

Permacol for treating anal fistulae

Medtech innovation briefing

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Summary

- The **technology** described in this briefing is Permacol, a collagen paste that is injected into anal fistulae.
- The **innovative aspect** is that, unlike collagen plugs, the paste expands to fill and seal the fistula tract. This is designed to make it less easily expelled when defaecating.
- The intended **place in therapy** would be as an alternative to other sphincter-saving surgical techniques used to treat anal fistulae.
- The **main points from the evidence** summarised in this briefing are from 5 studies in the UK and Europe including a total of 152 adults. They report that Permacol is a safe treatment for anal fistulae. Large randomised studies are needed to fully assess its healing rates and effectiveness compared with other treatments.
- **Key uncertainties** are that the evidence base is still developing and that long-term healing and recurrence rates are unknown.

- The **cost** of Permacol is £724.19 per unit, excluding VAT and additional procedure costs. The **resource impact** may be similar to or less than standard care if the additional device costs were offset by reductions in complications or recurrence, but there is currently no evidence for this.

The technology

Permacol collagen paste (Medtronic) is a minimally invasive treatment for anal fistulae. The paste is made of acellular, porcine dermal collagen suspended in saline. When injected into the fistula tract, the paste expands to fill the internal shape of the fistula, enabling closure of the channel. Permacol may be used as a single treatment option or in conjunction with another treatment such as the LIFT (ligation of intersphincteric fistula tract) technique.

Permacol is supplied in a sterile 3-ml syringe, and comes with a sterile guiding catheter. It is used under general anaesthetic with the patient in the lithotomy position (legs in stirrups with the perineum at the edge of the table). The fistula tract is de-epithelised and granulation tissue is removed, before being cleaned with dilute hydrogen peroxide followed by saline. The guiding catheter is connected to the Permacol syringe and the other end is inserted into the external opening of the fistula. The paste is injected into the fistula until it is visible at the internal opening, and then the guiding catheter is slowly withdrawn.

The internal opening of the fistula is closed using resorbable stitches. The external opening is partially closed, using resorbable stitches if needed, to allow any inflammatory fluid to drain out without allowing the Permacol paste to escape.

Innovations

The potential innovation is that Permacol fills the exact shape of the tract. This is intended to reduce the risk of it being expelled from the body when defaecating, which can happen with collagen plugs.

Current NHS pathway or current care pathway

Surgery is usually necessary to treat anal fistulae as they rarely heal by themselves. Several surgical techniques are currently used within the NHS. The choice of technique depends on the position of the fistula and the person's medical history. MRI scans are

usually done before surgery to assess the extent and location of complex or transphincteric fistula tracts, and recurrent fistulae. The aim of surgery is to drain infected material so that the fistula can heal, while ensuring that the function of the anal sphincter is preserved. If the fistula does not heal properly it may reoccur and need another surgical procedure ([Dudukgian et al. 2011](#)). The procedure is done by a colorectal surgeon.

Fistulotomy is the most common type of anal fistula surgery. This involves cutting open the whole length of the fistula, from the internal opening to the external opening, before the surgeon cleans out the contents and flattens it out. This leaves an open wound which must be cleaned and dressed while healing; after 1 to 2 months, the fistula will heal into a flat scar. This surgery is usually done as a day-case procedure under general anaesthesia. Depending on the position of the fistula, a fistulotomy may involve cutting the anal sphincter which can lead to faecal incontinence.

Seton placement is often used if the person is considered to be at high risk of developing faecal incontinence. This technique involves threading a stitch (the seton) through the fistula tract and back out through the anus where it is loosely tied. The anal sphincter is not cut. Two types of seton may be used: a silicone draining seton, or a silk or polyester cutting seton. A draining seton allows a fistula tract to drain for several weeks or months before a surgical procedure. A cutting seton is a non-absorbable stitch placed in the fistula tract and tightened periodically, to slowly cut through the fistula. Several seton procedures or a combination of seton and other techniques may be needed to treat a single fistula. Seton placement is done under general anaesthesia.

LIFT and mucosal advancement flaps are alternative procedures that also avoid cutting the sphincter muscle. LIFT involves opening the space between the muscles to access the fistula tract, whereas a mucosal advancement flap involves closing the internal opening of the fistula with a flap of tissue and cleaning out the fistula tract.

NICE has produced interventional procedures guidance on [closure of anal fistula using a suturable bioprosthesis plug](#), made from porcine or human tissue. The guidance states that the evidence of the efficacy of these is limited, and recommends that they should only be used with special arrangements for clinical governance, consent and audit or research. NICE also recommends that, where patients are treated outside a clinical trial, clinical outcomes are audited and reviewed.

NICE has also produced a medtech innovation briefing on [VAAFT \(video-assisted anal fistula treatment\)](#), a surgical kit for treating anal fistulae.

Population, setting and intended user

Permacol is intended as an option for adults and children with anal fistulae in place of current standard surgical approaches. In people with multi-channel fistulae, Permacol could be used to treat smaller channels alongside more invasive surgical approaches being used for the main fistula. It is used by a colorectal surgeon in a secondary care setting, and is done as a day-case procedure under general anaesthesia.

Costs

Table 1 Device costs

Description	Cost	Additional information
Indicative price of technology	£724.19 (excluding VAT)	–
Average cost per treatment	£1,893.19	Day-case procedure done under anaesthesia £1,169 (2014/15 national schedules, day-case FZ21C)

Costs of standard care

Fistulotomy is the most common treatment for anal fistula. It is usually done as a day-case procedure under general anaesthesia, costing £1,169. Additional costs are incurred if a draining seton is used before surgery.

Resource consequences

Permacol costs more than standard care, but this could be offset if it led to a reduction in post-operative wound care, recurrence or faecal incontinence. The management of faecal incontinence is estimated to cost up to £2,635 per person per year. Minimal training will be needed for theatre staff and surgeons.

Regulatory information

Permacol was CE marked as a class III device in May 2012.

A search of the Medicines and Healthcare products Regulatory Agency website revealed that no manufacturer field safety notices or medical device alerts have been issued for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

People with anal fistulae are limited by pain and the management of their condition. If the condition is severe and has a significant and long-standing effect on their ability to carry out activities of daily living, they may be considered to have a disability. People with diseases that increase the risk of anal fistulae (for example, Crohn's disease) may also be considered to have a disability if the condition has similar effects on daily living. Disability is a protected characteristic under the Equality Act 2010.

Permacol collagen paste is derived from porcine tissue. Porcine products may be unsuitable for people with certain religions and beliefs that prohibit pork consumption. Religion and belief is a protected characteristic under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

This briefing summarises 5 studies including 152 patients with anal fistulae. These studies were selected as they were the highest-quality evidence and included the most patients. They report that Permacol is safe and may help some anal fistulae to heal.

Table 2 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

The evidence base for Permacol is still developing and is currently limited in size and quality. In particular, some studies are only available as conference abstracts. The Maserati 100 trial, which is not yet published in full, will improve the level of evidence. The final results of this study are reported in the conference abstract by Giordano et al. (2016), which is summarised in table 2. One study took place in an NHS setting, but was only reported as an abstract. None of the studies compared Permacol with any other method of treatment for anal fistulae.

Fistula healing rates after Permacol was injected ranged from 20% to 83%. More evidence is needed about healing rates with Permacol.

Table 2 Clinical evidence summary

<u>Fabiani et al. 2017</u>	
Study size, design and location	Case series in 21 consecutive patients having treatment for complex anal fistulae. Located in Italy.
Intervention and comparator(s)	All patients had fistulectomy and seton 6 to 8 weeks before the trial. All patients had endoscopic ultrasonography and/or MRI before Permacol.

Key outcomes	<p>Continence was evaluated before (0.33 ± 0.57) and 12 months after Permacol injection (0.61 ± 1.02) using the faecal incontinence severity index. There was no significant difference between these 2 scores ($p=0.27$) and no reported worsening of continence.</p> <p>Postoperative pain was measured using the visual analogue scale; none of the patients reported severe pain (VAS score >7).</p> <p>Mean operative time was 30 minutes and median hospital stay was 1 day.</p> <p>At 12-months follow-up, 10 patients (including 1 with Crohn's disease) had a closed external orifice and were considered to be healed, providing a success rate of 47.6%.</p>
Strengths and limitations	<p>Permacol was used alongside fistulectomy and draining seton, meaning that any results may not be because of Permacol alone. It should also be noted that only complex fistulae were treated in this study. The study shows that Permacol is safe and well tolerated.</p>
<p><u>Ahmad et al. (2015)</u></p>	
Study size, design and location	<p>Case series in 11 patients with anal fistulae (12 fistulae in total). Located in UK. Presented as a conference abstract.</p>
Intervention and comparator(s)	<p>All patients had previous incision and drainage of perianal abscess. Twelve fistulae were injected with Permacol and followed-up within 2 months. Two patients had diagnosed Crohn's disease.</p>
Key outcomes	<p>After 2 months the fistula site was examined to assess tract healing and cessation or continuation of leakage.</p> <ul style="list-style-type: none"> • 10 tracts (83.3%) were seen to have healed and no leakage was reported at follow-up. • 1 fistula tract had reduced leakage but had persistent openings. • 1 fistula tract in a patient with Crohn's disease demonstrated ongoing drainage; they had a repeat procedure at 5 months with the tract having healed at subsequent 3-month follow-up.
Strengths and limitations	<p>There is limited detail in the reporting of methods and results for this study. The study was done in the NHS.</p>

<u>Giordano et al. (2016)</u>	
Study size, design and location	Prospective, observational clinical trial in 28 patients with anal fistulae in 10 centres in the UK, Italy and Denmark.
Intervention and comparator(s)	All anal fistulae were treated with Permacol and followed-up at 1, 3, 6 and 12 months.
Key outcomes	<p>During follow-up fistula healing, faecal continence, patient satisfaction and adverse events were recorded. The primary end point was fistula healing rate.</p> <p>At 6-month follow-up, 15 of 28 (54%) were healed, and the healing rate was maintained at 12 months. No difference in healing was found between intersphincteric and transphincteric fistulae or primary and recurrent fistulae. One adverse event (perianal abscess) occurred that was possibly related to the treatment. 60% of patients were satisfied or very satisfied with the operation.</p>
Strengths and limitations	The study used data from the 30 patients that were initially enrolled in the Maserati 100 trial; 2 patients did not have data at 6-month follow-up. More information will be available when this study is published. This study was sponsored by Medtronic.
<u>Giordano et al. (2015)</u>	
Study size, design and location	Conference abstract reporting on the final results of the Maserati 100 prospective, observational clinical trial in 100 patients with intersphincteric or transphincteric anal fistulae, cryptoglandular primary or recurrent, from 10 centres in UK, Italy and Denmark.
Intervention and comparator(s)	All fistulae were treated with Permacol and followed-up at 1, 3, 6 and 12 months.

Key outcomes	<p>During follow-up fistula healing, faecal continence, patient satisfaction and adverse events were recorded. The primary end point was fistula healing rate.</p> <p>Median operative time was 21 minutes, and median time for patients to return to work was 7 days. At 6-month follow-up, 55 of 97 patients (56.7%) had a healed anal fistula. Fistula healing rate at 12 months was 53.5%. Over 70% of patients reported satisfaction at their final assessment. No serious adverse events were recorded.</p>
Strengths and limitations	<p>This conference abstract reported on the final results of the Maserati 100 trial. More information will be available when this study is published. This study was sponsored by Medtronic.</p>
<u>Zawadzki et al. (2014)</u>	
Study size, design and location	<p>Conference abstract detailing a case study of 20 consecutive patients, 15 with cryptoglandular and 5 with Crohn's-related fistulae. Located in Sweden.</p>
Intervention and comparator(s)	<p>Fistulae were drained with loose setons before treatment with Permacol. 3D anal ultrasound diagnostics was done before and after surgery. Patients had antibiotics for 10 days after treatment.</p>
Key outcomes	<p>After 6 months, 4 of 20 (20%) fistulae had healed, as assessed by clinical and anal ultrasonic investigation.</p>
Strengths and limitations	<p>There is limited detail on the methods and results. The results showed a much lower healing rate than that found in other studies. This indicates that there may be a high degree of variance in centre success rates.</p>

Recent and ongoing studies

Ongoing studies

- [ClinicalTrials.gov identifier: NCT02686580](https://clinicaltrials.gov/ct2/show/study/NCT02686580): Feasibility Study to Assess the Early Use of Porcine Cross-linked Collagen Paste in Cryptoglandular Anorectal Fistulas (FIX-IT1). Status: Not yet recruiting. Primary comparator: n/a. Expected enrolment: 12. Expected completion date: December 2017. Location: UK.

Completed studies

- [ClinicalTrials.gov identifier: NCT01624350](https://clinicaltrials.gov/ct2/show/study/NCT01624350): A Prospective, Multicenter, Observational Study of the Use of Permacol Collagen Paste to Treat Anorectal Fistulas (MASERATI 100). Primary comparator: n/a. Enrolment: 100. Completion date: June 2015. Location: Denmark, Italy, UK. Publications: n/a.

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Two specialist commentators had used Permacol before; 4 others were familiar with it.

Level of innovation

All specialist commentators agreed that Permacol is a variation on existing technologies such as fibrin glue and fibrin plugs. One specialist commentator noted that the evidence for these techniques suggests that they have a low efficacy. One specialist commentator noted that the injection of stem cells into fistula tracts to induce healing is a new technique that is currently being evaluated and which may eventually supersede Permacol. One specialist commentator felt that the fistula plug had probably superseded Permacol already.

Potential patient impact

The specialist commentators considered that Permacol had a number of potential patient benefits, including fewer hospital visits for post-operative wound care, reduced recurrence of fistulae and reduced post-operative incontinence. However, they noted that most of these benefits would only be realised if long-term healing rates were high. One specialist commentator noted that people having Permacol report high satisfaction and minimal pain.

One specialist commentator noted that the evidence did not indicate a particular patient group that would benefit from Permacol, because most of the evidence was from treating idiopathic fistulae and not fistulae in people with Crohn's disease. Two commentators noted that there was some evidence that Permacol may be more beneficial in shorter,

lower fistula tracts, but another noted that most of these can be managed safely by fistulotomy.

Another specialist commentator noted that Permacol may be of particular benefit to women with occult sphincter injury after childbirth.

One specialist commentator stated that Permacol would have very similar benefits to collagen plugs, and that people with high transphincteric fistulae would benefit the most from this kind of treatment.

Potential system impact

All specialist commentators agreed that few changes would be needed to facilities and NHS services for Permacol to be implemented. They stated that training would be minimal, suggesting that a demonstration video or one-off instructional course would suffice.

One specialist commentator stated that Permacol could lead to cost savings for the NHS by reducing the number of procedures needed to heal an anal fistula and the need for long-term wound care. Two specialist commentators noted that these benefits might be realised but that further evidence should be gathered to test this. One specialist commentator stated that they were unsure of any benefits because of the uncertainty of the evidence. Another 2 stated that system benefits were unlikely unless higher healing rates were realised.

General comments

One specialist commentator noted that healing in the trials may have simply been because the internal opening was closed and not because of Permacol. They suggested that a direct comparison of Permacol with closure of the internal opening only would be needed to test this.

One specialist commentator noted that in the Maserati 100 trial, failure to heal seemed to be related to residual infection at the time of injection. They felt that Permacol should not currently be used outside of a clinical trial setting.

Patient organisation comments

The Crohn's in Childhood Research Association provided the following comments on Permacol.

Permacol could offer significant benefits in terms of quality of life for patients. Anal fistulae cause nagging pain that can make it difficult to sit down, and any treatment that can alleviate this would improve quality of life. Further research may be able to identify a particular patient subgroup that would benefit the most from Permacol.

Specialist commentators

The following clinicians contributed to this briefing:

- Mr Janindra Warusavitarne, consultant colorectal surgeon, St Mark's Hospital, Association of Coloproctology of Great Britain and Ireland. No conflict of interest declared.
- Mr Baljit Singh, consultant colorectal surgeon and honorary senior lecturer, University Hospitals Leicester. Received funding for speaking events from Medtronic regarding the Permacol surgical implant for anal fistula.
- Mr Mark Potter, consultant colorectal surgeon and honorary clinical senior lecturer, Western General Hospital. No conflict of interest declared.
- Mr Christopher Morris, consultant colorectal surgeon, University Hospital of Wales. No conflict of interest declared.
- Mr Gordon Buchanan, consultant general and colorectal surgeon, Coloproctology Section, Royal Society of Medicine. No conflict of interest declared.
- Mr Robin Gupta, consultant general and colorectal surgeon, Chesterfield Royal Hospital. No conflicts of interest declared.

Representatives from the following patient organisations contributed to this briefing:

- Crohn's in Childhood Research Association (CICRA).

Development of this briefing

This briefing was developed by NICE. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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