PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Therapeutic management of complex anal fistulas by installing a nitinol closure clip: study protocol of a multicentric randomized controlled trial – FISCLOSE
AUTHORS	Dubois, Anne; Carrier, Guillaume; Pereira, Bruno; Gillet, Brigitte; Faucheron, Jean-Luc; Pezet, Denis; Balayssac, David

VERSION 1 - REVIEW

REVIEWER	Ruediger L. Prosst Proctological Institute Stuttgart Esslinger Str. 40 70182 Stuttgart Germany Ruediger L. Prosst has advised Ovesco Endoscopy AG in regulatory affairs and product development.
REVIEW RETURNED	18-Sep-2015

GENERAL COMMENTS	Dubois et al. describe the design of prospective, randomized, controlled, single-blind, bicenter and interventional study which is intended to evaluate the efficacy and safety of a nitinol closure clip, the OTSC Proctology device, in comparison to the advancement flap technique for the surgical treatment of complex anal fistulas. Aim of the study is the assessment of the healing rate of the fistulae (short and long-term at 3, 6 and 12 months after surgery), as well as the postoperative pain, fecal incontinency, quality of life, the number of re-interventions and therapeutic management costs. There are only a few suggestions before the study will be conducted, respectively before final analysis of the results: - page 4, line 41: “These fistulas usually do not affect any muscle.” Incorrect statement. - page 6, line 39: Another objective should be the behavior of the clip in terms of spontaneous detachment, ingrowth, migration, etc. - page 7, line 8: Intersphincteric and distal transsphincteric fistulae are usually treated by simple fistulectomy and do not require sophisticated plastic repair. Therefore these types of fistulae could be excluded from the study. - page 8, line 48: Fistula tract debridement should be performed in both procedures with the same type of fistula brush (preferably with the OTSC fistula brush) to exclude any differences of tract preparation. - page 10, line 22: After clip placement on the internal fistula opening, water tightness of the closure should be tested by irrigation over the external fistula opening. In case of leakage the clip has to be removed and replaced by a new one until definitive closure is

	achieved. - page 12, line 12: Concerning statistical considerations it should be kept in mind that the success rate of 90% with the clip device described in literature was seen in patients without Crohn's disease. As the proposed study will also include patients with Crohn the success rate will probably be lower. In conclusion, the intention of the study is of high clinical importance as the OTSC Proctology device represents a very promising tool for the treatment of anorectal fistulae. The study design is reasonable and clinically realizable. Recommendation: Acceptance of manuscript with minor revision.

REVIEWER	Marc Schurr Steinbeis University Berlin, IHCI, Tuebingen, Germany Member of the Executive Borard of Ovesco Endoscopy AG, Tuebingen, Germany
REVIEW RETURNED	20-Sep-2015

GENERAL COMMENTS	The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Ruediger L. Prosst
Institution and Country: Proctological Institute Stuttgart, Germany.
Dubois et al. describe the design of prospective, randomized, controlled, single-blind, bicenter and interventional study which is intended to evaluate the efficacy and safety of a nitinol closure clip, the OTSC Proctology device, in comparison to the advancement flap technique for the surgical treatment of complex anal fistulas.
Aim of the study is the assessment of the healing rate of the fistulae (short and long-term at 3, 6 and 12 months after surgery), as well as the postoperative pain, fecal incontinency, quality of life, the number of re-interventions and therapeutic management costs.
There are only a few suggestions before the study will be conducted, respectively before final analysis of the results:

Q6. page 4, line 41: "These fistulas usually do not affect any muscle." Incorrect statement.
A6. Yes, the reviewer is right, it's a misinterpretation.
This sentence has been removed.

Q7. page 6, line 39: Another objective should be the behavior of the clip in terms of spontaneous detachment, ingrowth, migration, etc.
A7. This secondary objective has been added to the study protocol.
"The secondary endpoints are anal fistula healing (6 months and 1 year after surgery), proctologic pain assessed with a visual analogic scale (VAS) (at days: 0, 1, 2, 3, 15, 30, 60, 90, 180 and 365), the fecal incontinence score assessed with the Jorge and Wexner questionnaire [20] (at days: 0, 15, 30, 60, 90, 180 and 365), digestive disorders, behavior of the clip (spontaneous detachment, ingrowth, migration) and quality of life assessed with the Gastrointestinal Quality of Life Index (GIQLI) [21] (at days: 0, 15, 30, 60, 90, 180 and 365) and the quality of life assessed with the Euroqol EQ5D-3L Questionnaire (at days: 0, 30, 90 and 365) [22] (Table 1). »

Q8. page 7, line 8: Intersphincteric and distal transsphincteric fistulae are usually treated by simple

fistulectomy and do not require sophisticated plastic repair. Therefore these types of fistulae could be excluded from the study.
A8. Intersphincteric and distal trans-sphincteric fistulae have been removed from the inclusion criteria and distal trans-sphincteric and intersphincteric fistulas have been added to exclusion criteria.

Q9. page 8, line 48: Fistula tract debridement should be performed in both procedures with the same type of fistula brush (preferably with the OTSC fistula brush) to exclude any differences of tract preparation.
A9. This precision has been added for both procedures.

Q10. page 10, line 22: After clip placement on the internal fistula opening, water tightness of the closure should be tested by irrigation over the external fistula opening. In case of leakage the clip has to be removed and replaced by a new one until definitive closure is achieved.
A10. This precision has been added for the clip procedure and for the MRAF procedure (such as supplementary sutures).

Q11. page 12, line 12: Concerning statistical considerations it should be kept in mind that the success rate of 90% with the clip device described in literature was seen in patients without Crohn's disease. As the proposed study will also include patients with Crohn the success rate will probably be lower.
A11. The Crohn disease has been removed from the inclusion criteria.

In conclusion, the intention of the study is of high clinical importance as the OTSC Proctology device represents a very promising tool for the treatment of anorectal fistulae.
The study design is reasonable and clinically realizable.
Recommendation: Acceptance of manuscript with minor revision.

Reviewer: 2
Reviewer Name: Marc Schurr
Institution and Country: Steinbeis University Berlin, IHCI, Tuebingen, Germany.

Q12. "These fistulas usually do not affect any muscle. The second group contains what is known as 'complex' fistulas."
This is not correctly phrased. They affect the muscle (up to about one third).
A12. As mentioned above, the sentence has been removed from the manuscript.

Q13. "Moreover, other authors underlined that these patients do not represent the core of the indication spectrum for the OTSC® closure clip but is rather at the margin of what this device is indicated for [19]."
It should also be nothed, that the study by Gauthier was criticised for the high primary technical failure rate of 76 % with continuing discharge from the fistula directly postop.
A13. Information has been added to the manuscript.
"The study by Gautier et al. has also a high technical failure rate with 53% difficult procedures and 64.7% clip migration [18]."

Q14. "To be included in the study, the patient must have a complex anal fistula (intersphincteric, trans-sphincteric, suprasphincteric, extrasphincteric), drained and requiring a closing intervention."
Given the number of cases (n=46) it is worth consideration to focus inclusion criteria to cryptogenic fistula only and to exclude Crohn's fistula.
A14. Yes. As mentioned above, The Crohn disease has been removed from the inclusion criteria.

Q15. "The estimated cost is currently €690 per procedure ($770) (data from the laboratory)."

One needs to specify that these are the cost in France. They are lower elswehere.
A15. The modification has been done in the text : “The estimated cost in France is currently €690 per procedure ($770) (data from the laboratory).”

Q16. “Thereafter, the seton is removed, the fistula tract eroded with the brush and flushed with diluted hydrogen peroxide solution.”
H2O2 has cytotoxic effects. It is also known that H2O2 can cause or entertain inflammation of the epithelia of the digestive tract. Thus, the administration of H2Os should be considered twice.
A16. The flush with diluted peroxide hydrogen has been replaced by a flush of « sterile saline solution ».

Q17. “The clip position is controlled by the closure of the internal opening of the fistula and clasps the muscular part without signs of local ischemia”
After clip placement the correctness of closure is normally tested by gentle retrograde injection of saline solution through the fistula tract. The Gauthier study was critised for a high number of primary technical failure.
A17. Yes, as mentioned above, this examination of the closure correctness has been added for both procedures:
“Finally, the water tightness of the closure will be tested by irrigation of sterile saline solution over the external fistula opening. In case of leakage, flap will be reinforced with one or several elective sutures.”
“The water tightness of the closure will be tested by irrigation of sterile saline solution over the external fistula opening. In case of leakage, the clip will be removed and replaced by a new one until definitive closure.”

Q18. “According to our previous works and the literature [16], the success rate (proportion of patients without healed anal fistula, 3 months after surgery) with the expected OTSC® Proctology technique should be equal to 90%. Therefore, considering a 60% success rate of the advancement flap procedure [4], n=42 patients per group would be required to highlight a significant difference between the two groups for a two-sided type-I error of 5% and 90% statistical power. Finally, a total of 92 patients will be considered. An interim analysis is planned after enrolment of the first 46 patients (n= 23x2) using the Obrien-Fleming method”
Concerning the sample size calculation it has to be stated, that a 30 % difference vs advancement flap is represents a high estimation, based on the trial by Prosst et al. But this trial included only cryptogenic fistula. The trial presented here also includes Crohn's fistula. While this is within the indication spectrum of the procedure, it would be fair to assume, that success rates may be lower in this group. Thus the expectable success rate in the clip group of the trial presented here may also be lower. This would influence the variables for sample size panning.
A18. As mentioned above, patients with a Crohn disease will be not included in the study.

Q19. “Covariates used for adjustment will be fixed according to (1) univariate results, (2) stratification factors and (3) clinical relevance such as: BMI, tobacco and drugs (anticoagulant, platelet antiaggregant, anti-inflammatory, immunosuppressant).”
Comorbidities with relevant influence on wound healing should be captured as covariates, such as diabetes.
A19. The modification has been made in the text: “stratification factors and (3) clinical relevance such as: BMI, diabetes, tobacco and drugs (anticoagulant, platelet anti-aggregant, anti-inflammatory, immunosuppressant).”

VERSION 2 – REVIEW

REVIEWER	PD Dr. Ruediger L. Prosst St. Anna Klinik and Proctological Institute Stuttgart, Stuttgart, Germany Ruediger L. Prosst has advised Ovesco Endoscopy AG in regulatory affairs and product development.
REVIEW RETURNED	07-Nov-2015

GENERAL COMMENTS	Highly interesting study! Good luck!

REVIEWER	Marc Schurr Steinbeis University Berlin IHCI Institute Member of the Executive Board of Ovesco Endoscopy
REVIEW RETURNED	09-Nov-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.