# National Institute for Health and Care Excellence

# IP2010 Laparoscopic insertion of an inactive implant for gastro-oesophageal reflux disease

**IPAC date: 3rd April 2025**

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| 1 | Consultee 1 | Not specified | I have used this procedure in my NHS practice over the past year or so and have seen first-hand results that are quite promising. I would strongly suggest that this procedure should be made available in specialised anti-reflux NHS hospitals to allow undertreated patients to get access to this treatment and potentially avoid future more complex surgeries. Many of my NHS patients like this procedure because of its low rate of postoperative adverse events, its simplicity, and, most importantly, its ability to restore natural anatomy without interfering or significantly altering the patient's food passageway. Specifically, GORD patients with poor oesophageal motility may be a particular group that receives more treatment benefits from this procedure. Still, I would like to highlight that I have also treated standard GORD patients without motility issues, and those patients have benefited from good outcomes as well. | Thank you for your comment.<br><br>The committee discussed this comment and noted that there is an unmet need in people with ineffective oesophageal motility so decided to change the recommendation for people with ineffective oesophageal motility to special arrangements. |
| 2 | Consultee 2 | Not specified | To whom it may concern: I have been following and reviewing the status of RefluxStop's application with anticipation. The findings and conclusion you are asking the public to comment on is that the technology does not yet have enough data to be offered as a benefit within the NHS and will be categorized as "for study purposes only".<br>As a former academic research chemist and a person that suffered from acid reflux and food regurgitation for over 20 years, I would like to share my perspective with you.<br>• The disease for many can be disabling. Yes, I know everyone | Thank you for your comment.<br><br>Please see NICE's response to comment 1. |

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| | | | thinks it is only reflux, but by the time I opted to pay for this procedure privately, I barely slept at night, I had lost weight as I could not eat properly. It is difficult to imagine how much of your life is impacted. Family life, productivity, exercise, social life, etc. Sadly, this seems to be a disease that has received little attention despite the economic and social impact on society in general.<br>• Solutions are currently limited, when lifestyle changes fail to work the standard approach suggested by NICE is the use of Proton Pump Inhibitors (PPI's). Whilst PPI's may offer some efficacy for many, for others they simply do not work, and long-term use may lead to further complications as current research would now seem to suggest. Current surgical solutions such as LYNX and Nissen fundoplication (including the Watson variety etc.) use the same mechanism of action, by applying pressure to the lower oesophageal sphincter with the goal of helping the sphincter to close. These solutions can lead to post-surgical complications of which the most common is dysphagia.<br>• IEM - Ineffective oesophageal motility is a disorder that frequently accompanies and is usually caused by acid reflux disease. PPIs are often ineffective in this patient group. Current surgical solutions are limited in this group of patients to partial fundoplication such as Toupet or Watson and even these options can lead to increased swallowing difficulty. This leaves this group of patients largely without any treatment options and with the risk of developing further complications such as Barrett's disease. As a former academic research scientist, I understand the conservative stance being applied to the acceptance of new technology, however I do believe that different criteria should apply to technologies that are able to address unmet patient treatment. I received RefluxStop on September 20th, 2022, as a private patient and can honestly say that the clinical outcome has been life-changing, like winding the clock back to a time before my digestive issues began. Patients deserve to get treatment when they need it especially when | |

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| | | | existing treatment options may be ineffective, and it is NICE's and the NHS's responsibility to provide it efficiently.<br>While I applaud you for offering the public the ability to comment, I also want to request that you to seriously reconsider the restriction of access to this solution in patients with inefficient oesophageal motility. | |
| 3 | Consultee 3 | 1 | [redacted] Patient<br><br>Would you please reconsider your decision to limit the access to Refluxstop procedure.<br>I used Proton Pump inhibitor medication, firstly Omeprazole and then Lanzoperazole, after 2 or 3 years the dose of this drug had to be doubled, beyond recommended limits.<br>I was also taking over the counter medications at the same time, but with no effect. I was suffering terribly, could not have Fundoplication or Linx procedure due to motility problems.<br><br>At the end of 2022 I learnt of Refluxstop, but it was not offered by most NHS or NICE recommendations, despite my surgeon sharing with me that nearly 1000 cases had been done here in Europe. I did my own research and felt the data was good. In the end I had to pay privately to receive the device.<br>I believe the option for this device is extremely important for patients' health. More than just data needs considering.<br><br>Most leading European countries' top surgeons have been performing it with success for many years.<br>Is there a way to offer access and manage risk, or is this just an excuse to not offer it to UK patients?<br>I strongly believe it is important that patients have access to alternate procedures and methods, even if the amount of data is | Thank you for your comment.<br><br>Please see NICE's response to comment 1. |

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| | | | not staggering.<br>A different approach is desperately needed and innovation is the only way.<br>You recommend further studies, why not approve this for NHS use and do surveillance of patients after the procedure as part of any due diligence, instead of taking this crucial option away from patients. | |
| 4 | Consultee 4<br>Heartburn Cancer UK | 1 | We are requesting that you reconsider your decision to limit the utilisation of this product to studies. As a patient group, we are committed to supporting patients and their families, and are all too familiar with the devastating impact of GORD on family life and patient health. Amongst these patients are a subgroup that have very limited treatment options. On top of suffering from GORD, they also have difficulty swallowing, which makes them ineligible for surgical treatment.<br>The following study explains it well: “It has been found that those with IEM experience infirmity in food transportation of the lower oesophagus that often provokes difficulty swallowing, with further aggravation by the effect of acid reflux on oesophageal musculature and nerve function. As a result, dysphagia is prone to exacerbation following conventional anti-reflux surgery (i.e., laparoscopic fundoplication) [15], particularly in reflux patients with oesophageal dysmotility managed by this mechanism.” (Tran S, Gray R, Kholmurodova F, Thompson SK, Myers JC, Bright T, et al. Laparoscopic Fundoplication Is Effective Treatment for Patients with Gastroesophageal Reflux and Absent Oesophageal Contractility. J Gastrointest Surg. 2021;25(9):2192-200.)<br>The truly frustrating part is that up to 53.4% of these patients do not get adequate relief from using medication and thus have no further treatment options available to them. I am sure the hopelessness of their situation can be understood by all. As | Thank you for your comment.<br><br>Please see NICE’s response to comment 1. |

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| | | | RefluxStop, this new innovative procedure, does not encircle the food passageway surgeons across Europe have been performing the procedure on this patient group with great success. Although the analysis shows that the data is still not enough to meet NICE's standards for approval, we feel that those patient having undergone the procedure to date are doing well with positive outcomes, and no harm has come to anyone. Published data up to four years show that outcomes stay consistent which means relief and a normal life for at least four years for this patient group. We believe that making this product only available via studies would make it impossible for this group of patients with no other options to receive treatment. Traveling to designated study sites will impact them both economically and compromise even more of their time to a disease that is already overshadowing their social and family lives. We request you consider making this procedure available to at least this group of patients via the NIH improved patient care and innovation to support quality of life is what we are all striving for. | |
| 5 | Consultee 5 Implantica AG | Not Specified | First, we would like to thank NICE for their invaluable efforts to prioritize and review the safety and efficacy of the innovative RefluxStop™ procedure for the NHS use considerations in England.<br><br>We appreciate the extensive evidence review of RefluxStop™ 's published safety and patient outcomes data along with a perspective on its future potential based on existing data and several ongoing real-world and research study projects aiming to further establish RefluxStop™ 's significant potential demonstrated in our one-of-its-kind 5-year CE Mark study with its study design and outstanding long-term clinical results. As noted, the 4-year long-term CE Mark study results have already been published in one of the most prestigious peer-reviewed scientific journals, | Thank you for your comment.<br><br>The committee considered the unpublished data provided by the company. Whilst the committee acknowledged the unpublished evidence shows similar safety and efficacy evidence, the committee thinks further evidence on long-term efficacy is needed. However, the |

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| | | | Surgical Endoscopy, in the U.S earlier this year. Furthermore, the phenomenal 5-year study results, similar to 4-year published data, that have recently been presented at many leading congresses are also expected to be published soon, along with several more publications from many independent real-world studies from top hospitals across Europe.<br><br>We are truly grateful and in agreement with NICE's key positive evidence observations and encouraging open-minded comments regarding RefluxStop™'s existing safety data and its potential role in treating more complex GORD cases, acknowledging that not only is there evidence that the RefluxStop™ procedure works but also confirming that the short-term safety evidence of the RefluxStop™ procedure suggests that this procedure is as safe as other common laparoscopic procedures for GORD. Moreover, we fully agree with NICE's review that for those with more complex GORD cases, such as GORD with ineffective oesophageal motility (IOM) disorders or larger Hiatal Hernia, there are limited treatment options where the RefluxStop™ procedure could provide a minimally invasive option for people with IOM disorders or for patients with chronic GORD whose symptoms have not responded adequately to lifestyle modification and drug therapy. The NICE committee also noted that the RefluxStop™ procedure does not encircle the oesophagus and that it may result in less bloating than other procedures.<br><br>Overall, we would like to applaud and echo NICE's positive perspective, observations, and reassuring comments about RefluxStop™'s existing safety profile and its potential role in treating more complex GORD cases. With its continued robust safety profile, we believe RefluxStop™ could transform the GORD treatment landscape for these hugely underserved subpopulations of severe GORD patients. | committee noted that there is an unmet need in people with ineffective oesophageal motility, so they decided to change the recommendation for people with ineffective oesophageal motility to special arrangements. |

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| | | | Having said that, we also understand from this preliminary guidance that the NICE IP Advisory Committee would like to see more long-term published data further validating long-term outcomes of the RefluxStop™ procedure before considering wider use 'Special Arrangements' recommendation (vs. 'Research Only') status for this procedure for NHS use.<br><br>Although we much appreciate NICE' IP positive recommendations to already allow RefluxStop procedure use in the NHS under 'Research Only' setting while continue to collect more data, we strongly believe this can lead to unintended consequences of blocking RefluxStop's access and availability for many eligible patients who will be deprived of possibly the only reasonable treatment they can get for GORD treatment. In this regard, we believe that a 'Special Arrangements' status for the RefluxStop™ treatment would be more suitable and appropriate to allow sufferers to opt for this procedure on an individual basis while also allowing the ultimate goal of collection of more data as part of ongoing Registry and other studies along the way.<br><br>Therefore, to further justify 'Special Arrangements' status for the RefluxStop™ procedure, we would like to provide NICE with the crucial additional information and data to enable NICE to make best-informed decision without causing a significant delay and blockage in patient access to a much needed and well-proven treatment.<br><br>So far, Implantica has provided NICE with 5-year long-term results from our European CE Mark study (expected to be published in coming months), which, in our understanding, is regarded as one of the "best designed with best-results" studies of its kind in antireflux surgery by many leading gastrointestinal surgeons and | |

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| | | | experts. According to our extensive literature review research and scientific discussions with experts, it is clear to us that this long-term clinical study is one of its kind, upholding the highest standards of a clinical trial, patient compliance and follow-up, and having the most objective endpoint (i.e., pH measurement) used as an accurate measure of antireflux surgery success at 5-year follow-up in addition to patient-reported outcomes (i.e., GERD-HRQL score), side-effects, and safety endpoints. The 5-year results have been used in our FDA filing and is on its way to be published.<br><br>Notably, 100% of the available patients still in the study performed the 5-year visit (i.e., three lost to COVID and three terminated early 3-6 months), which is very unusual after 5 years. The objective pH measurement was normal in all patients (presented as in the LINX FDA Summary Memorandum). Only one patient took PPI medication after 5 years compared to 100% before surgery. Such results are unheard of; for example, in the LINX FDA study 36% of subjects failed the pH test at 1 year and the same failure rate is expected among PPI users (39%) [1]. The excellent outcomes from such a high-quality trial demonstrate the significant evidence of long-term and sustained outcomes of the RefluxStop™ procedure.<br><br>The data from this crucial RefluxStop™ CE Mark study is important because it is both high quality and with long-term follow-up. The FDA accepted that study size alone is not the only consideration, but, in fact it is crucial to consider the study size in relation to the outcome of the study in achieving statistical significance. The 5-year results of this study are well-established and statistically significant when compared to the standard of care. The recently published literature review of standard-of-care Nissen fundoplication (in European Surgery) on 63 randomised controlled | |

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| | | | trials is the largest of its kind and is helpful for a comparison to other treatments, see Appendix at the end of this letter.<br><br>The excellent results from the RefluxStop™ CE Mark study have now been replicated in real-world settings with data from ~10 hospitals. Many of these leading independent experts are now in the process of publishing respective real-world clinical data (up to 4 years) in top-tier and renowned peer-reviewed journals within the next 1-6 months. An overview of the articles in the pipeline follows with most articles having been submitted to journals already:<br><br>• >400 patients' safety data from multiple European hospitals.<br>• 5-year pivotal study data, with very high-quality prospective data and exceptional results.<br>• Two-centre study with 60 IOM patients.<br>• Two-centre study with large and small hernia (i.e., 52 and 50, respectively) patients.<br>• Single-centre on 79 patients, a positive review to be published after a minor revision.<br>• Single-centre 4-year data on 22 patients.<br>• Single-centre data on 60 patients.<br><br>Ultimately, RefluxStop™ procedure is expected to be supported by effectiveness and safety data on more than 450 patients, as well as an additional 400 patients with safety data only (including maybe 150 patients overlap). These imminent datasets collectively represent the vast breadth and depth of experience and evidence on the RefluxStop™ procedure from dozens of leading universities and teaching hospitals across Europe that we believe will significantly help NICE source adequate clinical evidence to make an informed decision on RefluxStop™ guidance for NHS use in 1-6 months from now. | |

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| | | | Here is additional background information on the overall RefluxStop™ experience and data development journey across Europe since 2018:<br><br>• Since CE approval in 2018, the RefluxStop™ device has been used in nearly 1,000 procedures in more than 40 renowned antireflux surgical centers (i.e., Public Universities, Teaching Hospitals, and Specialized Centers) across Germany, Switzerland, Austria, UK, Italy, Spain, Sweden, and Norway that are active users of RefluxStop™. Since the surgeons involved in the IPAC meeting had very limited or no experience with RefluxStop™, it could be beneficial for the committee to receive feedback from some of the leading antireflux key opinion leaders that actively perform RefluxStop™ surgeries; if it would be of interest to NICE, independent and experienced RefluxStop™ users could join the next IPAC meeting.<br><br>• Many NHS hospitals are currently very interested in beginning to perform the RefluxStop™ procedure. About 20 UK surgeons spent a day joining our 2024 user meeting; however, it will take some time before they reach the pan-European experience level.<br><br>• In any medical device review, the importance of safety cannot be understated, and this consideration was central to the design of the RefluxStop™ device and surgical procedure development. As a surgeon in this field, I saw first-hand the suffering of patients, not only from the disease itself but also from the side effects of standard-of-care acid reflux surgery. I also gained much insight and experience from developing the Swedish Adjustable Gastric Band (SAGB), which I was able to apply when inventing the RefluxStop™ system. The key experience has been summarised in the procedure as follows: | |

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| | | | o RefluxStop™ is encapsulated in a pouch of stomach wall placed on the outside of the stomach. Therefore, any possible harm can only be caused if RefluxStop™ leaves the pouch. This pouch hangs in a teardrop shape down into the stomach cavity and is sutured with a row of sutures above. Therefore, in the unlikely event that the device erodes or migrates, it ends up in the stomach cavity. Due to the device design in pieces, it will pass out through the digestive tract without any symptoms or reoperative measures, with the patient still treated. We analysed all migrations in gastric banding involving 468 SAGB articles, and no emergency surgery occurred in this literature review for migration because tissue heals at the same speed as the device migrates. Therefore, RefluxStop™ has shown to be extremely safe.<br><br>• While complications related to surgery may always occur, in the RefluxStop™ CE mark study between years 1-5, only two minor procedure-related AEs occurred, one temporary mild dysphagia and one moderate dyspepsia.<br>• The RefluxStop™ design has now been proven in real-world settings to function as intended based on the first 1,000+ patients operated on, where all complications have been tracked in our complaint system. In a few cases, the pouch has been sutured too tightly with the result that the device penetrated early into the stomach cavity, mainly unnoticed and still with a treated patient.<br><br>Implantica's Overall Conclusion and Request to NICE<br><br>In summary, once again, we fully agree with NICE's key observations and statements that not only is there evidence that the RefluxStop™ procedure works but also confirming that the short-term safety evidence of the RefluxStop™ procedure suggests that this procedure is as safe as other common laparoscopic procedures for GORD while also highlighting that | |

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| | | | RefluxStop™ may be the appropriate treatment options for those with more complex cases, such as those with oesophageal dysmotility (such as IOM disorders), larger HH, or preoperative dysphagia.<br><br>Accordingly, we believe that RefluxStop™ NICE IP guidance process should be delayed for another 9-months period based on the following two crucial issues that can also help improve care and access for British GORD patients:<br><br>1. We believe the imminent additional clinical data would tremendously help the IPAC process to further conclude that RefluxStop™ procedure is safe and effective not only in short-term but also in the long-term and real-world setting shown in over 1000 patients.<br>a. The 5-year CE Mark study results, that are expected to be published within the next 1-6 months, represent long-term data of the highest quality and was used for our PMA application to the FDA. And for real-world data, there are several other articles from various hospitals that are expected to be published within the next 1-6 months as well, will dramatically increase the quantity of high-quality data NICE has reviewed thus far to solidify RefluxStop™ 's safety and efficacy in all settings.<br><br>2. Subject to extensive IOM data availability (40+20 patients' data from 3 centers across Switzerland, UK, and Austria) so far and more to come during the next 1-6 months, we believe NICE should consider approving broader "Special Arrangements" category at least for IOM patient population as a starting position, which would be more in line with NICE conclusive remarks that there is a huge patient unmet need in IOM group due to lack of any appropriate treatment solutions.<br>a. An additional 60 IOM patients are included in this data package | |

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| | | | showing excellent results over 3-47 months of follow-up, adding to the two already-published articles with 40 and 20 IOM patients, respectively.<br>b. These patients have no suitable treatment today and need special consideration due to the severe dysphagia experienced, resulting from weak food transportation in the oesophagus. The RefluxStop™ mechanism of action of not encircling the food passageway, in contrast to the existing care treatments such as Magnetic Sphincter Augmentation (MSA) or Nissen fundoplication, logically demonstrates that the RefluxStop™ treatment is particularly beneficial in treating IOM patients, as supported by real-world evidence outcomes.<br>c. The request to grant “Special Arrangement” status, at least for the IOM patient group, is not only supported by the existing (and upcoming) peer-reviewed scientific evidence articles but is also heavily fueled by logic. These IOM subjects have no contractile power in oesophageal musculature and experience weak transport of food in the food passageway, causing severe swallowing difficulties if operated on with standard-of-care procedures that encircle the food passageway. RefluxStop™ does not encircle the food passageway and, therefore, does not cause additional swallowing difficulties based on its mechanism of action. This has been shown in real-world evidence, including two articles with 60 and 40 IOM patients from University Hospitals (respectively): one published and the second submitted and foreseen to be published within the proposed delay of the review. These outcomes have also been summarized in the Appendix.<br><br>Therefore, in line with the above two key issues, we urgently request NICE to delay the IPAC decision process for another 9 months so all new crucial data can be included in the NICE review, enabling the committee to make the most informed decision for British patients. | |

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| | | | We sincerely appreciate your leadership and your team's significant reports on this project. We believe such a delay in the decision will be of great justice to your tremendous reports and resources spent, the larger reflux medical community's extensive scientific and clinical work, and, most importantly, to patients who can rightly benefit from this treatment option. Therefore, we hope NICE will allow an additional 9 months of delay in this IP guidance decision process.<br><br>References after the Appendix below.<br><br><br>APPENDIX, we refer to the Appendix included in the letter sent to Prof. Clutton-Brock<br><br>The appendix includes a summary of the outcome of two key articles that are expected to be published in the near-term (in 1-6 months), during the proposed delay of the review process.<br>A) The IEM article of 60 subjects 3-47 months follow-up.<br>B) The 5-year article used in the FDA submission<br><br>A: DYSPHAGIA, SAFETY, AND EFFECTIVENESS OF THE REFLUXSTOP PROCEDURE IN GERD PATIENTS WITH INEFFECTIVE ESOPHAGEAL MOTILITY (IEM): MULTICENTER RESULTS IN SWITZERLAND FOR UP TO 4 YEARS<br>Joerg Zehetner, Dino Kröll, Yannick Fringeli, Ioannis Linas, Sarah Gerber, Yves Borbély<br>Submitted to Surgical Endoscopy – in peer review [3].<br><br>Background<br>Patients treated with the RefluxStop procedure with gastroesophageal reflux disease (GERD) and Ineffective | |

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| | | | Esophageal Motility (IEM) followed for up to 4 years.<br><br>Results<br>Sixty (n=60) subjects with IEM underwent the RefluxStop procedure, with a follow-up<br>ranging between 3-47 months (mean 13 months). Median (Q25-Q75) improvement in<br>GERD-HRQL score was 89% (83-96%) with statistical significance (p<0.001; Wilcoxon<br>test). At last follow-up, 92% of the subjects experienced >50% improvement in GERDHRQL score. Of the 40 subjects that reached 1-year follow-up, n=14/40 (35%) had dysphagia at baseline, which resolved or improved in 12 subjects and worsened in one subject. Thus, there is a significant higher likelihood of dysphagia improvement compared to unchanged or worsened status (p=0.013).<br><br>Conclusion<br>RefluxStop surgical management for GERD e>ectively treats subjects with IEM (n=60),<br>who currently have no optimal treatment, while maintaining excellent results for up to 4 years with excellent improvement of GERD-HRQL score (median 89%) and dysphagia (86% resolved or improved at 1 year).<br><br>Key Results<br>Total GERD-HRQL score improvement in 60 subjects with GERD and IOM treated by the<br>RefluxStop procedure at two centers in Switzerland, with a follow-up ranging between 3-47 months.<br>• There was a significant reduction in GERD-HRQL score (p<0.001; Wilcoxon test).<br>• At last follow-up, a mean of 13 months (3-47 months), five | |

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| | | | (n=55/60) subjects experienced <50% improvement of GERD-HRQL total score.<br>• Thus, 92% of the subjects had >50% improvement of the GERD-HRQL score.<br>• The median (Q25-Q75) improvement in GERD-HRQL score was 89% (83-96%) with a range (min-max.) of improvement (24-100%).<br><br>IEM subjects with preoperative dysphagia, operated on with the RefluxStop procedure at two centers in Switzerland with a follow-up of 1 year (n=40) operated on at University Inselspital and Hirslanden Clinic Beau-Site with n=14/40 (35%) of subjects having dysphagia at baseline. Among these,<br>• Twelve (n=12) improved or resolved.<br>• One (n=1) was unchanged.<br>• One (n=1) worsened.<br>• The probability of improvement was 86%.<br>• There was a significantly higher probability of improvement compared to unchanged or worsened status (p=0.013).<br><br>B: 5-YEAR RESULTS OF THE REFLUXSTOP™ CE STUDY USED IN THE FDA SUBMISSION<br><br>The extensive literature review that has recently been published (European Surgery) searched for all articles on Nissen fundoplication, the standard-of-care surgical treatment in this field, wherein 63 randomised controlled trials had been selected for analysis. This is a very relevant platform to compare RefluxStop™ against Nissen fundoplication, the standard of care.<br>Data between Nissen fundoplication and RefluxStop™ compared at 5 years:<br><br>Inability to belch and/or vomit occurs in<br>o Nissen fundoplication 39.8% | |

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| | | | o RefluxStop™ 0.0%;<br><br>Swallowing difficulties / Dysphagia AE occurs in<br>o Nissen fundoplication 28.9%<br>o RefluxStop™ 2.3%;<br><br>PPI use occurs in<br>o Nissen fundoplication 12.0%<br>o RefluxStop™ 2.0%<br><br>Reoperation occurs in<br>o Nissen fundoplication§ 8.7%<br>o RefluxStop™ 2.0%.<br><br>LINX FDA summary memorandum and RefluxStop™ CE study compared results at 1 year:<br><br>Dysphagia AE<br>o LINX 68%<br>o RefluxStop 2%<br><br>Failed 24-hour pH testing<br>o LINX 36%.<br>o RefluxStop™ 2%<br><br>About 48,000 people in the US and EU alone die from oesophageal adenocarcinoma. In a large registry study in Sweden (i.e., >790,000 subjects) by Brusselears et al. (2018), 38% of these cancer patients had been taking PPI medications. If I perform endoscopy (gastroscopy) on acid reflux sufferers in general, I find 10-20% with precancerous changes (Barrett's oesophagus). This is a very strong indication that most of these 48,000 deaths are caused by acid reflux by way of Barrett's oesophagus, which we | |

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| | | | know results in fulminant cancer. Considering the effort taken to detect breast cancer and the observation of ~48,000 persons dying annually from oesophageal cancer without paying heed, it is an unacceptable situation for patients suffering from GORD without adequate treatment. We know, for example from the study by Becker et al., that patients treated by PPI therapy also fail 24-hour pH testing in 39% of cases.<br><br>In a nutshell, the current 5-year data and evidence demonstrates that the RefluxStop™ procedure is significantly superior to both fundoplication and LINX. This evidence is growing with more independent research and real-world experience that is being published rapidly.<br><br>While more evidence is always preferred, for new disruptive technologies it is also crucial to show timely utilisation in the market space to show it can effectively reach patients that need it the most.<br><br>Implantica is a small company that is dedicated to research and bringing new technologies into the world. We are not a corporate or large medical company with multiple commercial products that can take decades to deliver high quality evidence. We have meticulously developed the crucial evidence base needed to demonstrate RefluxStop™'s impact on patients and the healthcare system and will continue to build the growing datasets showing robust scientific rigor of this breakthrough procedure.<br><br>References<br>1. Becker V, Bajbouj M, Waller K, Schmid RM, Meining A. Clinical trial: persistent gastro-oesophageal reflux symptoms despite standard therapy with proton pump inhibitors - a follow-up study of intraluminal-impedance guided therapy. Aliment Pharmacol Ther. | |

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| 6 | Consultee 5 Implantica AG | 1.1 1 Draft recommendations | Thank you for the in-depth review of the clinical data of RefluxStop™. We understand that NICE only reviews published data, however, the CE-study with 5-year follow-up is the most important and most high-quality data collected on RefluxStop™, which is expected to be published within the next few months. However, the 5-year CE Mark data has been presented at several leading congresses and has also been used in our highly demanding PMA submission process to the FDA (for approval to sell in the US). This means that these data are currently under rigorous control by the FDA and their response to this review of the 5-year CE Mark study data (central part of the clinical section submitted to FDA) is expected within 1-3 months.<br><br>In addition, a third article will soon be published on another 60 patients with ineffective oesophageal motility (IOM), resulting in a total amount of 40+20+60 = 120 patients with IOM. This group of patients cannot be successfully treated with standard-of-care surgery due to causing worsened dysphagia/swallowing difficulties instead of improving such symptoms, as observed in this latest IOM article on the RefluxStop™ procedure. Furthermore, this is strongly supported by the fact that RefluxStop™ does not encircle the food passageway, as is the case with standard-of-care treatments, making it an obviously better treatment for this patient category of severe sufferers that lack good treatment today.<br><br>As previously communicated in the Implantica's overall summary statement, we would like to request an additional 9 months (delay) in the decision-making process pertaining to the status of RefluxStop™ NICE IP Guidance on [GID-IPG10345]. This would allow for the imminent publication of several clinical studies that | Thank you for your comment.<br><br>Please see NICE's response to comment 5. |

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| | | | are currently in peer review and expected to be in the public domain in the next 1-6 months. This clinical data is pertinent to the queries pending from the NICE IP guidance committee, encompassing broadened understanding of the indicated patient population, bolstering of patient-reported outcomes (i.e., quality of life), and presentation of long-term safety and efficacy. This upcoming package of data will both supply high quality 5-year long-term data as well as substantially more real-world data currently not taken into account by NICE.<br><br>NICE noted that the patient population should be further defined. We would like to highlight for NICE that the CE Mark study included a group of standard acid reflux sufferers who were well treated at 5-year follow-up. The improvement in outcome is substantial and since there is a published, very extensive and high-quality literature review performed on Nissen fundoplication, we have reasonable ground to compare non-randomised data with results, which delineates a night and day comparison. See the Appendix included in the section named 'Comment on this document'.<br><br>This essentially means that the RefluxStop procedure is well-suited for all standard severe acid reflux patients, so not only the ones who traditionally qualify for other anti-reflux surgeries, but also a large number of previously untreatable patients, including the following 3 key subpopulations where RefluxStop real-world data shows exceptional patient outcomes as well:<br>A) Ineffective oesophageal motility [IOM],<br>B) Hiatal hernia size >3 cm (usually 3-8cm), or<br>C) Revisional surgery patients (with failure of previous antireflux surgery - potentially precluding subsequent treatment due to technical considerations and physiologic implications). | |

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| | | | Regarding appropriate patient population for RefluxStop procedure:<br><br>First and foremost, in Europe, the RefluxStop™ device is CE Marked, approved, and indicated for any patient suffering from GORD, including those who no longer wish to continue PPI usage. Given the far superior treatment results evidenced by RefluxStop™ outcomes as well as the seriousness of the disease not only by patient-reported symptoms but also by the potential progression to Barrett's oesophagus and eventual oesophageal adenocarcinoma if left untreated or undertreated (as in the case with up to 40% of PPI users), there is a need for availability of this new antireflux treatment for sufferers. RefluxStop™ was first operated with in patients in the CE Mark clinical investigation eight years ago in December 2016, and has 5-year follow-up data available, the manuscript of which is under development and expected to be submitted for publication in the beginning of 2025. Therefore, a delay in the decision-making process at NICE would allow these long-term outcomes to be included in your assessment. This is important for the sufferers to have an additional safe and effective treatment option. To be precise, as confirmed by the experienced European users of RefluxStop™, this procedure has the potential to revolutionise this treatment field and can potentially become the standard of care for GORD in future.<br><br>As such, ideally, we would like to advocate for an updated status of 'Special Arrangements' for the RefluxStop™ procedure in general given the overall substantial unmet needs of UK patients with GORD. However, at a minimum, we believe that the IOM patient group should be considered as a first priority patient group where the RefluxStop™ procedure could be approved for NICE IP Guidance with a "Special Arrangement status for IOM patients". | |

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| | | | Having said the above, we should always remember every patient is unique, different, and patient preferences or outcomes can always be a question how long-time patients must wait for dramatically better treatment. In Implantica's global experience in working with the finest of all GORD specialized surgeons, we believe the 5-year data of a prospective high-quality study combined with a multitude of real-world data is widely considered as more than sufficient for a 'Special Arrangements' status approval where patients could decide which procedure they want (subject to surgical expert's opinion), which we believe will be the case after a 9-month delay of this process.<br><br>More data is not changing the fact that the NICE-recommended standard-of-care antireflux procedures in the UK today are associated with a substantial burden of unmet needs (i.e., postoperative sequelae) and are not approved or considered appropriate for sizable patient sub-populations with difficult-to-treat comorbidities. We encourage the NICE evidence review team to please carefully review the literature review of standard-of-care Nissen fundoplication published in European Surgery [1]. It may seem unimportant that 40% of the patients can't belch or vomit compared to 0% when operated with the RefluxStop™ procedure, however, it is quite the opposite and very important for patients; this is just one of many examples of adverse events that is important for the patients.<br><br>Therefore, Implantica requests a 9-month delay to be able to build support for a higher reference level. Ultimately, we believe that this evidence base, encompassing a broadened patient population representative of real-world settings, merits consideration toward a 'Special Arrangements' status for RefluxStop™ to help satiate the unmet needs of sufferers and eagerness of UK surgeons. | |

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| | | | In summary: As the significant existing and emerging evidence base on the RefluxStop™ procedure shows, not only is it approved and safe in the standard GORD population, but it is also the first-ever treatment that effectively provides considerable benefit to the broader patient population with difficult-to-treat comorbidities, as mentioned above.<br><br>To date, safety and effectiveness data for RefluxStop™ is available for over 450 patients, with an additional 400 patients pertaining to safety data only (including ~150 patients of overlap) and has been rigorously presented/discussed in the international GORD scientific community of experts in the US, UK, and Europe. Much of this data is also published in peer-reviewed journals with additional clinical data expected to be published in the next 1-6 months or so, which adds to the data available for your review, should you agree to a delay in your decision.<br><br>Clinical results from the RefluxStop™ CE mark trial showed excellent safety and effectiveness that remained consistent and stable from 1 to 5 years. This evidence is demonstrated in the published 1-, 3- (accepted for publication in Digestive Diseases and Sciences since filing with NICE), 4-year results, with the 5-year outcomes to undergo peer review soon. Together, the outcomes from respective follow-up periods show that RefluxStop™ is effective in sustained treatment of GORD with an exemplary safety profile that is enduring in the long term. For instance, data from 5-year follow-up of the RefluxStop™ CE mark trial with an exceedingly high rate of compliance and follow-up show that the procedure resulted in:<br>• No cases of re-herniation.<br>• No cases of device dislocation.<br>• No cases of device migration. | |

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| | | | • No cases of explantation.<br>• No cases of oesophageal dilatation.<br><br>Furthermore, only two cases of procedure-related adverse events (i.e., one case of temporary, mild dysphagia and one case of moderate dyspepsia) and no severe adverse events occurred during years 1-5. The patient with dysphagia had a GERD-HRQL Dysphagia sub score of 5 (maximum) at baseline, which improved to a score of 2 at 3-year follow-up, indicative of improvement rather than a postoperative adverse event. Together with the plethora of data from investigator-initiated studies, this posits the vast breadth and depth of experience with the RefluxStop™ procedure sourced from dozens of leading academic centers (i.e., universities) and teaching hospitals across Europe, likely to significantly bolster the informing evidence for guidance by NICE and would justify waiting another 9 months before finalising the NICE decision.<br><br>Since introduction of RefluxStop™ in 2018, over 1,000 cases have been performed at more than 40 renowned anti-reflux surgical centers. Based on our understanding from extensive discussion with UK surgeons, there is substantial interest from many NHS hospitals and UK GORD patients that are sub-optimally managed with existing treatment options pertaining to the availability of RefluxStop™ in the UK. Moreover, additional pan-European safety and effectiveness evidence is expected in 2025 regarding a large registry, randomised controlled trial (RCT) against Nissen fundoplication (with a substantial proportion of UK patients enrolled at a NHS hospital), and a RCT against PPI therapy. Thus, we believe that an updated ‘Special Arrangements’ status would provide an avenue for both surgeons and patients in the UK that will also contribute to regional research.<br><br>References | |

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| | | | 1. Zehetner, J., Hoffsten, J., Das, S. et al. Looking back on a gold standard: a systematic literature review of laparoscopic Nissen fundoplication as an anti-reflux treatment option. Eur Surg 56, 143–171 (2024). https://doi.org/10.1007/s10353-024-00836-z | |
| 7 | Consultee 5 Implantica AG | 1.2 1 Draft recommendations | Although we much appreciate NICE' IP positive recommendations to already allow RefluxStop procedure use in the NHS under 'Research Only' setting while continue to collect more data, we strongly believe this can lead to unintended consequences of blocking RefluxStop's access and availability for many eligible patients who will be deprived of possibly the only reasonable treatment they can get for GORD treatment. In this regard, we believe that a 'Special Arrangements' status for the RefluxStop™ treatment would be more suitable and appropriate to allow sufferers to opt for this procedure on an individual basis while also allowing the ultimate goal of collection of more data as part of ongoing Registry and other studies along the way.<br><br>Therefore, to further justify 'Special Arrangements' status for the RefluxStop™ procedure, we would like to provide NICE with the crucial additional information and data to enable NICE to make best-informed decision without causing a significant delay and blockage in patient access to a much needed and well-proven treatment.<br><br>Moreover, as part of our review of NICE's initial assessment, we have provided identification and correction of important factual inaccuracies of clinical data pertaining to RefluxStop, some of which directly address NICE's concerns regarding data perception (e.g. statistical significance, p-value about treatment effect), that bolster the overall treatment effect of RefluxStop and are applicable for 'Special Arrangements' consideration. | Thank you for your comment.<br><br>Please see NICE's response to comment 5. |

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| 8 | Consultee 5 Implantica AG | 1.3 1 Draft recommendations | 1.3.1 Patient Population<br><br>We understand that there are some queries regarding the patient population indicated for management of GORD with RefluxStop™. Beyond the strictly controlled patient population of the RefluxStop™ CE mark trial, the procedure has shown to have exemplary potential in a broader patient population that includes those with IEM, hiatal hernia >3 cm, and/or failure of previous anti-reflux surgery.<br><br>IOM patients: Pertaining to the IOM population of GORD patients, three retrospective studies have been published with up to 60 patients having IOM, one of which included UK patients, and demonstrated excellent clinical effectiveness with an impressive safety profile as indirectly compared to standard-of-care treatment [1-3]. This observation prompted a longer-term multicentre, investigator-initiated study in Switzerland with results up to 3 years [4]. This manuscript is currently in peer review and publication is anticipated in the next few months. Collectively, these reports evidence the excellent improvement in GORD symptoms, quality of life, reliance on medical therapy, acid exposure, and aversion of postoperative dysphagia (i.e., typical following standard-of-care antireflux surgery and likely due to RefluxStop™'s pioneering and non-encircling mechanism of action), indicative of a favourable and comprehensive treatment effect.<br><br>Hiatal hernia patients >3 cm in size: Regarding GORD patients with hiatal hernia size >3 cm, an arduously managed demographic often experiencing re-herniation that necessitates re-operation, two studies have been published and delineate the aptitude of RefluxStop™ in treatment of such patients with some patient overlap [5,6]. These reports prompted a comprehensive multicentre study comparing clinical outcomes of RefluxStop™ | Thank you for your comment.<br><br>Please see NICE's response to comment 5. |

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| | | | surgery in patients with either small (<3 cm) or large (4-10 cm) hiatal hernia and found equally favourable and excellent outcomes for both safety and effectiveness [7]. The results of this soon expected to be published study were quite comparable regardless of hernia size, and in conjunction with the published data contend a broader applicability of RefluxStop™ in patients with large hiatal hernia that have limited treatment options.<br><br>Failure of previous antireflux surgery (revisional surgery): Previous antireflux surgery with fundoplication techniques (i.e., Nissen, Toupet, and Dor fundoplication), MSA, EndoStim, and the BICORN procedure are variably associated with treatment failure. In such cases, technical considerations and physiologic implications (e.g., fibrosis of fundus tissue from fundoplication) may preclude subsequent surgical management, thus limiting decision-making capabilities. Recently, a multicentre report of 24 patients describing the feasibility and surgical technique of conversion to RefluxStop™ surgery from MSA (38%), Toupet fundoplication (29%), Nissen fundoplication (13%), Dor fundoplication (8%), BICORN (8%), and EndoStim (4%) was submitted to DDW 2025 conference and is anticipated to be submitted to journal in early 2025. Briefly, the authors state that conversion to RefluxStop™ from previously failed antireflux surgery is feasible and is particularly easier from MSA or EndoStim. Further study is required to delineate the clinical outcomes in such cases but the feasibility of conversion to RefluxStop™ indicate an additional patient demographic that may benefit from availability of the procedure on a ‘Special Arrangements’ basis.<br><br>In addition to the reports solely comprised of patients with IOM or hiatal hernia size >3 cm, many of the investigator-initiated studies currently in peer review include significant proportions of patients | |

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| | | | with either condition [8-10] and are expected in the public domain soon. Ultimately, we believe that this evidence base, encompassing a broadened patient population representative of real-world settings, also merits consideration toward a 'Special Arrangements' status for RefluxStop™ to help satiate the unmet needs of sufferers and eagerness of UK surgeons.<br><br>References<br>1. Fringeli Y, Linas I, Kessler U, Zehetner J. Short-term results of laparoscopic anti-reflux surgery with the RefluxStop device in patients with gastro-esophageal reflux disease and ineffective esophageal motility. Langenbecks Arch Surg. 2024 Feb 29;409(1):78. doi: 10.1007/s00423-024-03264-5. PMID: 38418718; PMCID: PMC10901965.<br>2. Fringeli Y, Linas I, Kessler U, Zehetner J. Exploring the feasibility and safety of laparoscopic anti-reflux surgery with the new RefluxStopTM device: a retrospective cohort study of 40 patients. Swiss Med Wkly [Internet]. 2024 Jul. 15 [cited 2024 Dec. 4];154(7):3365. Available from: https://smw.ch/index.php/smw/article/view/3365<br>3. Feka, J., Saad, M., Boyle, N. et al. Multicentric short term and safety study of ineffective esophageal motility patients treated with RefluxStop device. Sci Rep 14, 15425 (2024). https://doi.org/10.1038/s41598-024-65751-5<br>4. Zehetner J, Kröll D, Fringeli Y, et al. Dysphagia, safety, and effectiveness of the RefluxStop procedure in GERD patients with ineffective esophageal motility (IEM): Multicenter results in Switzerland for up to 3 years. In peer review with Surgical Endoscopy. 2024.<br>5. Fringeli, Yannick MD*; Linas, Ioannis MD†; Kessler, Ulf MD*; Zehetner, Joerg MD, MMM*. Laparoscopic Large Hiatal Hernia Repair With RefluxStop: Outcomes of Six Months Follow-up in Thirty Patients. Surgical Laparoscopy, Endoscopy & Percutaneous | |

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| | | | Techniques 34(2):p 143-149, April 2024. \| DOI: 10.1097/SLE.0000000000001256<br>6. Fringeli Y, Linas I, Kessler U, Zehetner J. Exploring the feasibility and safety of laparoscopic anti-reflux surgery with the new RefluxStopTM device: a retrospective cohort study of 40 patients. Swiss Med Wkly [Internet]. 2024 Jul. 15 [cited 2024 Dec. 4];154(7):3365. Available from: https://smw.ch/index.php/smw/article/view/3365<br>7. Borbély Y, Kröll D, Fringeli Y, et al. A safety and effectiveness evaluation of RefluxStop in the treatment of acid reflux comparing large and small hiatal hernia groups: Results from 99 patients in Switzerland. In peer review with Hernia. 2024.<br>8. Lehmann T, Šimkus M, Oehler C. A retrospective study assessing RefluxStop surgery for gastroesophageal reflux disease: Clinical outcomes in 79 patients from Germany. In peer review with Surgery Open Science. 2024.<br>9. Elshafei M. Experience with an innovative surgical treatment for gastroesophageal reflux disease: Results of 28 patients in a retrospective analysis. In peer review with Journal of Laparoendoscopic & Advanced Surgical Techniques. 2024.<br>10. Borbély Y, Prevost G, Haltmeier T, et al. RefluxStop: 3-year results of a novel procedure to address gastroesophageal reflux disease. In peer review with Surgical Endoscopy. 2024.<br><br>1.3.2 Patient-Reported Outcomes<br><br>Patient-reported outcomes are important in discerning quality of life following surgical treatment of GORD. As such, we believe that the published and unpublished clinical evidence denotes the excellent patient-reported outcomes, as measured by GERD-HRQL score, symptoms reduction of GERD, satisfaction that are significant and sustained from 1- to 5-year follow-up in the RefluxStop™ CE mark trial [1-4] and further bolsters by impressive | |

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| | | | results in real-world settings (as described above in the response to patient population queries). The total GERD-HRQL score improved by mean 86% (p<0.001) [1], median 93.1% (p<0.001) [2], median 90% (p<0.001) [3], and median 90% (p<0.001) [4] at 1, 3, 4, and 5 years, respectively. Moreover, at 5 years 92.5% (n=41/44) of patients had no or minimal regurgitation, 88.6% (n=39/44) had no gas-bloating or significant improvement, and only one patient was dissatisfied (i.e., had pathologic 24-hour pH testing result in which postoperative x-ray showed borderline positioning of the device too low) [4]. These results show the excellent and sustained quality of life in the short, mid, and long term.<br><br>Furthermore, these subjective outcomes are supported by measures of true effectiveness, such as pH testing and DeMeester score. For instance, the short-term results of RefluxStop™ surgery result in substantial reductions in acid exposure time (i.e., percent time with pH <4) from 16.35% at baseline to 0.8% at 6 months with 98% of patients achieving normalisation [1]. This objective treatment effect was maintained up to 5 years as appreciated by a low acid exposure time of 1.57%, 90.4% mean reduction on pH testing, and 91.5% (n=43/47) of patients achieving normalisation on 24-hour pH testing with only three (n=3) pathologic DeMeester scores (i.e., categorized as low, mild) [4].<br><br>In summary, clinical effectiveness measured by patient-reported outcomes is substantial and maintained in the long term, supported by objective measures to denote a comprehensive (i.e., subjective and objective) treatment effect.<br><br>References<br>1. Bjelović M, Harsányi L, Altorjay Á, Kincses Z, Forsell P; Investigators of the RefluxStop™ Clinical Investigation Study | |

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| | | | Group. Non-active implantable device treating acid reflux with a new dynamic treatment approach: 1-year results : RefluxStop™ device; a new method in acid reflux surgery obtaining CE mark. BMC Surg. 2020 Jul 20;20(1):159. doi: 10.1186/s12893-020-00794-9. PMID: 32689979; PMCID: PMC7370422.<br>2. Harsányi L, Kincses Z, Altorjay Á. Acid reflux management with the RefluxStop implant: A prospective multicenter trial with 3-year outcomes. In peer review with Digestive Diseases and Sciences. 2024.<br>3. Harsányi L, Kincses Z, Zehetner J, Altorjay Á. Treating acid reflux without compressing the food passageway: 4-year safety and clinical outcomes with the RefluxStop device in a prospective multicenter study. Surg Endosc. 2024 Oct;38(10):6060-6069. doi: 10.1007/s00464-024-11114-0. Epub 2024 Aug 13. PMID: 39138680; PMCID: PMC11458627.<br>4. Implantica. Data on file (provided to NICE as supplementary data). 2024.<br><br>1.3.3 Long-Term Outcomes<br><br>We understand that long-term data is necessary to safely and adequately advocate for novel surgical treatment options in the management of GORD. As such, we believe that the clinical evidence of RefluxStop™ surgery indicates favourable mid- to long-term safety and effectiveness even in patients representative of real-world settings while several ongoing and upcoming studies will continue to add to the growing evidence base.<br><br>The primary source of long-term data is the RefluxStop™ CE mark trial, provided to NICE as supplementary data [1]. RefluxStop has very high-quality 5-year prospective data, which was used in our PMA submission to the FDA. It would be beneficial for NICE decision-making to provide a delay in the process (as proposed, a | |

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| | | | 9-month delay) since these data will not be published until Q2 2025, although the manuscript has been accepted by SAGES conference 2025, which may speed up the process. The manuscript will be submitted for peer review in early 2025. At 6 months, the acid exposure time after RefluxStop™ surgery decreased to 0.8% from a baseline of 16.35% [2] with only 2% pH failures. In comparison, 36% failed the pH test at 1 year in the LINX Summary Memorandum of their FDA trial. At 5-year follow-up of the RefluxStop™ CE mark trial, no patient failed the pH test using the same definition as in the LINX Memorandum [1], indicative of substantial treatment effect in the long term by both objective and subjective measures, respectively.<br><br>Pertaining to safety, 5-year results of the RefluxStop™ CE study showed excellent safety that was consistent and sustained in the long term [1]. Briefly, the safety outcomes are summarised as follows:<br>• No cases of migration during the entire study period (5 years).<br>• No explantation during the entire study period (5 years).<br>• No rehneriation during the entire study period (5 years).<br>• No oesophageal dilatation during the entire study period (5 years).<br>• Only two minor procedure-related AEs (i.e., one case of mild dysphagia with GERD-HRQL dysphagia subscore 5 (maximum) at baseline reduced to 2 at 5-year follow-up, indicative of improvement as opposed to postoperative AE; and one case of moderate dyspepsia) that occurred between 1- and 5-year follow-up.<br>Furthermore, 11 patients experienced 16 procedure-related adverse events (AEs) related to the procedure. All serious events and most AEs (n=14/16) occurred before 1-year follow-up. Five patients experienced seven AEs classified as serious (i.e., one patient had three infection-related events) which were all resolved | |

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| | | | satisfactorily.<br><br>One patient only took PPIs at the 5 year follow-up. Postoperative dysphagia AE, inability to belch/vomit, PPI use, and reoperation during the full study period occurred in 2%, 0%, 2%, and 2% of cases after RefluxStop™ surgery at 5 years [1]. The systematic literature review on Nissen fundoplication presents much higher rates of each of these postoperative outcomes at 5 years: dysphagia (29%), inability to belch/vomit (40%), PPI use (12%), and reoperation (8.7%) [3]. Similarly, the pilot prospective, multicentre trial of MSA reported 15% pH failures, although only 45% of the patients performed this test, and a reoperation rate of 6.8% at the comparable 5-year follow-up [5]. In addition, any kind of follow-up was only performed in 75% of subjects, excluding many failure patients from the results, such as a device removal.<br><br>In summary, the long-term clinical outcomes of the RefluxStop™ CE mark trial demonstrate excellent clinical effectiveness and safety at 5 years, particularly with indirect comparison to the available clinical data on currently employed surgical options in the UK (i.e., Nissen fundoplication and MSA). In addition to this data, results of RefluxStop™ surgery in real-world settings (that includes UK patients) presented in response to the query for patient populations bolster short- (i.e., 1 year) and mid-term (i.e., ³3 years) safety and effectiveness even in difficult-to-treat patients.<br><br>References<br>1. Implantica. Data on file (provided to NICE as supplementary data). 2024.<br>2. Bjelović M, Harsányi L, Altorjay Á, Kincses Z, Forsell P; Investigators of the RefluxStop™ Clinical Investigation Study Group. Non-active implantable device treating acid reflux with a new dynamic treatment approach: 1-year results : RefluxStop™ | |

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| | | | device; a new method in acid reflux surgery obtaining CE mark. BMC Surg. 2020 Jul 20;20(1):159. doi: 10.1186/s12893-020-00794-9. PMID: 32689979; PMCID: PMC7370422.<br>3. Zehetner, J., Hoffsten, J., Das, S. et al. Looking back on a gold standard: a systematic literature review of laparoscopic Nissen fundoplication as an anti-reflux treatment option. Eur Surg 56, 143–171 (2024). https://doi.org/10.1007/s10353-024-00836-z<br>4. LINX Reflux Management System; FDA Executive Summary Memorandum; prepared for the January 11, 2012, Metting of the Gastroenterology and Urology Devices Advisory Panel. https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100049c.pdf<br>5. Saino G, Bonavina L, Lipham JC, et al. Magnetic sphincter augmentation for gastroesophageal reflux at 5 years: Final results of a pilot study show long-term acid reduction and symptom improvement. J Laparoendosc Adv Surg Tech A. 2015;25(1):787-92. | |
| 9 | Consultee 5 Implantica AG | 2.2 Current treatments | Currently available surgical treatment options for GORD in the UK include laparoscopic Nissen fundoplication, as the gold standard, and MSA. Unfortunately, these treatments either completely encircle or significantly augment the distal esophagus, the a priori mechanism by which several postoperative sequelae occur. For instance, a recent systematic literature review of 63 RCTs delineated substantial rates of gas-bloating (52.7%), inability to belch/vomit (39.8%), dysphagia (28.9%), and heartburn and epigastric/sternal pain (27%) after 5 years [1].<br><br>Furthermore, dysphagia is prone to exacerbation after fundoplication techniques [2], especially in cases of GORD with concomitant oesophageal dysmotility (i.e., IOM). With up to 36% of GORD patients suffering from IOM [3-7], surgical management of this demographic with existing treatment options is likely to result in manifestation of unwanted postoperative sequelae and | Thank you for your comment.<br><br>Please see NICE's response to comment 5. |

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| | | | contribute to the already substantial burden of disease. In fact, clinical practice guidance from the British Society of Gastroenterology, for UK-specific considerations, recommends that those undergoing antireflux surgery have major oesophageal motility disorders excluded at before operation by manometry, to determine surgical suitability [8]. This is supported by US practice guidance from the American College of Gastroenterology (2022) [9] and the Society of American Gastrointestinal and Endoscopic Surgeons (2023) [10] pertaining to both Nissen fundoplication and MSA. IOM also poses challenges in patients managed by MSA. For instance, Baison et al. showed that new-onset dysphagia and esophageal dilatation rates after MSA are 17% and 18% in IOM patients after only 1 year, as compared to the non-IOM comparison group, with rates of 10% and 11%, respectively [11]. RefluxStop™ utilises a novel treatment principle that does not encircle the esophagus and logically results in lower rates of postoperative sequelae such as dysphagia in IOM patients; this is supported by the real-world clinical data presented to NICE.<br><br>Similarly, those with hiatal hernia >3 cm in size are difficult to manage with existing antireflux surgical options. A high rate of reherniation independent of mesh use is appreciated with up to 55% of cases resulting in recurrence by 5 years, as per a RCT by Watson et al. [12]. Even in the short term, hernia recurrence after antireflux surgery results in a 15% reherniation rate by 20-month follow-up [13]. As such, hiatal hernia size is an independent predictor of reherniation after antireflux surgery [13]. By comparison, RefluxStop™ employs a pioneering mechanism of action in which the oesophagogastroplication and device invagination, in conjunction with cruroplasty, serve as a mechanical stop that prevents reherniation.<br><br>In an attempt to clarify the mechanisms of treatment | |

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| | | | success/failure, research has investigated factors predicting outcomes of antireflux surgery overall [14], or specifically laparoscopic Nissen fundoplication [14-16], MSA [17], and antireflux mucosectomy (ARMS) [18]. Which type of preoperative patient data that might contribute to success or failure seem to depend on treatment option, as previous research does not display a similar set of predictive factors to consider [14-19]. There is no consensus on the definition of 'treatment success/failure', as literature showcase that the outcome 'treatment success/failure' is used differently [15, 17-22].<br><br>Ultimately, access to novel surgical treatment options is necessary to circumvent the troublesome postoperative sequelae of Nissen fundoplication and MSA while providing excellent treatment effective for GORD patients. As such, we believe that a 'Special Arrangements' status for RefluxStop™ is one such avenue for better treatment availability in GORD patients with limited options (i.e., IOM and/or large hiatal hernia).<br><br>References<br>1. Zehetner, J., Hoffsten, J., Das, S. et al. Looking back on a gold standard: a systematic literature review of laparoscopic Nissen fundoplication as an anti-reflux treatment option. Eur Surg 56, 143–171 (2024). https://doi.org/10.1007/s10353-024-00836-z<br>2. Tran S, Gray R, Kholmurodova F, et al. Laparoscopic fundoplication is effective treatment for patients with gastroesophageal reflux and absent esophageal contractility. J Gastrointest Surg. 2021;25(9):2192-200.<br>3. Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0©. Neurogastroenterol Motil. 2021;33(1):e14058.<br>4. Abdel Jalil AA, Castell DO. Ineffective esophageal motility (IEM): the old-new frontier in esophagology. Curr Gastroenterol Rep. | |

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| 10 | Consultee 5 Implantica AG | 3.2 The evidence | We agree with NICE that key efficacy endpoints for treatment success include GERD-HRQL, odynophagia, PPI use, and 24-hour pH testing. These are all delineated in the RefluxStop CE mark study with impressive, sustained, and statistically significant results that are also reported in independent studies with real-world patients that includes those with IOM and large hiatal hernia. A detailed summary of this evidence is provided in section 1.3. | Thank you for your comment. |
| 11 | Consultee 5 Implantica AG | 3.5 Committee comments | We are truly grateful and in full agreement with NICE's positive evidence observations and very encouraging open-minded comments regarding RefluxStop™'s existing safety profile and potential role in treating more complex GORD cases, acknowledging that not only is there evidence that the RefluxStop™ procedure works but also confirming that the short-term safety evidence of the RefluxStop™ procedure suggests that this procedure is as safe as other common laparoscopic procedures for GORD. Moreover, we fully agree with NICE's review that for those with more complex GORD cases, such as GORD with ineffective oesophageal motility (IOM) disorders or larger hiatal hernia, there are limited treatment options where RefluxStop™ procedure could provide a minimally invasive option for people with IOM disorders or for patients with chronic GORD whose symptoms have not responded adequately to lifestyle modification and drug therapy. The NICE committee also noted that the RefluxStop™ procedure does not encircle the oesophagus and that it may result in less bloating than other procedures.<br><br>Overall, we would like to applaud and echo NICE's positive perspective, observations, and reassuring comments about RefluxStop™'s existing safety profile and its potential role in treating more complex GORD cases. With its continued robust safety profile, we believe RefluxStop™ could transform the GORD | Thank you for your comment.<br><br>Please see NICE's response to comment 5. |

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| | | | treatment landscape for these hugely underserved subpopulations of severe GORD patients.<br><br>Undoubtedly, there is a large unmet need in the GORD population treated by standard-of-care antireflux surgery. As previously described, patient subpopulation with concomitant IOM are arduously managed and typically suffer from postoperative dysphagia, an often-debilitating manifestation following Nissen fundoplication and MSA. With up to 36% of the GORD population suffering from IOM, this patient demographic is hugely underserved and will likely benefit from RefluxStop™ surgery as per the clinical data provided to NICE from real-world studies.<br><br>It is our strong belief and experience that a 'Research Only' status for RefluxStop™ will deprive IOM patients of reasonable treatment for GORD and will not optimally mitigate further healthcare resource utilisation to manage postoperative complications. In this regard, we believe that a 'Special Arrangements' status for the RefluxStop™ treatment would be more suitable and appropriate to allow sufferers to opt for this procedure on an individual basis. | |
| 12 | Consultee 5 Implantica AG | 3.6 Committee comments | The RefluxStop™ procedure is easy to conduct for surgeons with even moderate experience in laparoscopic antireflux surgery. RefluxStop™'s manufacturer, Implantica (Zug, Switzerland), is responsible for surgeon training in the RefluxStop™ procedure and enrols surgeons in a well-established training program guided by proctor surgeons. We feel that the training program ensures appropriate surgical technique in the RefluxStop™ procedure and optimises safety and effectiveness outcomes for the benefit of both patients and the healthcare system. | Thank you for your comment. |

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| 13 | Consultee 5 Implantica AG | Not specified | This manuscript is now accepted for publication in Digestive 'Diseases and Sciences', and the final copy can be provided before the next iPAC committee meeting. | Thank you for your comment.<br>The Harsányi (2024) paper added to the updated literature review appendix table 5 in the overview.<br>The text in overview has been amended to there is 1 unpublished paper for 5-year follow-up results. These manuscripts have not yet been accepted for publication so cannot be included in this overview. |
| 14 | Consultee 5 Implantica AG | Not specified | This is incorrect. The correct inclusion criteria was as following: Total distal oesophageal pH must be ≤4 for ≥4.5% of the time during a 24-h monitoring. | Thank you for your comment.<br>Table 2 in overview has been amended to state that “Total distal oesophageal pH must be less than 4 for more than 4.5% of the time during a 24-hour monitoring” |
| 15 | Consultee 5 Implantica AG | Not specified | This is incorrect, the published article reported p-value in table 2: where p-value was p<0.001 | Thank you for your comment.<br>Table 2 in overview has added p<0.001 to GERD-HRQL questionnaire scores of Harsanyi (2024) study. . |
| 16 | Consultee 5 Implantica AG | Not specified | It is incorrect, it is not at year 1; 29.5 is the median GERD-HRQL score at baseline. | Thank you for your comment.<br>Overview has been amended to state that “At baseline, the median |

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| | | | | had been 29.5 (IQR 24 to 33) which decreased to 3.0 (IQR 0 to 9.2) by year 4." |
| 17 | Consultee 5 Implantica AG | Not specified | The authors referenced Velanovich 2007 (reference number 16) which indicates the 10-question version of the GERD-HRQL questionnaire which has maximum score of 50. | Thank you for your comment.<br><br>Overview has been amended to state that "The authors referenced Velanovich 2007 indicates the 10-question version of the GERD-HRQL questionnaire which has maximum score of 50." |
| 18 | Consultee 5 Implantica AG | 24 Patient satisfaction relating to GORD – score of additional question in GERD-HRQL questionnaire | This is not correct. p-value was provided with the figure-1 in the main manuscript and it was reported as p<0.001 | Thank you for your comment.<br><br>Overview has been amended to state that "This is a dissatisfaction reduction of 90% (p<0.001) (Feka 2024)." |
| 19 | Consultee 5 Implantica AG | 24 Postoperative dysphagia | In fact, this study clearly mentioned that three patients had post-operative dysphagia and all of them had IOM and two of them had pre-operative dysphagia. This may suggest that only one patient had new onset of dysphagia. The other manuscript by Fringeli et al clearly mentioned that only one patient had new onset of dysphagia and that patient had severe ineffective oesophageal motility. | Thank you for your comment.<br><br>Overview has removed "1 study was not clear about whether the postoperative dysphagia was new onset or if the participants experienced dysphagia before the operation (Fringeli 2024c)." |

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| 20 | Consultee 5 Implantica AG | 24 Validity and generalisability | This is not correct, Joerg Zehetner is not an author in the Feka et al manuscript. He is an author in the Harsanyi et al manuscript. | Thank you for your comment.<br>Overview has been amended to “Joerg Zehetner, who was an author in the Fringeli (2024a, 2024b, 2024c) papers was also an author on the Harsanyi (2024) paper.” |