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| **Barwon Health Reference:** | 19/118 |
| **Project Title** | Botulinum toxin for the treatment of anal fistulae – a double blinded randomized trial |
| **Protocol Version No.** | 2.0 |
| **Protocol Date** | 4 December 2019 2019 |
| **Body Responsible for this Project** | Department of Surgery, Deakin University |
| **Location** | University Hospital Geelong |
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1. **Background**

Anal fistula is a common disease, with an annual incidence of approximately 10 per 10,000 population. It manifests with chronic purulent drainage from the fistula, and recurrent episodes of pain and abscess formation. Although the majority of these can be healed with simple operations, the more complex cases remain a formidable challenge in surgery.

The most effective operation for treating anal fistulae is fistulotomy (i.e. dividing the tissue overlying the fistula (skin, subcutaneous tissue and sphincter muscle) and allowing it to heal by secondary intention), with recurrence rates as low as 2% ([Simpson, Banerjea et al. 2012](#_ENREF_14)).

This procedure carries a significant risk of incontinence however, especially in high or complex fistulae where a significant part of the sphincter complex is traversed by the fistula.

The use of cutting Seton drains, in which a suture is passed across the fistula and slowly tightened over several weeks, is a well described technique for managing high fistulae. By gradually cutting through the sphincter muscle, and allowing healing by fibrosis to occur above the Seton, incontinence may theoretically be prevented. The results of this technique have been disappointing, however, both in terms of high recurrence rates and also high rates of faecal incontinence ([Hammond, Knowles et al. 2006](#_ENREF_6)).

For high or complex fistulae, ‘gold standard’ operation is a mucosal advancement flap (usually combined with coring out of the fistula tract). This procedure carries a low risk of incontinence. The success rate is highly variable, however, with recurrence rates of up to 80% reported, even in expert centres ([Simpson, Banerjea et al. 2012](#_ENREF_14)).

Less invasive procedures such as fistula plugs or fibrin glue insertion have been reported, but there is little evidence that they are at all effective ([Simpson, Banerjea et al. 2012](#_ENREF_14)). The LIFT (Ligation of the Intersphincteric Fistula Tract) procedure has was described in 2007 by Rojanasakul and colleagues ([Rojanasakul, Sahakitrungruang et al. 2007](#_ENREF_13)). In this procedure, the intersphincteric tract is dissected, and the fistula tract ligated in this space. An internal sphincterotomy (i.e dividing the internal sphincter below the fistula but leaving the external sphincter intact) is often performed as part of the procedure. The initial reports of a 90% success rate for healing fistulae with this procedure have not been widely replicated, and failure rates of up to 60% have been reported ([Zirak-Schmidt and Perdawood 2014](#_ENREF_17)).

In summary, fistulotomy is an effective and safe procedure for treating low simple fistulae. All described procedures for high or complex fistulae have been found to have either low or variable success rates in healing the fistula or carry unacceptably high rates of faecal incontinence.

* 1. **Why do anal fistulae persist?**

The most widely accepted explanation for the aetiology of anal sepsis remains the cryptoglandular theory proposed by Eisenhammer in 1956 ([Eisenhammer 1956](#_ENREF_4)). He proposed that obstruction of the anal glands by faecal debris leads to infection of these glands. The anal glands penetrate the internal anal sphincter, and the abscess accumulates at the site where the gland terminates.

Peri-anal abscesses are treated by simple incision and drainage, but in a proportion of cases they will progress to form a chronic fistula (the proportion of cases that lead to fistula has been variably reported, with estimates ranging from 5 to 83% ([Sozener, Gedik et al. 2011](#_ENREF_15))). The reasons why chronic sepsis and fistula formation occur are not fully known. Parks([Parks 1961](#_ENREF_12)) proposed that the diseased anal gland could become a source of chronic sepsis. Although this theory is widely accepted, there is little experimental data to support it. Lunniss et al ([Lunniss, Sheffield et al. 1995](#_ENREF_8)) studied a series of anal fistulae histologically, and reported that a chronically infected gland was seldom present, but that epithelialisation of the tract was commonly observed.

They therefore proposed that epithelialisation of the tract was an important factor leading to persistence of the fistula tract.

Fistulae that occur elsewhere in the gastro- intestinal tract are well known to heal spontaneously in the majority of cases. One well recognised situation in which gastrointestinal fistulae do not heal spontaneously is where there is incomplete obstruction distal to the fistula site. In the anus, the resting anal tone creates a functional obstruction distal to the fistula, which may lead to persistent passage of small amounts of stool through the fistula tract. It is possible that the division of the internal sphincter, as performed in a fistulotomy or in some variants of the LIFT procedure may contribute to the healing of the fistula not just by laying open the fistula, but also by the mechanism of obliterating internal sphincter tone distal to the fistula. This led to the hypothesis that temporarily weakening the anal sphincters by medical means may allow fistula healing to occur. In summary; Botox injection to the anal sphincter is a safe and efficacious for aiding healing in anal fissure cases by relieving the muscle tone. This same mechanism may prevent small amounts of faeces from entering the fistula tract, thereby preventing recurrence in anal fistula cases.

* 1. **Botulinum toxin reduces anal resting tone temporarily**

Anal fissure is a common disease, in which increased internal sphincter tone causes severe anal pain associated with a non- healing anal ischaemic ulcer. The standard operation for this condition is an internal anal sphincterotomy, in which part of the internal anal sphincter is divided in order to relieve the anal sphincter spasm. This is an effective operation in relieving the symptoms of this disease, but it carries a risk of faecal incontinence. For this reason, botulinum toxin (Botox) injection to the internal anal sphincters has been widely used to temporarily decrease anal tone in order to allow the fissure to heal.

* 1. **Botox safety**

The safety of Botox injection to the anal sphincter is well established. The risk of incontinence is low, and when it occurs is typically minor and transient. Farouk([Farouk 2014](#_ENREF_5)) reported 141 consecutive patients treated with anal Botox injections. Eleven of these (8%) reported faecal urgency (no actual incontinence) which resolved within 12 weeks in all cases. A total of 248 patients have been enrolled in randomized trials of Botox vs. anal sphincterotomy in the treatment of anal fissure, and a total of 15 (6%) minor complications were recorded. All of these were related to the injection site (five haematomas, two self- limiting bleeds and eight echymoses at the injection site).

In total, 7/248 (3%) of subjects who underwent Botox injection experienced transient faecal incontinence, but this resolved in all cases ([Mentes, Irkorucu et al. 2003](#_ENREF_10); [Arroyo, Perez et al. 2005](#_ENREF_3); [Iswariah, Stephens et al. 2005](#_ENREF_7); [Massoud, Baharak et al. 2005](#_ENREF_9); [Abd Elhady, Othman et al. 2009](#_ENREF_2); [Nasr, Ezzat et al. 2010](#_ENREF_11); [Valizadeh, Jalaly et al. 2012](#_ENREF_16)).

There are no major adverse events due to Botox injection to the anal sphincters reported in the medical literature. There have been extremely rare reports of severe muscular weakness after Botox injection to other sites, when the toxin is absorbed systemically into the blood stream. This has usually occurred in when Botox has been used in children or patients with underlying neuromuscular disease, or when higher than usual doses are given (2013).

Botox is currently registered by the Australian Therapeutic Goods Administration (TGA) for the following indications (note that this includes the purely cosmetic indication of improving the appearance of forehead lines etc.):

* Prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).
* Treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents.  This does not include idiopathic overactive bladder.
* Treatment of strabismus in children and adults.
* Treatment of blepharospasm associated with dystonia, including benign blepharospasm and VII nerve disorders (specifically hemifacial spasm) in patients twelve years and older.
* Treatment of cervical dystonia (spasmodic torticollis).
* Treatment of focal spasticity of the upper and lower limbs, including dynamic equinas foot deformity, due to juvenile cerebral palsy in patients two years of age and older.
* Treatment of severe primary hyperhidrosis of the axillae.
* Treatment of focal spasticity in adults.
* Treatment of spasmodic dysphonia.
* Temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.
1. **Botox for anal fistula – preliminary results from a pilot study**

We recently completed the first study of Botox injection for anal fistulae (Barwon Health HREC Ref 16/148). In this prospective pilot study, patients with complex anal fistulae with a Seton drain in situ had the fistula tract de- epithelialized, and 40U Botox injected in two sites in the intersphincteric plane. Of the ten patients enrolled in the study, seven (70%) had complete healing of the anal fistula after a median follow up of five months (range three to thirteen). Three patients experienced minor transient incontinence symptoms (one had impaired incontinence for flatus, and the other two experienced urgency. No patient experienced any episodes of faecal leakage). There were no other adverse events. This study has not yet been published. The full report of the pilot study is attached as Appendix 1.

1. **Limitations of previous studies**
	1. The only previous study of Botox use for fistula in ano is the pilot study described above. Although the results of this pilot study are encouraging, they need to be interpreted with caution. The study involved a small number of patients at a single institution, and the placebo effect of being enrolled in a pilot study such as this may have caused patients to claim that their symptoms had resolved even if they had persistence of the fistula. It is also possible that the fistulae were adequately treated by the Seton drain and de- epithelialisation of the tract, and the Botox did not contribute to the successful outcomes.
	2. **Why is this project important and what will it add to the literature or how may it improve patient care?**

All currently performed operations for complex anal fistula have a high recurrence rate and/or high risk of (permanent) incontinence. Botox treatment of anal fistula, if it is effective, will offer a simple and minimally invasive treatment for this condition.

1. **Botox for anal fistula – Summary**
* Temporary weakening of the anal sphincters in order to reduce functional obstruction distal to the fistula provides a plausible mechanism for Botox to lead to healing of anal fistulae.
* Botox injection to the anal sphincters is known to be safe from previous studies of anal fissures.
* The results of our pilot study suggest that Botox injection may be effective in treating anal fisulae (with a 70% success rate).
1. **Botox for anal fistula – need for a blinded randomized trial**

Although the results of the pilot study are encouraging, they need to be interpreted with caution. It is possible that the fistulae were adequately treated by the Seton drain and de- epithelialisation of the tract, and the Botox did not contribute to the successful outcomes. In a long- term study by Buchanan et al [2004], 4/20 (20%) complex anal fistulae were healed by insertion of a loose Seton (along with division of the internal anal sphincter but not a full fistulotomy involving the external sphincter) followed by removal of the Seton drain once the sepsis had resolved. It is also possible that the placebo effect of being enrolled in a pilot study such as this may have caused patients to claim that their symptoms had resolved even if they had persistence of the fistula.

These questions will best be answered with a blinded randomized trial of Botox injection with removal of the Seton drain and de- epithelialisation of the tract compared with Seton removal and de- epithelialisation alone.

1. **Proposed study design and methodology**

This study will investigate the efficacy and safety profile of Botox injections to the anal sphincter for the treatment of anal fistula. The primary outcome is whether fistula healing occurs. In addition, patients will be assessed for possible faecal incontinence or other adverse effects of Botox.

### **Inclusion criteria**

Patients over the age of 18 years referred to University Hospital Geelong will be screened for recruitment. Adult patients with a complex anal fistula who have had a Seton drain placed as their initial treatment are eligible to be included in the study. Note that Seton drain placement is the standard initial (not definitive) treatment for complex anal fistulae.

A complex fistula is any anal fistula in which the treating surgeon is of the opinion that a fistulotomy carries a significant risk of incontinence due to the amount of sphincter muscle that would be divided. This is a pragmatic definition in keeping with the American Gastroenterological Association guidelines (Sandborn et al 2003) which includes all trans- sphincteric, suprasphincteric, extrasphincteric and high intersphincteric fistulae.

Information collected during the initial consultation will be considered by a member of the research team for the purposes of inclusion/exclusion from the study.

A member of the research team (other than the treating clinician) will then make initial contact with the candidate regarding the study, either at their next appointment or via telephone.

### **Exclusion criteria**

### The following groups will be excluded:

* All patients under 18 years of age.
* Patients with known Crohn’s disease of anorectal malignancy.
* Patients with rectovaginal or anovaginal fistulae.
* Patients with known generalised musculoskeletal disease.
* Patients with known sensitivity to Botox.
* Pregnant or breast- feeding women.
* Any person who cannot understand the consent form or who declines consent to be enrolled in the study.
	1. **Assessment and selection**

All subjects will have had a soft, loose, draining Seton placed at their initial surgery, and be reassessed after one month by examination under anaesthetic (EUA) and magnetic resonance imaging (MRI) to confirm the fistula tract and to ensure that there is no undrained sepsis (this is the current standard initial treatment of patients with complex fistulae). If there is evidence of undrained sepsis, or of there are multiple fistula tracts, the patient will be excluded from the study.

**6.3.1 Recruitment and consent**

Candidates for recruitment will be screened from patients attending the Surgical Outpatients department at University Hospital Geelong. Patients who meet the inclusion criteria will be approached by a General Surgery fellow or registrar (other than their treating surgeon) and invited to participate. The potential subject will be approached in person at the time of their attendance at the Outpatients Department, and given a copy of the PICF. The patient will be advised that participation is entirely voluntary, and that their decision to participate or not will not influence the quality or timing of their care. Patients who accept the invitation to participate will then be contacted by a member of the research team, who will explain the study in detail, and obtain informed consent (if the patient chooses) for participation in the study.

* 1. **Intervention**

In theatre under anaesthetic (at the same anaesthetic as the EUA), the Seton drain will be removed and the fistula tract de- epithelialized using an endometrial cytology brush.

40 units (U) of Botox or placebo (normal saline) will be injected into the intersphincteric plane of the anus at the 3 o’clock (left lateral) and 9 o’clock positions (total 80U Botox).

This will be performed by the patient’s treating surgeon.

* 1. **Follow up**

The fistula will be judged to have healed if the following criteria are met:

* The external opening has healed.
* The internal opening cannot be palpated on digital rectal examination.
* The patient does not complain of any ongoing drainage from the fistula site.

The presence and severity of faecal incontinence will be documented using the St. Mark’s Incontinence Score. This is a self- reported assessment of the patient’s experience of their continence. It includes both objective statements of the frequency of incontinence episodes (to solid or liquid stool or flatus) as well as a more general perception of how frequently incontinence affects their lifestyle. This is a widely used and well validated questionnaire, the results of which have been shown to correlate well with other measures of quality of life (Maeda et al 2008). The scoring system is illustrated below:



Follow up will be performed by a surgeon investigator who is blinded to the treatment the patient has received (Botox or placebo). Any patients in whom the fistula has not healed will be offered treatment according to the standard protocols of the treating team.

* 1. **Randomization**

Randomization will be done at the time of surgery, after the patient has been anaesthetised. Randomization will be done by sealed envelopes, and will be performed by one of the co- investigators (Dr. Moore). The operating surgeon will not be aware of the patient’s allocation. The co- investigator who performs the randomization will not be involved in the patients’ care or post- operative assessment. The study drug or placebo will be drawn up into a syringe by the same co- investigator (Dr. Moore) who has performed the randomization. The unmarked syringe will then be handed to the treating surgeon for administration to the patient in theatre.

1. **Protocol Summary**

The study protocol is summarised below:



1. **Study Procedures**
	1. **How will the specific study be carried out?**

After obtaining informed consent, patients will have an MRI scan and be examined under anaesthesia a minimum of four weeks after placement of the Seton drain in order to exclude undrained sepsis or unidentified multiple fistula tracts. This is part of the current standard initial treatment for anal fistula.

Eligible patients (with no sign of undrained sepsis and without multiple fistula tracts) will then be randomized to have 40 units (U) of Botox or placebo (normal saline) injected into the intersphincteric plane of the anus at the 3 o’clock (left lateral) and 9 o’clock positions (total 80U Botox). This will be done at the same anaesthetic as the examination under anaesthesia.

Participants will then be reassessed by a specialist surgeon investigator after three, twelve and 24 weeks to determine if the fistula has healed and for the presence of any side effects (particularly any impaired faecal continence). Any patients in whom the fistula tract has not healed will be offered current standard surgical treatment of the fistula. The surgeon performing follow up will be blined to the patients’ treatment arm.

* 1. **What will the participants have to do during the study, when and how often?**

Participants will undergo treatment per initial consultation for anal fistula, including assessment under anaesthesia and by magnetic resonance imaging after one month. Participants will then have Botox injection to the intersphincteric plane of the anus. Participants will then be asked to return for clinical assessment after three, twelve and 24 weeks.

* 1. **What will the investigator do and when?**

The investigator will contact the candidate after the candidate has given medical consent to undergo treatment for anal fistula (obtained at the first consultation). To ensure a clear separation between clinician and researcher roles, the treating consultant will not try to recruit the participant, even though the treating consultant may be a member of the research team. By having another member of the research team make initial contact with the candidate with regard to participation the unequal relationship between clinician and patient will be avoided.

For eligible participants; the aims and study methodology will be described by a member of the research team. The candidate will be re-assured that the decision to participate or not to participate in research will not change their access to medical care. The participant will then be given an opportunity to give consideration to participating. Depending on the urgency of the procedure, candidates will typically have up to one month during which to consider whether they wish to participate.

Should the participant choose to participate, the investigator will record the participant’s medical history and personal particulars into a password-secured study database stored. Treatment outcomes will be assessed as aggregate results.

* 1. **Data management**
		1. **What data will be collected and how (from medical records, questionnaires)?**

General information

Information that will be collected directly from the participant includes personal particulars (e.g. name, date of birth, gender, postcode, cultural identity), and medical history (diagnosis, comorbid conditions, medication use).

Fistula diagnosis- specific information

The duration of the patients’ symptoms and details of any previous surgery will be recorded, as well as the MRI and examination under anaesthetic findings.

Follow up information

The status of the fistula at follow up (healed or not healed) will be recorded. Any potential complications will be recorded. The incontinence scores (collected by questionnaire) will be recorded for all patients.

* + 1. **How will data be stored (electronically, paper, etc)?**

During and after the research project, all information will be stored securely in a password-protected location on the Barwon Health server. Access to the study database will be restricted only to those researchers that need access; these will be identified to the Barwon Health Human Research Ethics Committee. All personal identifiers will be removed once all information has been correctly attributed to all participants. Paper records (completed PICFs) will be stored in a locked office in designated folders and retained according to the record retention policies of Barwon Health.

* + 1. **How long will data be stored and how will it be destroyed?**

Disposal of information will be in accordance with state legislation and the *Australian Code for the Responsible Conduct of Research.* Barwon Health requires a retention time of 7 years from date of publication. The Director of Surgery of the Department of Surgery, University Hospital Geelong will be responsible for the disposal of information in accordance with appropriate policy that applies after the study ends. Information will be disposed by permanent deletion from the Barwon Health server.

The Director of Surgery, University Hospital Geelong will seek the advice of technical specialists employed by Barwon Health for the permanent and secure deletion of the study database. At the end of the retention period, the head of department will engage the secure document destruction service provider for Barwon Health to ensure secure and confidential document destruction.

Unblinding will occur at completion of the study, or earlier if there are any medical indications for an individual patient, or if there are any safety concerns for the study overall.

* 1. **Data Analysis**
		1. **Justification of sample size:**

Assuming a 30% healing rate in the placebo group, we would require 21 participants in each arm to provide 80 per cent power to detect a healing rate to 70% in the Botox group with a two‐sided significance level of p=.05. To allow for drop out, we aim to enroll 25 participants in each arm of the study. An interim analysis will be done after ten patients have been enrolled into each arm of the study.

* + 1. **Proposed means for analyzing the data citing specific statistical techniques:**

As this is a double blinded randomized trial with 25 participants in each arm, aggregate outcomes will be assessed to provide a preliminary indication of the effect of Botox injections in anal fistula patients. Outcomes (complete healing of fistula, faecal incontinence) will be compared between groups (treatment, and placebo) at follow up to estimate the effect sizes of using Botox.

The Chi-squared test will be used to compare between the groups at each time point. Time to recurrence on longer- term follow up will be ascertained using Kaplan- Meier survival techniques.

* 1. **Dissemination of Results**

Aggregate results will be discussed at departmental meetings so as to improve medical practitioners' knowledge. Aggregate results will be published in appropriate scientific journals so as to benefit the wider community. Participants will be offered a written plain language summary of the aggregate study results.

1. **Data and Safety Monitoring board (DSMB)**

The DSMB will periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and efficacy. The DSMB may make recommendations to the Principle Investigator concerning the continuation, modification, or termination of the trial. If the DSMB believes that there are significant safety concerns in the study, it will have the authority to terminate the study.

The DSMB will be chaired by Prof. Glenn Guest (a senior Colorectal Surgeon at University Hospital Geelong and Deakin University Professor of Surgery). He may recruit any other members to the DSMB as he sees fit.

1. **References:**

NICE (National Institute for Health and Care Excellence): Chronic anal fissure: botulinum toxin type A injection. (2013)

Retrieved 1/9/2015, from [www.nice.org.uk/advice/esuom14/chapter/key-points-from-the-evidence](http://www.nice.org.uk/advice/esuom14/chapter/key-points-from-the-evidence).

Abd Elhady HM, Othman IH, et al. Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphincterotomy for treatment of chronic anal fissure. S Afr J Surg. 2009;47(4):112-114.

Arroyo A, Perez FS, et al. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study. Am J Surg. 2005;189(4):429-434.

Buchanan GN, Owen HA, et al. Long-term outcome following loose-seton technique for external sphincter. Br J Surg. 2004;91(4):476-80.

Eisenhammer S. The internal anal sphincter and the anorectal abscess. Surg Gynecol Obstet. 1956;(103):501-506.

Farouk R. Sphincter-Preserving Therapy for Treating a Chronic Anal Fissure: Long-term Outcomes. Ann Coloproctol. 2014;30(132-4).

Hammond TM, Knowles CH, et al. The Snug Seton: short and medium term results of slow fistulotomy for idiopathic anal fistulae. Colorectal Dis. 2006;8:328-337.

Iswariah H, Stephens J, et al. Randomized prospective controlled trial of lateral internal sphincterotomy versus injection of botulinum toxin for the treatment of idiopathic fissure in ano. ANZ J Surg. 2005;75(7):553-555.

Lunniss PJ, Sheffield JP, et al. Persistence of idiopathic anal fistula may be related to epithelialization. Br J Surg. 1995;82:32-33.

Maeda Y, Parés D, Norton C, Vaizey CJ, Kamm MA. Does the St. Mark's incontinence score reflect patients' perceptions? A review of 390 patients. Dis. Colon Rectum. 2008 Apr;51(4):436-42

Massoud BW, Mehrdad V Fau Baharak T, et al. Botulinum toxin injection versus internal anal sphincterotomy for the treatment of chronic anal fissure. Ann Saudi Med. 2005;25(2):140-142.

Mentes BB, Irkorucu O, et al. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. Dis Colon Rectum. 2003;46(2):232-237.

Nasr M, Ezzat H, et al. Botulinum toxin injection versus lateral internal sphincterotomy in the treatment of chronic anal fissure: a randomized controlled trial. World J Surg. 2010;34(11):2730-2734.

Parks AG. Pathogenesis and treatment of fistuila-in-ano. Br Med J. 1961;1:463-469.

Rojanasakul A, C Sahakitrungruang C, et al. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. J Med Assoc Thai. 2007;90(3):581-586.

Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB; American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. Gastroenterology. 2003 Nov;125(5):1508-30.

Simpson JA, Banerjea A, et al. Management of anal fistula. BMJ. 2012;345:1756-1833.

Sozener U, Gedik E, et al. Does adjuvant antibiotic treatment after drainage of anorectal abscess prevent development of anal fistulas? A randomized, placebo-controlled, double-blind, multicenter study. Dis Colon Rectum. 2011;54(8):923-929.

Valizadeh N, Jalaly NY, et al. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure: randomized prospective controlled trial. Langenbecks Arch Surg. 2012;396(7):1093-1098.

Zirak-Schmidt S, Perdawood SK. Management of anal fistula by ligation of the intersphincteric fistula tract - a systematic review. Dan Med J. 2014;61:A4977.