study Office, The University of Birmingham, Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Appendix J: 6-Month Follow-Up Form

The FIAT Trial
6- MONTH FOLLOW-UP FORM

Part A – Identifying Details

Patient Forename:…….. **FIAT** Trial No:…… Hospital:……

Patient Surname:…… Hospital No:…… Consultant Radiologist:……

D.O.B (dd-mon-yyyy) ……/……/19……. NHS No:…… Consultant Surgeon:……

Date of follow-up visit: ……../……../…… (dd) (mon) (yyyy)

1. Evidence of fistula healing*: Is the patient symptom free? Yes ☐ No ☐

If No, please give details: ……..

Is there ongoing perianal sepsis/drainage Yes ☐ No ☐

Is the internal opening closed? Yes ☐ No ☐ Unable to assess ☐

Is the external opening closed? Yes ☐ No ☐

Has the fistula healed? Yes ☐ No ☐

(*Fistula healing defined as: No evidence of ongoing sepsis or discharge & closed internal and external openings).

2. General Complications: Were there any postoperative complications? Yes ☐ No ☐ If Yes, were they:

Bleeding: Yes ☐ No ☐

If Yes, was a transfusion required? Yes ☐ No ☐ → If Yes, no. of units transfused:……...

Was re-intervention required? Yes ☐ No ☐ → If Yes, please give details:……

……

Unexplained pain: Yes ☐ No ☐

If Yes, was intervention required? Yes ☐ No ☐ → If Yes, please give details:……

……

Septic event: Yes ☐ No ☐ → If Yes, please give details:……

……

Was re-intervention required for this? Yes ☐ No ☐ → If Yes, please give details:……

……

Other: Yes ☐ No ☐ → If Yes, please give details: ……

……

3. Other Events: Has the patient had:

Cutting Seton patients only: Is the seton in situ? Yes ☐ No ☐

→ If No, please state the date the seton was removed/came out: ……../……../……

Plug patients only: Is there ongoing serous discharge? Yes ☐ No ☐

→ If No, please state the date the discharged stopped: ……../……../……

Fistulotomy patients only: Wound related problems? Yes ☐ No ☐

→ If yes, please give details:……

Advancement flap patients only. Flap related problems? Yes ☐ No ☐

→ If yes, please give details:……

Other specific events? Yes ☐ No ☐

→ If yes, please give details:……

4. Other Re-Intervention Since 6-week follow-up: Has the patient had other interventions? Yes ☐ No ☐

→ If yes, please give details:……

Did the patient require a hospital stay? Yes ☐ No ☐ If yes, for how long? _____days

5. What is the patient's St Mark's incontinence score (from 0 to 24)? _____

Name of person completing form:……**Tel No**……

Date form completed: ……/……/20……

Please return this form to: **FIAT** Study Office, The University of Birmingham, Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Appendix K: 6-Month Cost Collection Form

The FIAT Trial
6-Month Cost Collection Form
(PLEASE ANSWER ALL QUESTIONS)

Patient Forename:…… **FIAT** Trial No:……

Patient Surname:…… D.O.B (dd-mon-yyyy) ……/……/19……

Please think about how your health has changed since your treatment began.

1. Your health since you last filled in this form (about 6 months ago).

Have you had to take any time off work because of your fistula (or complications) since six weeks after your discharge from hospital? Yes ☐ No ☐

→ If yes, how long were you off sick? **…….Days**

Do you feel your health is back to where it was before your fistula? Yes ☐ No ☐

Do you feel you are able to enjoy your usual activities now? Yes ☐ No ☐

→ If yes, when were you first able to enjoy your usual activities after treatment? **…….Weeks**

Please think about your recent contact with the NHS.
If you are unsure about anything then please write in your best guess.

2. **Who have you seen recently?**

Other than at the fistula clinic, who else have you seen in the NHS about your fistula or any other complications resulting from your treatment from six weeks after discharge until now:

			How many times since six weeks after discharge?
Your GP	Yes ☐	No ☐	_____
A nurse at the GP's surgery	Yes ☐	No ☐	_____
A district nurse at your house (to change dressings)	Yes ☐	No ☐	_____
A district nurse at your house (for any other reason)	Yes ☐	No ☐	_____
Walk in centres	Yes ☐	No ☐	_____
Accident and emergency	Yes ☐	No ☐	_____

If you have seen anyone else for your fistula who isn't listed above (e.g. a dietician), then please tell us about it below:

_____

_____

_____

_____

3. What treatments have you received?

In the time since you last filled in this form (approximately six weeks after discharge) you may have received a prescription for your fistula or for any complications you have had after your treatment. This might be medication (such as antibiotics), could be something to help manage a problem with controlling your bowels (such as absorbent pads), or might be something else entirely.

Have you been given a prescription by the fistula clinic from six weeks after discharge until now?
(We won't ask anything more about this because we can ask the clinic about this.) Yes ☐ No ☐

Have you been given a prescription by anyone else in the NHS from six weeks after discharge until now?
Yes ☐ No ☐

What were you prescribed?	How long did you use it for? How often?

Have you paid for anything else out of your own pocket from six weeks after discharge until now?
Yes ☐ No ☐

What did you buy?	How much did it cost you?

Thank-you for taking the time to complete this form.
Please return this form to your surgeon, who will send it on to:

FIAT Study Office, University of Birmingham Clinical Trials Unit,
FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Edgbaston,
Birmingham, B15 2TT

Appendix L: 12-Month Follow-Up Form

The FIAT Trial
12- MONTH FOLLOW-UP FORM

Part A – Identifying Details

Patient Forename:…….. **FIAT** Trial No:…… Hospital:……

Patient Surname:…….. Hospital No:…… Consultant Radiologist:……

D.O.B (dd-mon-yyyy) ……/……/19……. NHS No:…….. Consultant Surgeon:……

Date of follow-up visit: **……../……../……**

1. Evidence of fistula healing*: Is the patient symptom free? Yes ☐ No ☐

If No, please give details: ……..

Is there ongoing perianal sepsis/drainage Yes ☐ No ☐

Is the internal opening closed? Yes ☐ No ☐ Unable to assess ☐

Is the external opening closed? Yes ☐ No ☐

Has the fistula healed? Yes ☐ No ☐

(*Fistula healing defined as: No evidence of ongoing sepsis or discharge & closed internal and external openings).

2. General Complications: Has there been any further complications since 6 month follow-up? Yes ☐ No ☐

If Yes, were they:

Bleeding: Yes ☐ No ☐

If Yes, was a transfusion required? Yes ☐ No ☐ → If Yes, no. of units transfused:……..

Was re-intervention required? Yes ☐ No ☐ → If Yes, please give details:……

……

Unexplained pain: Yes ☐ No ☐

If Yes, was intervention required? Yes ☐ No ☐ → If Yes, please give details:……

……

Septic event: Yes ☐ No ☐ → If Yes, please give details:……

……..

Was re-intervention required for this? Yes ☐ No ☐ → If Yes, please give details:……

……

Other: Yes ☐ No ☐ → If Yes, please give details: ……

……..

3. Other Events: Has the patient had:

Cutting Seton patients only: Is the seton in situ? Yes ☐ No ☐

→ If No, please state when the seton was removed/came out: ……../……../20…..

Plug patients only: Is there ongoing serous discharge? Yes ☐ No ☐

→ If No, please state when the discharged stopped: ……../……../20……

Fistulotomy patients only: Wound related problems? Yes ☐ No ☐

→ If yes, please give details:……..

Advancement flap patients only. Flap related problems? Yes ☐ No ☐

→ If yes, please give details:……

Other specific complications? Yes ☐ No ☐

→ If yes, please give details:……..

4. Other Re-Intervention Since 6-month follow-up: Has the patient had other interventions? Yes ☐ No ☐

→ If yes, please give details:……

Did the patient require a hospital stay? Yes ☐ No ☐ If yes, for how long? _____days

5. What is the patient's St Mark's incontinence score (from 0 to 24)? _____

Name of person completing form:……**Tel No**……

Date form completed: ……../……../20……

Please return this form to: FIAT Study Office, The University of Birmingham, Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

Appendix M: 12-Month Cost Collection Form

The FIAT Trial
12-Month Cost Collection Form
(PLEASE ANSWER ALL QUESTIONS)

Patient Forename:…… **FIAT** Trial No:……

Patient Surname:…… D.O.B (dd-mon-yyyy) ……/……/19……

Please think about how your health has changed since your treatment began.

1. Your health since the last time you filled in this form (6 months ago).

Have you had to take any time off work because of your fistula (or complications) in the past six months? Yes ☐ No ☐

→ If yes, how long were you off sick? **……Days**

Do you feel your health is back to where it was before your operation? Yes ☐ No ☐

Do you feel you are able to enjoy your usual activities now? Yes ☐ No ☐

→ If yes, when were you first able to enjoy your usual activities after treatment? **……Weeks**

Please think about your recent contact with the NHS since you last filled in this form.
If you are unsure about anything then please write in your best guess.

2. **Who have you seen since recently?**

Other than at the fistula clinic, who else have you seen in the NHS about your fistula or any other complications resulting from your treatment in the past six months:

			How many times in the past six months?
Your GP	Yes ☐	No ☐	_____
A nurse at the GP's surgery	Yes ☐	No ☐	_____
A district nurse at your house (to change dressings)	Yes ☐	No ☐	_____
A district nurse at your house (for any other reason)	Yes ☐	No ☐	_____
Walk in centres	Yes ☐	No ☐	_____
Accident and emergency	Yes ☐	No ☐	_____

If you have seen anyone else for your fistula who isn't listed above (e.g. a dietician), then please tell us about it below:

_____

_____

_____

_____

Appendix M: 12-Month Cost Collection Form

3. What treatments have you received since the last time you filled in this form 6-months ago?
In the last time since you filled in this form (approximately six months after discharge) you may have received a prescription for your fistula or for any complications you have had after your treatment. This might be medication (such as antibiotics), could be something to help manage a problem with controlling your bowels (such as absorbent pads), or might be something else entirely.

Have you been given a prescription by the fistula clinic in the past six months? Yes ☐ No ☐
(We won't ask anything more about this because we can ask the clinic about this.)

Have you been given a prescription by anyone else in the NHS in the past six months? Yes ☐ No ☐

What were you prescribed?	How long did you use it for? How often?

Have you paid for anything else out of your own pocket in the past six months? Yes ☐ No ☐

What did you buy?	How much did it cost you?

Thank-you for taking the time to complete this form.
Please return this form to your surgeon, who will send it on to:

FIAT Study Office, University of Birmingham Clinical Trials Unit,
FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Edgbaston,
Birmingham, B15 2TT

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Appendix N: 12-Month Radiology MRI Form

The FIAT Trial

FOLLOW UP RADIOLOGY MRI FORM

(EITHER CLINICAL RELAPSE OR 12-MONTH FOLLOW UP)

Part A – Identifying Details

Patient Forename:…… **FIAT** Trial No:…… Hospital:……..

Patient Surname:…….. Hospital No:…….. Consultant Radiologist:……

D.O.B (dd-mon-yyyy) ……/……/19…….. NHS No:…… Consultant Surgeon:……

Radiology Reference Number…… Radiology Report Date ……/……/20……..

Part B - Fistula Location and Characterisation (define according to position on clock face)

1. Please select: MRI performed for routine 12-month follow up Yes☐ No☐
   MRI performed for clinical relapse Yes☐ No☐
2. Is this interpretation compared with the pre-treatment MRI scan? Yes☐ No☐
3. Is no abnormality present or residual fibrosis only? Yes☐ No☐ (If Yes, proceed to part C)
4. Is this a new fistula? Yes☐ No☐ If Yes, complete the rest of part B and C.
   If No, is this a recurrent fistula? Yes☐ No☐
   (If Yes, complete the rest of part B and part C).

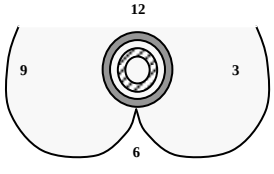
Number of fistula	**1**		
Internal opening (Clock position):			
External opening (Clock position):			
Seton present in track?	Yes☐	No☐	Cant identify ☐
Fistula type: Choose <u>one</u> from the following - is it? Superficial Intersphincteric Transsphincteric Supralevator Extrasphincteric Blind Sinus	☐ ☐ ☐ ☐ ☐ ☐		
Are extensions* present: *defined as an area of sepsis branching away from the primary fistula track (includes horseshoe extensions and blind ending sinus tracks)	Yes☐ No☐ If yes, total number of extensions:…….		
Location of extension: Intersphincteric Ischioanal fossa Supralevator	☐ ☐ ☐	<u>Number</u>	

<u>DIAGRAMMATIC SUMMARY</u>:

<u>Sagittal Diagram</u>

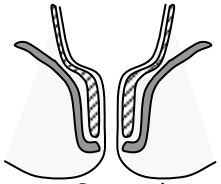
Draw path of fistula and extensions.

<u>Internal and External Opening(s)</u>



Mark <u>each</u> with a <u>separate</u> cross

<u>Fistula tracks and collections:</u>



Coronal.

Draw the path of the fistula with an unbroken black line.

Appendix N: 12-Month Radiology MRI Form

IMPORTANT INCIDENTAL FINDINGS:

_____

_____

_____

Part C – MRI parameters

Imaging sequences acquired in axial and coronal plane: Yes☐ No ☐
Inclined to anal canal: Yes☐ No ☐
Additional plane(s) acquired: Yes☐ No ☐

MRI sequences performed: STIR ☐ Fat Suppressed T2 ☐
SPIR/SPARE ☐ Post Gad T1 ☐

Slice thickness (mm):……..

Part D

Has the original fistula healed? Yes☐ No ☐
Has the fistula recurred? Yes☐ No ☐

Please return this form to: **FIAT** Study Office, The University of Birmingham, Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

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Appendix O: SAE Form

The FIAT Trial
SERIOUS ADVERSE EVENT FORM

Please report immediately any SERIOUS ADVERSE EVENTS (see protocol page 14 for definition and expected SAEs within the trial) by completing all of the details below and faxing this form to the FIAT Trial Office on +44 121 415 8871. *Causality and expectedness MUST be assigned to the SAE – this can only be done by a clinician.*

Patient identification

Full Name: …… DOB: ……/……/……

Hospital Name: …… Hospital No:……

Responsible Surgeon: …… FIAT Trial No: ……

SAE description

Date of Surgery ……/……/…… Date Event started……/……/……

Date event ceased……/……/……

Outcome: Fatal ☐ Recovered ☐ Continuing ☐

Details of Adverse Event (please attach copies of relevant reports)……

……

……

……

Please describe final outcome if event continuing at time of faxing initial report……

……

……

……

Was the event life threatening? Yes ☐ No ☐

Was the event fatal? Yes ☐ No ☐ If Yes, Date of Death: ……/……/……

Did the event require or prolong hospitalisation? Yes ☐ No ☐ If 'Yes', how many days? ……

Do you consider the SAE to be: ☐ Definitely related to trial ☐ Probably related to trial

☐ Possibly related to trial ☐ Probably not related to trial

Please give reasons if you consider the event to be treatment-related: …… ….

……

……

Was the SAE **unexpected**? Unexpected ☐ Expected ☐

Name of Reporting Clinician:…… Telephone number: ……

Position: ……

Signature:…… Today's Date:……

For BCTU use only

Date reported to BCTU: ……/……/…… Date reported to CI: ……/……/……

CI comments: ……

……

Date due to be reported to MREC: ……/……/……

When you have faxed the form, please then send this form (with copies of any relevant reports) to the FIAT Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham B15 2TT

Appendix P: Data Collection & Clinical Follow-Up

i) Baseline data collection:

A baseline case report form [Appendix E] will collect data on:

- Patient demographics (name, date of birth, sex, height, weight)
- Co-morbidity (e.g. diabetes, renal failure, cigarette smoking, relevant medication such as steroid use etc.)
- Mode of presentation (acute abscess, fistula, recurrent perianal sepsis or fistula)
- Fistula history (previous abscess/fistulae, previous fistula surgery)
- Previous anorectal surgery

Baseline generic and symptom-specific QoL data will be collected [Appendix Q].

A baseline CRF [Appendix E] will collect data on:

- Fistula classification according to Parks [25]
- Site of internal and external openings
- Height of internal opening in relation to the dentate line and extent of incorporation of the external sphincter complex
- Length of primary fistula tract
- Presence of secondary tracts & horse-shoe extensions
- Active sepsis/abscess
- Co-existent anorectal pathology including haemorrhoidal disease
- Details of seton insertion

A baseline Radiology MRI CRF [Appendix F] will collect data on:

- Fistula classification according to Parks [24]
- Site of internal and external openings
- Assessment of the extent of incorporation of the external sphincter complex
- Presence of extensions (secondary tracts & horse-shoe extensions)
- Presence of undrained collections
- Co-existent anorectal pathology including haemorrhoidal disease

ii) Operative data collection

An intraoperative CRF [Appendix H] will collect data on:

- Date of admission
- Date of surgery
- Length of time seton has been in situ
- Fistula classification according to Parks [25]
- Site of internal and external openings
- Height of internal opening in relation to the dentate line and extent of incorporation of the external sphincter complex
- Length of primary fistula tract
- Presence of secondary tracts & horse-shoe extensions
- Active sepsis/abscess
- Co-existent anorectal pathology including haemorrhoidal disease
- Whether the baseline MRI scan was of value in guiding surgery
- Date of baseline MRI scan in relation to the timing of surgery
- Details of operative intervention performed (fistula plug, cutting seton, fistulotomy, advancement flap)
- Details of any intraoperative complications
- Length of time of operation

iii) Postoperative data collection

A postoperative CRF [Appendix I] will collect data on:

- Use of postoperative analgesia
- Postoperative complications (also recorded on Adverse Events CRF)
- Re-interventions
- Date of discharge
- Reasons for delayed discharge

iv) Follow-up data collection at 6-weeks, 6- & 12-months

Patients will be followed up in the out-patient clinic at 6-weeks, 6 months and 12 months post-randomisation.

Appendix P: Data Collection & Clinical Follow-Up

At each clinic visit the following will be assessed:

- Evidence of fistula healing:

  The fistula is deemed to be clinically healed if the patient is symptom-free, with no evidence of on-going perianal sepsis/drainage, and no evidence of residual internal or external fistulous opening.
- Details of complications (also recorded on Adverse Events CRF)
- Details of any additional treatment or re-intervention
- Health resource utilisation

At 6- & 12-month visits an assessment of faecal incontinence will be performed using the St. Marks' faecal incontinence score [Appendix R].

In addition, at 12 months all patients will:

- undergo unenhanced MRI fistulography (unless MRI performed for post operative fistula recurrence/treatment failure prior to this)
- complete quality of life questionnaires

A proportion of patients will require re-interventions either for the treatment of complications or for on-going treatment of the fistula. This is particularly likely for those treated with a "cutting seton" in the Surgeon's Preference group; further intervention is frequently necessary to tighten the seton or for completion fistulotomy. Re-interventions for on-going fistula treatment will be recorded on the appropriate follow-up CRF. Re-interventions for complications will be recorded on the adverse events CRF.

Appendix Q: EQ-5D Form

Health Questionnaire

(English version for the UK)

(Validated for use in Eire)

Patient Forename:……	Patient Surname:…….……
FIAT Trial No:…….	Consultant: …….…….
Patient Hospital No:……	Hospital:…….……...…..
Date of Birth:..……/……..…....../……. dd mm yyyy	Today's date: ……/……..…....../……. dd mm yyyy

Appendix Q: EQ-5D Form

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

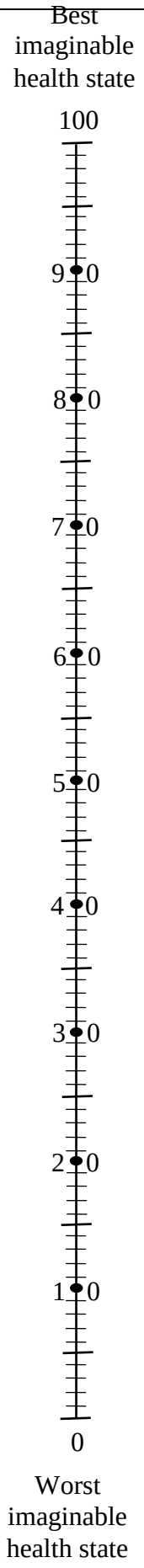
I am extremely anxious or depressed ❑

Appendix Q: EQ-5D Form

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix R: Faecal incontinence Quality of Life

The FIAT Trial
Faecal Incontinence Quality of Life Form

Patient Forename:…… **FIAT** Trial No:……

Patient Surname:…… D.O.B (dd-mon-yyyy) ……/……/19……

Hospital No :…….. Date this form was filled in: ……/……/20……

PART A

1. In general, would you say your health is:

Excellent ☐ Very Good ☐ Good ☐

Fair ☐ Poor ☐

PART B

2. For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage:

	Most of the time	Some of the time	A little of the time	None of the time
I am afraid to go out.	☐	☐	☐	☐
I avoid visiting friends.	☐	☐	☐	☐
I avoid staying overnight away from home.	☐	☐	☐	☐
It is difficult for me to get out and do the things like going to a movie or to church.	☐	☐	☐	☐
I cut down on how much I eat before I go out.	☐	☐	☐	☐
Whenever I am away from home, I try to stay near a restroom as much as possible.	☐	☐	☐	☐
It is important to plan my schedule (daily activities) around my bowel pattern.	☐	☐	☐	☐
I avoid travelling.	☐	☐	☐	☐
I worry about nor being able to get to the toilet in time.	☐	☐	☐	☐
I feel I have no control over my bowels.	☐	☐	☐	☐
I can't hold my bowel movement long enough to get to the bathroom.	☐	☐	☐	☐
I leak stool without even knowing it.	☐	☐	☐	☐
I try to prevent bowel accidents by staying very near a bathroom.	☐	☐	☐	☐

PART C

3. Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following:

	Strongly Agree	Somewhat Agree	Somewhat Disagree	Strongly Disagree
I feel ashamed.	☐	☐	☐	☐
I cannot do many things that I want to do.	☐	☐	☐	☐
I worry about bowel accidents.	☐	☐	☐	☐
I feel depressed.	☐	☐	☐	☐
I worry about others smelling stool on me.	☐	☐	☐	☐
I feel like I am not a healthy person.	☐	☐	☐	☐
I enjoy life less.	☐	☐	☐	☐
I have sex less often than I would like.	☐	☐	☐	☐
I feel different from other people.	☐	☐	☐	☐
The possibility of bowel accidents is always on my mind.	☐	☐	☐	☐
I am afraid to have sex.	☐	☐	☐	☐
I avoid travelling by plane or train.	☐	☐	☐	☐
I avoid going out to eat.	☐	☐	☐	☐
Whenever I go somewhere new, I specifically locate where the bathrooms are.	☐	☐	☐	☐

4. During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?

Extremely So – to the point where I have just about given up ☐
Very Much So ☐
Quite a bit ☐
Some - enough to bother me ☐
A Little Bit ☐
Not at all ☐

Thank-you for taking the time to complete this form.
Please return this form to your surgeon, who will send it on to:

FIAT Study Office, University of Birmingham Clinical Trials Unit,
FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Edgbaston,
Birmingham, B15 2TT

Version 1.0 15th April 2010

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