The American Society for Gastrointestinal Endoscopy PIVI on
Endoscopic Bariatric Procedures
(short form)

Please see related White Paper: "A Pathway to Endoscopic Bariatric Procedures," published in GIE:Gastrointestinal Endoscopy
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The PIVI Initiative

The PIVI initiative is an ASGE program that aims to identify important clinical questions related to endoscopy and to establish a priori diagnostic and/or therapeutic thresholds for endoscopic technologies designed to resolve these clinical questions. Additionally, PIVIs may also outline the data and or the research study design required for proving an established threshold is met. Once endoscopic technologies meet an established PIVI threshold, those technologies are appropriate to incorporate into clinical practice presuming the appropriate training in that endoscopic technology has been achieved. The ASGE encourages and supports the appropriate use of technologies that meet its established PIVI thresholds.

The PIVI initiative was developed primarily to direct endoscopic technology development toward resolving important clinical issues in endoscopy. The PIVI initiative is also designed to minimize the possibility that potentially valuable innovations are prematurely abandoned due to lack of utilization and to avoid widespread use of an endoscopic technology before clinical studies documenting their effectiveness have been performed. The following document, or PIVI, is one of a series of statements defining the diagnostic or therapeutic threshold that must be met for a technique or device to become considered appropriate for incorporation into clinical practice. It is also meant to serve as a guide for researchers or those seeking to develop technologies that are designed to improve digestive health outcomes.

An ad hoc committee under the auspices of the existing ASGE Technology and Standards of Practice Committees Chairs develops PIVIs. An expert in the subject area chairs the PIVI committee, with additional committee members chosen for their individual expertise. In preparing this document, evidence-based methodology was employed, using a MEDLINE and PubMed literature search to identify pertinent clinical studies on the topic. PIVIs are ultimately submitted to the ASGE Governing Board for approval, as is done for all Technology and Standards of Practice documents. This document is provided solely for educational and informational purposes and to support incorporating these endoscopic technologies into clinical practice. It should not be construed as establishing a legal standard of care.

Endoscopic Bariatric Procedures PIVI

(Short form)

I. General clinical area of this PIVI:

This PIVI is intended to establish thresholds for the adoption of endoscopic bariatric therapy (EBT) in the context of obesity class and comorbid disease. Obesity is a complex metabolic disease of excessive fat accumulation associated with a host of co-morbid conditions including heart disease, hypertension, dyslipidemia, type II diabetes, osteoarthritis, sleep apnea, certain malignancies, and all-cause mortality. Obesity is increasing worldwide. Medical treatment for obesity and associated metabolic comorbidities includes lifestyle modification, diet and pharmacologic agents. However, these approaches have limited effectiveness and limited durability, with high rates of attrition. Bariatric surgical interventions have been more effective, yielding significant and sustainable weight loss along with resolution of metabolic comorbidities in up to 80% of patients. While effective, these laparoscopic and open surgical bariatric procedures have morbidity rates of 3% to 20% and mortality rates of 0.1 to 0.5%. For these and other reasons, including limited access to care, only 1 in 400 morbidly obese individuals undergo bariatric surgery in the US. Given that all current surgical procedures require general anesthesia and have procedure specific complications, there is a need for less invasive weight loss interventions to potentially reduce morbidity and improve access. A range of novel endoscopic modalities may fit this profile. Any new endoscopic or nonsurgical weight loss intervention should include a defined threshold of efficacy, balanced with risks of the intervention. EBT, performed entirely through the gastrointestinal tract using flexible endoscopes, offers the potential for ambulatory weight loss procedures with a superior safety and cost profile compared to bariatric surgery. Such benefits would increase the appeal and acceptance of this therapy to patients. EBT shown to be feasible, safe, and effective may be appropriate intervention for individuals with lower classes of obesity.

II. Threshold(s) recommended for this PIVI:

- Based on available evidence and expert opinion, the Taskforce recommends that an EBT intended as a 'primary' obesity intervention in Class II/III obese individuals (Body Mass Index [BMI] > 35 kg/m^2) achieve a mean minimum threshold of 25% Excess Weight Loss (%EWL) measured at 12 months.
- This goal will vary depending on the category or intent of endoscopic bariatric procedure.
- EBT should be compared to a second treatment group, not sham.
- In addition to the absolute threshold of weight loss, the mean % EWL difference between a 'Primary' EBT and control groups should be a minimum of 15% EWL, and be statistically significant.
- We advocate using 5% of total body weight (%TBW) lost as the absolute minimum threshold for any 'non-primary' EBT (e.g., early intervention, bridging or metabolic therapy).
- The risk associated with EBP should equate to $\leq$5% incidence of serious adverse events.

- If a low risk EBT proves to have a significant impact on one or more obesity-related co-morbidities, the threshold for intervention may extend to Class I obese individuals (BMI 30-35 kg/m^2).

III. Summary explanation of threshold recommended for this PIVI

The weight loss threshold for the adoption of any new endoscopic procedures should be balanced against the risk of that procedure. Currently there are no thresholds established for endoscopic bariatric interventions. However, in general it is expected that endoscopic modalities should achieve weight loss superior to that anticipated with medical and intensive lifestyle interventions and approach that of operative therapies.

Assessment of weight loss

Weight loss after currently accepted interventions varies greatly. Comparison of nonsurgical and operative interventions is limited by differences in the primary outcome measure. The majority of medical therapy trials use the percent of total body weight lost (%TBW) to define efficacy. Weight loss after bariatric surgery is calculated as either changes in the baseline BMI or the percent of excess weight loss (%EWL). The %EWL is defined as:

$$\frac{\text{Amount of weight loss}}{\text{[Patient's initial weight – Ideal body weight based on gender and height]}} \times 100$$

Ideal body weight is most commonly obtained from the Metropolitan Life Insurance table. Moreover, actual weight lost can be a deceiving outcome measure, particularly among class II and III obese individuals. But the overall magnitude of average weight loss attributed to operative interventions is significantly greater than that achieved with non-surgical therapies. In a meta-analysis published by Buchwald *et al*, Roux-en-Y-gastric-bypass (RYGB) achieves a mean excess weight loss of 68%, gastroplasty achieves 69%, and gastric banding 50% at varying follow-up time intervals. An EBT with a considerably lower risk profile compared to surgery may be held to a comparable reduction in expected weight loss for the surgical intervention but exceeding that for accepted non-surgical therapies.

Intent of endoluminal therapies

The primary goal of EBT is to induce enough weight loss to decrease obesity related metabolic co-morbidities and improve quality of life. Higher risk EBTs would be expected to yield substantial and sustainable positive outcomes to achieve a favorable risk/benefit profile; accordingly, a lower risk EBT would be afforded a comparable adjustment in efficacy threshold. With this concept in mind, EBT have many potential applications in obesity management.

Primary Therapy

The goal of primary EBT is to induce weight loss and improvement in medical co-morbidities, with a safety and efficacy profile similar to operative bariatric therapy. An EBT with a risk profile comparable to laparoscopic adjustable gastric banding should hold similar efficacy, with the potential to achieve approximately 40 % EWL. Alternatively, lower efficacy is acceptable for an EBT with a lower risk profile. Such a treatment would be for would patients with severe obesity (Class II, III), with or without obesity related co-morbidities. Therefore, based on

available evidence and expert opinion, the Taskforce recommends that an EBT intended as a primary obesity intervention achieve a mean minimum threshold of 25% EWL measured at 12 months. EBT should be compared to a second treatment group, not sham. Sham groups in comparative trials evaluating the efficacy of bariatric therapies have shown considerable variability in weight loss (3-13%EWL). In addition to the absolute threshold of weight loss, the mean %EWL difference between a 'Primary' EBT and control groups, should be a minimum of 15% EWL, and be statistically significant.

Early Intervention / Preemptive Obesity Therapy

Patients with Class I and II obesity are at risk for disease progression, have a higher cardiovascular risk profile, and have a substantially increased relative risk of all-cause mortality. There is evidence that patients with Class I obesity respond well to surgical intervention. As a result, the FDA has recently approved the use of gastric banding for patients with Class I obesity and at least one associated-comorbidity. Since the goal of 'Early Intervention/Preemptive Therapy' is to achieve modest weight loss, the risk/benefit profile of gastric banding should serve as baseline for any EBT proposed for this indication. In this category, the durability or repeatability of an EBT would be important.

Bridge Therapy

The intent of 'Bridge Therapy' is to promote weight loss specifically to reduce the risk from a subsequent intervention, including bariatric surgery. Patients with Class III (BMI>50) and those with metabolic comorbidities present greater technical challenges and surgical risk than less obese, healthier patients. Furthermore, these effects are more pronounced in patients with BMI>60 where there is a 2-3 times greater risk of morbidity or mortality. Examples of procedures which may benefit from preoperative weight loss include orthopedic, cardiovascular, organ transplant, and bariatric operations. Efficacy would be primarily measured by a reduction in post-operative morbidity and mortality following the intervention that required bridging. The magnitude of weight loss can be lower, since the primary objective is to significantly reduce the risk of a subsequent intervention. Similarly, durability is a less important feature.

Metabolic Therapy

EBT may be justified in patients with less severe obesity (Class I), where improvement in metabolic illness is the primary concern. In particular, comorbidities such as type II diabetes, hyperlipidemia, and hypertension, may improve or resolve with even modest weight loss. Procedures which aim to effect metabolic disease should have a lower risk profile and greater durability compared to therapies which specifically aim to induce massive weight loss. Substantial weight loss may not be necessary in order to achieve metabolic benefits in less severely obese individuals. Obese patients who lose 5% of their total body weight benefit from significant reductions in diabetes and cardiovascular risk factors including hypertension and dyslipidemia. Therefore, we advocate using 5% of total body weight lost as the absolute minimum threshold for any non-primary EBT (e.g., early intervention, bridging or metabolic therapy).

IV. Areas for research

As an EBT is developed and modified to address specific clinical needs various types of studies are required as to accommodate the regulatory process. Rigorous preclinical evaluation should be followed by feasibility studies in a limited number of human subjects as described in FDA guidance documents. With an emphasis on technical feasibility and safety, there are typically no efficacy targets and results are used to direct modification and to calculate sample size and establish parameters for a larger pivotal trial.

The emphases of pivotal trial investigation are efficacy and safety. Pivotal trial design should vary depending on the category and intention of the specific EBT. Efficacy in terms of weight loss or resolution of comorbidities is most accurately assessed by comparison to a control group. Randomized controlled trials provide the highest level of evidence and are the preferred design. Importantly, EBT should be compared to a second treatment group, rather than a sham group. Sham groups in bariatric trials have proven to be unreliable with considerable variability in weight loss (3-13%EWL). Additionally, this type of design may put sham subjects at unnecessary risk. Studies must be designed to best evaluate the intended outcomes of the specific EBT, and the control group should be considered a reasonable alternative regarding potential risks and benefit. 'Primary' EBT that might be considered an alternative to traditional surgery should have an absolute threshold of weight loss that is established based on its particular risk profile. Additionally, the mean %EWL difference between this type of EBT and a medical control group should be a minimum of 15% EWL, and should be statistically significant. If a surgical control group is thought to be more relevant, a non-inferiority trial design would be preferred. Similarly, for an 'early intervention' EBT a non-inferiority design with randomization to a medical control group may be optimal.

Intended duration of effect and study length will also depend on the category of EBT being evaluated. 'Bridge' procedures should require a shorter interval (3-6 month) outcome assessment, since the objective is simply to reduce the risk of a downstream procedure. Similarly, some 'early interventions' that are low risk and easily repeated may require shorter trial durations, however, long term studies would likely be necessary for 'primary' EBT devices. For other devices, such as those in the 'metabolic' EBT category, weight loss may only be a secondary endpoint. Control groups for these trials would be very different, and may involve medical treatment of DM, or other related conditions.

Reduction in obesity-related co-morbidities

Clinical studies have shown that sustained moderate weight loss achieved through dietary and lifestyle intervention lowers blood pressure, improves glucose control, prevents diabetes, and improves dyslipidemia, hemostatic and fibrinolytic factors. Obese patients who lose 5% of their total body weight benefit from significant reductions in diabetes and cardiovascular risk factors including hypertension and dyslipidemia. Therefore, we advocate using 5% of total body weight lost as the absolute minimum threshold for any non-primary EBT (e.g., early intervention, bridging or metabolic therapy). In light of this evidence, it is intuitive that EBT has the potential to induce significant metabolic effects; among them, an improvement in or resolution of obesity-related co-morbidities such as diabetes mellitus, hypertension, obstructive sleep apnea and nonalcoholic fatty liver disease (NAFLD). If a low risk endoscopic intervention proves to have a significant impact on one or more of these co-morbidities, the threshold for intervention may extend to Class I obese individuals (BMI 30-35 kg/m^2).

In addition to lowering the prevalence of co-existent obesity-related metabolic illnesses, there is potential for an EBT to primarily prevent these comorbidities by promoting weight loss in mildly obese individuals. In this population, it is important that improvement/resolution of comorbidities be significantly better for endoscopic therapies compared to that of control groups, given the risks associated with any intervention despite how minimal they may be. Improvement and resolution of comorbidities should be defined using objective and standardized criteria.

Changes in quality of life

Weight loss can lead to a significant improvement in quality of life, anxiety and depression. Furthermore, the short-term improvements in body dissatisfaction and mood can positively affect long-term weight loss. Changes in quality of life, work productivity, and underlying psychological disorders represent important secondary endpoints in trials of EBT.

V. Training issues/establishment of competency

Weight loss interventions have been demonstrated to achieve superior outcomes when the intervention is performed as part of a comprehensive, multidisciplinary treatment program. EBT should also be performed in this context in order to achieve maximal benefit. Nutritional support, experienced nursing care, behavioral medicine specialists, and physicians experienced in the management of obese patients, are essential components of such programs. In addition, the ability and availability of physicians and surgeons willing and able to manage potential complications in obese patients is advised. Training and skill acquisition with EBT techniques and technologies are mandatory before clinical application is undertaken, and should include didactic as well as hands-on practical education. Importantly, any practitioner who is interested in performing an EBT should also be educated in the clinical management of obese patients. The duration and type of training is likely to depend on the complexity of a particular EBT. For all EBTs, early studies should assess the learning curve in order to guide subsequent training and credentialing processes.

VI. PIVI Committee

ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy
Gregory G. Ginsberg, MD, Chair
Bipan Chand, MD, Co-Chair
Gregory A. Cote, MD
Ramsey M. Dallal, MD
Steven A. Edmundowicz, MD
Ninh T. Nguyen, MD
Aurora Pryor, MD
Christopher C. Thompson, MD

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