



Challenges of developing and executing a multi-site registry for a novel device with evolving indications for use

Jennifer L. Maranki¹ · Steven D. Schwaitzberg² · Reem Z. Sharaiha³ · Vladimir M. Kushnir⁴ · Dilhana S. Badurdeen⁵ · Vivek Kumbhari⁶ · Victoria Gómez⁶ · Nikhil A. Kumta⁷ · Jerome D. Waye⁷ · Jose Nieto⁸ · Michael B. Ujiki⁹ · Petros C. Benias¹⁰ · Larry S. Miller¹¹ · Prashant Kedia¹² · Paul Tarnasky¹² · Abraham Mathew¹ · John M. Levenick¹ · Sumant Inamdar¹³ · Benjamin Tharian¹³ · Yanina Nersesova¹⁴ · Lydia Fredell¹⁴ · Sonya Serra¹⁴ · Michael L. Kochman¹⁵

Received: 27 February 2022 / Accepted: 6 June 2022 / Published online: 3 August 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract

Background The introduction of new technologies in endoscopy has been met with uncertainty, skepticism, and lack of standardization or training parameters, particularly when disruptive devices or techniques are involved. The widespread availability of a novel endoscopic suturing device (OverStitch™) for tissue apposition has enabled the development of applications of endoscopic suturing.

Methods The American Gastroenterological Association partnered with Apollo Endosurgery to develop a registry to capture in a pragmatic non-randomized study the safety, effectiveness, and durability of endoscopic suturing in approximating tissue in the setting of bariatric revision and fixation of endoprosthesis devices.

Results We highlight the challenges of the adoption of novel techniques by examining the process of developing and executing this multicenter registry to assess real-world use of this endoscopic suturing device. We also present our preliminary data on the safety and effectiveness of the novel device as it is applied in the treatment of obesity.

Conclusions The Prospective Registry for Trans-Orifice Endoscopic Suturing Applications (ES Registry) was an effective Phase 4, postmarketing registry aimed at capturing pragmatic, real-world use of a novel device. These findings serve to solidify the role of endoscopic suturing in clinical practice.

Keywords Endoscopic suturing · Bariatrics · Novel technologies · Registry · Endoprosthesis

The emergence of natural orifice endoscopic procedures has provided the opportunity to perform more complex per-oral interventions, which has clearly created the need for effective suturing devices and techniques. The introduction of these innovative suturing techniques into clinical practice has been met with enthusiasm as well as apprehension and controversy. Historically, the adoption of new technology is often confounded by competing studies with non-comparable study designs with differing endpoints defined by different groups of clinicians and thought leaders. These issues cloud the safety, efficacy, and value propositions of the innovations and delays acceptance by providers and payors. In the worst case this may delay the discontinuance of ineffective therapies or introduction of unsafe technologies that

might not be detected until after Food and Drug Administration (FDA) clearance or approval. Many concerns are often grounded in issues related to the rising costs of healthcare delivery and the utility of a technology without measurable clinical benefit.

Invariably, when new techniques or technology are introduced, challenges of efficacy and defining training and competency arise with various paths to resolution. While novel endoscopic innovations may have grown out of ex-vivo and animal studies, followed by small pilot studies, much of the body of evidence supporting the use of these innovations is developed from multiple cohort studies. For training, oftentimes no curriculum or guideline for assessing competency are initially available or distinct from industry suggestions for training paradigms. Furthermore, evaluating technical outcomes requires an understanding of the learning curve. Such is the case for flexible endoscopic intraluminal suturing and the use of the novel OverStitch™ device.

✉ Jennifer L. Maranki
jmaranki@pennstatehealth.psu.edu

Extended author information available on the last page of the article

Flexible endoscopic intraluminal suturing allows for the placement of full-thickness sutures using either interrupted or running techniques. In 2011, Apollo Endosurgery (Austin, TX) launched their redesigned endoscopic suturing system, the Overstitch™ device. With its streamlined profile and compatibility with common double-channel therapeutic endoscopes, the device became the most widely used endoscopic suturing system and spurred a variety of novel endoscopic therapies involving tissue apposition. At the time development of this prospective pragmatic registry, the device had been used in over 10,000 cases.

Since then, use of the OverStitch™ device has become a widely deployed technique for the management of complications associated with bariatric surgery. It has been found to be useful for treatment of postsurgical leaks, closure of gastrogastic fistulae, and to treat weight regain following bariatric surgery attributed to dilation of the gastrojejunal anastomosis [1]. Professional endoscopy societies have developed position statements on the use of these techniques in endoscopic bariatric therapies, as well as recommendations on training and credentialing for use, but clinical use continues to be somewhat nuanced and non-standardized [2, 3]. The device has also been used in endoscopic full thickness resection, closure of acute perforations and mucosal defects after endoscopic mucosal resection or dissection.

In 2017, the American Gastroenterological Association (AGA) partnered with Apollo Endosurgery to develop the *Prospective Registry for Trans-Orifice Endoscopic Suturing Applications* (ES Registry) (ClinicalTrials.gov NCT03776188) to capture in a pragmatic non-randomized study the safety, effectiveness, and durability of endoscopic suturing in approximating tissue in the setting of bariatric revision and fixation of endoprosthesis devices, compared to published data on comparable endoscopic, laparoscopic, or open surgical repairs. Challenges of investigator-initiated studies related to new technologies have been reported [4]. We further expand on issues related to protocol development, data management, investigator selection, publication, and funding.

Initial considerations

A small multidisciplinary team of Principal Investigators (PI) (JM, SS) with an AGA study champion (MK) was assembled, reflecting the proceduralists who are stakeholders in endoscopic suturing. The initial task was to determine how a registry study would contribute to understanding of the applications of endoscopic suturing. We first assessed the existing literature and use of the device and identified the gaps in our knowledge surrounding endoscopic suturing. We determined a rationale for performing the study, developed clinical questions applicable to the study, and formulated

a plan to answer those clinical questions. We then set to define our research questions and assessed whether those questions could be addressed through a registry. The existing data concerning the Overstitch™ device demonstrated the clinical safety of the device already approved by the FDA, which is often insufficient to support adoption and clinical reimbursement. An evaluation of clinical effectiveness that could support reimbursement for the use of the device was a driver of our study. There is no question that valuable technologies and techniques are not infrequently denied reimbursement even after FDA clearance or approval. Solid outcome data is usually necessary to provide the rationale for reimbursement. Our primary objectives were to define the patient outcomes, including survival, morbidity, and the need for additional interventions among patients undergoing endoscopic suturing; to evaluate the efficacy and safety of endoscopic suturing therapy in preventative fixation of stents and in bariatric revision; and to collect data on the common use of endoscopic suturing therapy in other indications.

Protocol development

In the process of developing and executing this registry a number of challenges arose, in part due to the evolving nature of the use of the device. Given the broad FDA indication for tissue apposition, the device is employed in wide-ranging applications with varying suturing techniques. Initial challenges involved writing a protocol that would apply to virtually any application of endoscopic suturing, including stent fixation (in a variety of scenarios), revision of bariatric surgery (including outlet reductions and post-operative leak repair), and other bariatric applications including endoscopic sleeve gastropasty. Ultimately, the study was powered to evaluate outcomes in two clinical scenarios: fixation of esophageal endoprosthesis stents for migration prevention and for revision of bariatric procedures. However, due to evolving variation in clinical practice and the exclusion of esophagogastric malignancy in the stent category, very few fixation cases were captured into the registry. This likely also partially reflects our investigator population and their bariatric focus of endoscopic practice. Additionally, we specified “esophageal stent” in the protocol, but in the course of the execution of the study, novel endoscopic techniques using lumen apposing stents became a popular use of the suturing device to secure the stent in place. We were readily able to enroll patients into bariatric categories, demonstrating the continuing adoption of this technology for bariatric applications. With the benefit of hindsight, we should have powered for additional bariatric categories and indications had we anticipated the rapid growth for this application.

Investigator selection

Given the novel technology of the Overstitch™ device, sites and investigators were selected based on their experience and expertise with the device to avoid those on the learning curve. Overall prior experience with the device and anticipated volume of cases per month were assessed. Investigators with a strong foundation and expertise in suturing were selected, because we wanted to eliminate the learning curve effect on outcomes. However, many of these investigators were also either receiving research support from Apollo Endosurgery or acting as consultants, both of which were considered conflicts of interest (COI) for a PI. In order to be compliant, other site investigators were often the site's PI although in some cases consulting and research relationships were forfeited by the PIs for the duration of the study to eliminate COI. Resources for research at sites varied greatly, ranging from a dedicated research coordinator to assist with all aspects of Institutional Review Board (IRB) approval, completion of consents, and data entry and rectification, to no local support beyond the site PI. Changes in local personnel and staffing over time further challenged data management.

Contracting and publication

Based on prior experience, contracting with university research contract offices on the independent right to publish is a challenge [4]. Instead, individual investigators were contracted to define the nature of their participation in the registry, including proposed volume of cases to be submitted, co-investigators at each site, providing resolution of conflicts of interest, and defining the right to publish their site data.

An authorship agreement was also drafted, so that there would be transparency in primary and senior authorship. Sequence of authors would be based on volume of cases submitted. All contributors would have the opportunity to review, offer edits, and approve any manuscripts that result from the trial. The initial publications that result from this registry are to be published through the AGA study group PIs (JM and SS) and will include the full complement of data retrieved from the registry, as these publications will represent the larger body of data and likely be most clinically impactful output of the registry.

Inevitably, budgetary issues arose at each site, each with varying challenges and issues. Developing the study site budgets became one of the most difficult tasks. Many institutions required significant additions to the budget that would exceed the actual total cost for the entire

multi-center study. As a result, while some investigators were interested in participating in the registry, they were limited by the budgetary requirements of their institutions.

A budget based on scheduled payments per patient was ultimately successfully employed. Centers were paid for providing each component of the required data, as well as overhead which accounted for 25–35% of the overall payment per site. For example, when the treatment visit was completed and the data completely entered, the site was paid. This approach was also an effective mechanism for achieving a complete data set, as sites were not compensated unless the data was properly entered.

Delays in IRB approval led in some instances to unavoidable delays and increased costs, which was unfortunate given the actual minimal risk (breach of data) of the study. These challenges arise since broad content expertise on these review boards is infrequent. Clarity around the concept that the actual research for this registry was the data acquisition and not the suturing procedure itself required clear and persistent communication to the IRBs. Ultimately the registry was initiated on November 1, 2018.

Data management

The process of selecting a contract research organization (CRO) was simplified as the AGA has an existing relationship and developed infrastructure with an international CRO (Applied Clinical Intelligence, Bala Cynwyd, PA) that has demonstrated facility in collaborative execution of device investigations. Subsequently, the protocol was collaboratively finalized with statistician defined and appropriately-powered endpoints.

The AGA implemented an Observational Study Monitoring Board (OSMB) to periodically review the registry design, review enhancement recommendations, and propose amendments to the registry design or database.

Issues related to data entry not surprisingly represented a major component of the challenges of the study. As the standard of care was not established regarding best practices for use of the device, procedural variations across investigators posed a risk of dilution of the data. Generally, clinical research coordinators at each site entered data, but in some cases, data were entered by the investigators. Further, novel procedures or techniques that were not initially included in the protocol were developed during the course of the study, and capturing this data was difficult and cumbersome. As part of routine clinical care, re-check endoscopy was commonly performed, and initially this aspect of care was not included in the data capture. It wasn't until our investigators asked that we capture this important aspect of care, which more accurately depicts the care involved in endoscopic suturing, that this data item was added. The data were

validated retroactively between the sites and the AGA study team. Our existing relationship with the CRO was critical to allowing nimbleness for data capture utilizing an easily modifiable platform for the electronic Case Report Forms (eCRF).

Capturing concomitant medications was considered an important aspect of data entry, especially to help determine how suturing procedures may contribute to modifications in health maintenance medications (i.e., endoscopic sleeve gastroplasty results in weight loss, thereby causing improvements in blood glucose and potentially eliminating the need for oral hypoglycemics). Similar scenarios may be proposed for medications to treat hypertension and hypercholesterolemia. Similarly, we set out to capture adverse events (AEs) associated with the use of the device, and it became challenging to discern which AEs were associated with the device as opposed to the natural sequelae of the underlying disease process. For example, some patients who were post-Roux-en-Y gastric bypass undergoing outlet reduction and developed nausea and vomiting, an expected and anticipated result of cinching the gastric outlet, and not an adverse event associated with the device.

Several technical aspects of the use of the device were to be captured, including method of suture placement. However, suturing patterns continued to evolve during the course of the registry, including the adoption of techniques not previously utilized in traditional surgical suturing training. The ability to capture these novel methods proved challenging from both definition and data integrity perspectives.

Post-procedural follow-up was variable; there was a wide range in clinical practice regarding repeat upper endoscopy for the stent fixation and bariatric indications for use of the device. Some investigators routinely performed endoscopy in follow-up, some obtained upper gastrointestinal tract fluoroscopy studies, while others did not perform routine follow-up unless clinically indicated. Due to this variation in clinical practice, we were unable to draw conclusions related to the routine follow-up care of patients undergoing suturing procedures.

Impact of the COVID-19 pandemic

In March of 2020, with the onset of the COVID-19 pandemic, both elective and research-related operations at medical centers throughout the United States were halted, effectively bringing acquisition of patients into the registry and follow-up information to a halt. These measures were in effect for roughly six months. To mitigate this disruption we were able to extend the study for four months in collaboration with the CRO and Apollo. Despite this measure, the pandemic continued to have an impact on enrollment into

the study, as many patients remained hesitant to undergo elective procedures.

Preliminary study results

In this national, prospective, multicenter registry focused on capturing the current use of trans-orifice endoscopic suturing applications, the most meaningful results were derived from the set of patients undergoing endoscopic sleeve gastroplasty (ESG). Data acquisition was from November 1, 2018 through August 31, 2021 and 80 consecutive patients from six sites undergoing ESG for treatment of obesity were enrolled. 62 patients were female and 18 male, with an average age of 47.8 years. Baseline body weight was 105.7 ± 22.7 kg. Percent total body weight loss (%TBWL) at 30 days, 3 months, and 6 months was $7.83 \pm 4.33\%$, $11.41 \pm 3.92\%$, and $13.86 \pm 6.88\%$, respectively Fig. 1. 91.3% (42/46) and 85% (23/27) of patients maintained at least 5% TBWL at 6 months and 1 year, respectively, while 76% (35/46) and 70% (19/27) of patients maintained at least 10% TBWL at 6 months and 1 year, respectively. Figure 2. Immediate adverse events occurred in 6 patients (7.5%), of which 4 (5%) were considered clinically relevant by the investigators, and consisted of nausea and/or vomiting, abdominal pain, and/or fever. All required additional medications (1), an emergency department visit (1), or a hospitalization (2). All of these adverse events were per protocol considered expected as a result of the suturing intervention. There were 3 (3.75%) delayed adverse events, all of which occurred within 30 days. One patient developed nausea and vomiting, one experience dehydration, and one developed a leak from dietary indiscretion and was treated conservatively. No patient underwent additional therapeutic endoscopy, interventional radiologic procedure, or surgery.

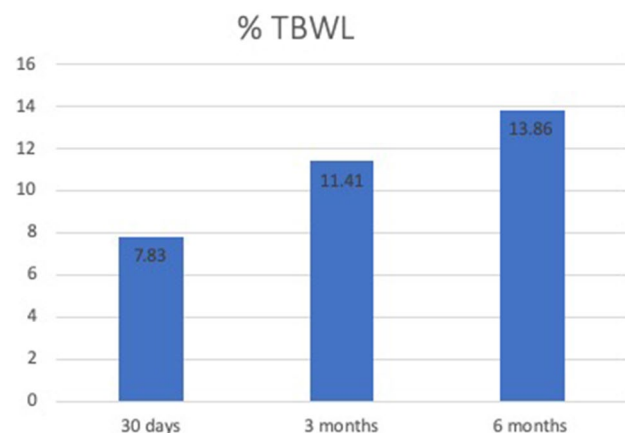


Fig. 1 Percent total body weight loss at 30 days, 3 months, and 6 months

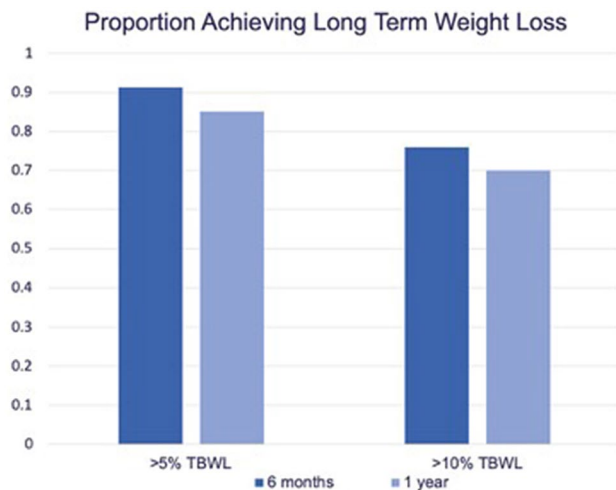


Fig. 2 Proportion of registry participants achieving at least 5% TBWL and at least 10% TBWL at 6 months and 1 year

In summary, preliminary data demonstrate that ESG is a promising minimally invasive technique for treatment of obesity, with a favorable adverse event profile.

Conclusion

The Prospective Registry for Trans-Orifice Endoscopic Suturing Applications (ES Registry) was an effective Phase 4, post-marketing registry aimed at capturing pragmatic real-world use of a novel device. The main challenges of the registry stemmed from the reality that use of the device for various application is not standardized, and only a small fraction of cases performed worldwide were captured in our registry. Our a priori assessment that stent fixations and outlet reductions would be the main drivers of the study was incorrect. In retrospect, the category of endoscopic sleeve gastroplasty should have been designated as a powered outcome. However, the study was successful in gathering data to demonstrate the evolving role of endoscopic suturing in the field of endoscopic surgery and the substantial impact that the availability of the novel Apollo OverStitch™ device has made on the practice of therapeutic endoscopy. These early findings serve to solidify the position of endoscopic suturing in clinical practice and provides evidence to support insurance reimbursement. The registry will continue to track these results over an extended period of time.


Disclosures Jennifer L. Maranki is a consultant for Boston Scientific Corp. Steven D. Schwaartzberg is a consultant with options for Human Extensions, Active Surgical, Arch Therapeutics, NuView Surgical, Levitra Magnetics, and Hai Technologies, and a <1% investor in Endolumik. Reem Z. Sharaiha is a consultant for Olympus and is both a consultant for and has received research support from Cook Medical and Boston Scientific Corp. Vladimir M. Kushnir is a consultant for Boston Scientific Corp. and Medtronic. Vivek Kumbhari is a consultant for Apollo Endosurgery, FujiFilm Medical, Boston Scientific Corp., Medtronic, and Pentax Medical, and has received research support from Apollo Endosurgery and ERBE. Victoria Gomez is a consultant for Olympus. Nikhil A. Kumta is a consultant for Apollo Endosurgery, Boston Scientific Corp., Intuitive Surgical, Olympus, and Safeheal. Michael B. Ujiki is on the scientific advisory board and has received fellowship grant funding from Boston Scientific Corp., is a consultant for Cook and Olympus, has received research grant funding and speaker honoraria from Medtronic, and is a consultant, speaker, and has received fellowship grant funding from GORE. Petros Benias is a consultant for Fujifilm and Apollo Endosurgery. Prashant Kedia is a consultant for Boston Scientific Corp., Olympus, and Medtronic. Abraham Mathew is a consultant for Olympus. Benjamin Tharian is a consultant for Boston Scientific Corp., Medtronic, and Olympus. Michael L. Kochman is a consultant for Olympus, Boston Scientific Corp., Medtronic, ACL, and Novella; a consultant with stock options for Virgo Systems; a consultant with stock and a limited partner with Dark Canyon Labs, and holds an equity position with Endolumik. Dilhana Badurdeen, Jerome D. Waye, Jose Nieto, Larry S. Miller, Paul Tarnasky, John M. Levenick, Sumant Inamdar, Yanina Nersesova, Lydia Fredell, and Sonya Serra have no disclosures.

References

- Schulman AR, Watson RR, Abu Dayyeh BK, Bhutani MS, Chandrasekhara V, Jirapinyo P et al (2020) Endoscopic devices and techniques for the management of bariatric surgical adverse events (with videos). *Gastrointest Endosc* 92(3):492–507. <https://doi.org/10.1016/j.gie.2020.04.002>
- Sullivan S, Kumar N, Edmundowicz SA, Abu Dayyeh BK, Jonnalagadda SS, Larsen M et al (2015) ASGE position statement on endoscopic bariatric therapies in clinical practice. *Gastrointest Endosc* 82(5):767–772. <https://doi.org/10.1016/j.gie.2015.06.038>
- Abdulfattah Bukhari M, Khashab MA (2020) Optimized training in the use of endoscopic closure devices. *Gastrointest Endosc Clin N Am* 30(1):197–208. <https://doi.org/10.1016/j.giec.2019.08.008>
- Schwaartzberg SD, Hawes RH, Rattner DW, Kochman ML (2013) Novel challenges of multi-society investigator-initiated studies: a paradigm shift for technique and technology evaluation. *Surg Endosc* 27(8):2673–2677. <https://doi.org/10.1007/s00464-012-2504-0>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Jennifer L. Maranki¹  · Steven D. Schwartzberg² · Reem Z. Sharaiha³ · Vladimir M. Kushnir⁴ · Dilhana S. Badurdeen⁵ · Vivek Kumbhari⁶ · Victoria Gómez⁶ · Nikhil A. Kumta⁷ · Jerome D. Waye⁷ · Jose Nieto⁸ · Michael B. Ujiki⁹ · Petros C. Benias¹⁰ · Larry S. Miller¹¹ · Prashant Kedia¹² · Paul Tarnasky¹² · Abraham Mathew¹ · John M. Levenick¹ · Sumant Inamdar¹³ · Benjamin Tharian¹³ · Yanina Nersesova¹⁴ · Lydia Fredell¹⁴ · Sonya Serra¹⁴ · Michael L. Kochman¹⁵

¹ Division of Gastroenterology and Hepatology, Department of Medicine, Penn State Hershey Medical Center, Hershey, PA, USA

² Department of Surgery, University of Buffalo, Buffalo, NY, USA

³ Gastroenterology Division, Department of Medicine, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA

⁴ Division of Gastroenterology, Washington University in St. Louis School of Medicine, St. Louis, MO, USA

⁵ Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD, USA

⁶ Division of Gastroenterology and Hepatology, Mayo Clinic Florida, Jacksonville, FL, USA

⁷ Henry D. Janowitz Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

⁸ Division of Gastroenterology, Borland-Groover Clinic, Jacksonville, FL, USA

⁹ Division of Gastrointestinal and General Surgery, NorthShore University Health System, Department of Surgery, Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

¹⁰ Division of Gastroenterology, Lenox Hill Hospital, Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, New York, NY, USA

¹¹ Division of Gastroenterology, Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, Manhasset, NY, USA

¹² Methodist Dallas Medical Center, Dallas, TX, USA

¹³ University of Arkansas for Medical Sciences, Little Rock, AR, USA

¹⁴ American Gastroenterological Association, Bethesda, MD, USA

¹⁵ Center for Endoscopic Innovation, Research, and Training, Gastroenterology Division, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA