Medical Devices with Indications Associated with Weight Loss - Clinical Study and Benefit-Risk Considerations

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Draft Guidance for Industry and Food and Drug Administration Staff

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For questions about this document, contact OHT3: Office of Gastro-Renal, ObGyn, General Hospital, and Urology Devices/DHT3A: Division of Renal, Gastrointestinal, Obesity, and Transplant Devices at (301) 796-7030.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

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Preface

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Medical Devices with Indications Associated with Weight Loss - Clinical Study and Benefit-Risk Considerations

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance document provides recommendations regarding clinical study design for devices with indications for use associated with weight loss, and also includes discussion on how FDA considers the benefit-risk analysis to support such indications.[1] Examples of indications associated with weight loss include indications for weight loss, weight reduction, weight management, or obesity treatment in patients who are overweight or have obesity.[2] Due to the wide variety of device designs, among other things, there can be variability in the demonstrated weight loss and risk associated with these devices. The recommendations reflect current review practices of premarket submissions (e.g., Premarket Approval (PMA) Applications, Investigational Device Exemption (IDE) Applications, Premarket Notifications (510(k)s), and De Novo classification requests) for these devices and are intended to promote consistency and facilitate efficient review of these submissions.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

[1] For further information on how FDA considers benefit-risk factors when evaluating substantial equivalence in 510(k)s generally, see https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.

[2] For further information on weight-loss and weight-management devices, see also https://www.fda.gov/medical-devices/products-and-medical-procedures/weight-loss-and-weight-management-devices.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Prior to issuing this draft guidance, FDA requested public comment on a concept for balancing the benefit of weight loss with the risks of adverse events in a discussion paper (September 2019).[3] FDA considered public comments and incorporated the feedback as appropriate in developing this draft guidance. The discussion paper continued FDA's efforts to be transparent and informative about how we regulate devices with indications associated with weight loss.

Additionally, FDA has previously engaged stakeholders regarding how we can help to ensure patients have access to appropriately safe and effective devices indicated for weight loss:[4]

- On November 16-17, 2005, FDA's Pediatric Advisory Committee held a public meeting on Clinical Trial Design Issues for Pediatric Obesity Devices.[5]
- On October 16-18, 2011, FDA, Dartmouth Device Development/GI at Dartmouth Medical School, and the Obesity, Metabolism and Nutrition Institute at Massachusetts General Hospital co-sponsored a two-day workshop, "Device Development in Obesity and Metabolic Disease (DDOMD)."
- On May 10-11, 2012, the Gastroenterology-Urology Devices Panel of the Medical Devices Advisory Committee discussed general issues related to obesity treatment devices and provided clinical study design recommendations to better evaluate the safety and effectiveness of obesity treatment devices.[6]
- In 2013, FDA published a benefit-risk assessment paradigm that could provide an a priori tool for systematic assessment of the risks associated with the devices intended for treatment of obesity and to suggest appropriate levels of benefit for devices with different risk levels.[7]

[3] See Docket No. FDA-2019-N-4060 (https://www.regulations.gov/docket?D=FDA-2019-N-4060).
[4] See also https://www.fda.gov/medical-devices/weight-loss-and-weight-management-devices/fda-activities-weight-loss-and-weight-management-devices.
[5] FDA Pediatric Advisory Committee, *Development of Trials to Assess the Safety and Efficacy Relevant to Scientific and Ethical Issues Surrounding Trials for Pediatric Devices for Weight Loss.* Gaithersburg, MD. Meeting materials can be accessed at https://wayback.archive-it.org/7993/20170403222257/https://www.fda.gov/ohrms/dockets/ac/oc05.html#Pediatric.
[6] 2012 Materials of the Gastroenterology-Urology Devices Panel can be accessed at https://wayback.archive-it.org/7993/20170113191551/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm286235.htm.
[7] Lerner, H., Whang, J., & Nipper, R. (2013). Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal. *Surgical endoscopy*, 27(3), 702-707.

- In 2015, FDA worked with the Research Triangle Institute Health Solutions (RTI-HS) to conduct the first national benefit-risk patient preference study to provide information on patient risk tolerance for weight loss devices.[8]
- On June 28, 2018, FDA held a listening session with patients who have used FDA-approved devices with indications associated with weight loss.

FDA refers the reader to the Q-Submission Program throughout this guidance document. For details on the Q-Submission Program, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[9]

III. Scope

The scope of this document is limited to devices with indications for use associated with weight loss, including weight loss, weight reduction, weight management, or obesity treatment in patients who are overweight or have obesity. This includes the existing product codes listed in Table 1 below:

Table 1. Existing product codes within the scope of this guidance

Product Code	Product Code Name	Regulation Number
LTI	Intragastric implant for morbid obesity	Not applicable[10]
OYF	Aspiration therapy system	Not applicable[11]
PIM	Neuromodulator for obesity	Not applicable[12]
ONY	Oral removable retainer for weight management	21 CFR 876.5981[13]
QFQ	Ingested, Transient, Space Occupying Device For Weight Management And/Or Weight Loss	21 CFR 876.5982[14]
QTD	Endoscopic Suturing Device For Altering Gastric Anatomy For Weight Loss	21 CFR 876.5983[15]

[8] Ho, M. P., Gonzalez, J. M., Lerner, H. P., Neuland, C. Y., Whang, J. M., McMurry-Heath, M., Hauber, A.B. & Irony, T. (2015). Incorporating patient-preference evidence into regulatory decision making. *Surgical endoscopy*, 29(10), 2984-2993.

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[10] This is a postamendments class III device.

[11] *Ibid.*

[12] *Ibid*.

[13] This classification regulation includes special controls. *See* 21 CFR 876.5981(b).

[14] This classification regulation includes special controls. *See* 21 CFR 876.5982(b).

[15] This classification regulation includes special controls established in the reclassification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210045.pdf. The publication of this classification in the Federal Register and codification in the Code of Federal Regulations are currently pending.

Although the product codes listed above are current as of the date of issuance of this draft guidance, new product codes or classification regulations may be created over time and could fall within the scope of this guidance. We recommend that you reference the product code database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm) or contact OHT3: Office of Gastro-Renal, ObGyn, General Hospital, and Urology Devices if you are uncertain whether this guidance applies to your device and the product code for your device is not already captured in this guidance.

Some of the recommendations in this guidance may assist in complying with some of the special controls for devices with indications associated with weight loss. For information regarding special controls for oral removable retainers for weight management, see 21 CFR 876.5981(b). For information regarding special controls for ingested, transient, space occupying devices for weight management and/or weight loss, see 21 CFR 876.5982(b). For information regarding special controls for endoscopic suturing devices for altering gastric anatomy for weight loss, see FDA's website.[16]

This draft guidance should be viewed as a complement to FDA's draft guidance entitled, "Medical Devices with Indications Associated with Weight Loss - Non-Clinical Recommendations,"[17] which, once finalized, will provide recommendations for the non-clinical testing to support marketing submissions for these devices.

IV. Clinical Performance Testing Considerations

Generally, non-clinical evaluation does not fully characterize all clinical experience, outcomes, and risks for these devices. We recommend submitters conduct *in vivo* (i.e., clinical) studies to evaluate device safety and effectiveness for new or significantly modified devices with indications associated with weight loss. For novel device designs, feasibility clinical studies can provide important safety and some effectiveness data that can be used to support a pivotal study. Pivotal studies can provide important safety and effectiveness data used to support marketing authorization.

Devices within the scope of this guidance document are generally considered significant risk devices and subject to all requirements of the Investigational Device Exemptions (IDE) regulation, 21 CFR part 812, for studies conducted in the United States (U.S.). See the FDA guidance titled, "Significant Risk and Nonsignificant Risk Medical Device Studies."[18] In addition to the requirements of 21 CFR part 812, sponsors of such trials of a device conducted in the U.S. generally must comply with the regulations governing institutional review boards (21 CFR part 56) and informed consent (21 CFR part 50).

[16] See reclassification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210045.pdf.
[17] When final, this guidance will represent FDA's current thinking on non-clinical testing for medical devices with indications associated with weight loss. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-indications-associated-weight-loss-non-clinical-recommendations.
[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.

Obesity represents a heterogeneous disease impacted by demographic, clinical and behavioral factors.[19] Additionally, culture and public health policy can impact weight loss.[20] Thus, FDA has encountered challenges about the applicability of foreign effectiveness data to the U.S. population for devices with indications associated with weight loss. Therefore, we recommend that pivotal studies be conducted in the U.S. If foreign data is collected, we recommend that no more than 50% of the pivotal study data be collected from outside the United States (O.U.S.). We also recommend that no more than 20% of the total enrollment population be from one site to avoid the study outcome being dominated by sites with large enrollment.

When data from clinical investigations conducted O.U.S. are submitted to FDA, the requirements of 21 CFR 812.28 may apply.[21] 21 CFR 812.28 outlines the conditions for FDA acceptance of clinical data from investigations conducted O.U.S. when submitted to support a premarket submission. For more information, see the FDA guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."[22]

A. Study Design

We recommend that pivotal studies to support a weight loss indication be double-blinded, randomized, controlled trials (RCTs). We recommend that additional study staff remain blinded throughout the study (e.g., dieticians, personnel collecting study data).

We recommend a sham-controlled study as a placebo effect is anticipated. A sham control in a clinical study can provide an important comparator from which to determine the effectiveness of device therapy in comparison to the placebo effect. Therefore, a sham control is beneficial to reduce the uncertainty regarding the treatment effects of the device. We recommend the sham device and/or sham procedure be designed in a way to minimize the subject's ability to determine whether they have the study device or the sham device. We recommend that submitters consider how blinding will be assessed if using a sham control. We appreciate that a sham control may not be appropriate in all circumstances. If a sham device or sham procedure is not appropriate for a clinical trial design, we recommend a concurrent control arm where the control and treatment groups follow the same lifestyle programs. For all study designs, we recommend standardized dietary and behavioral study aspects between study arms and among centers involved in the study, and that these study aspects be representative of real-world diet and behavior regimens.

[19] Jimenez, M. P., Green, M. A., Subramanian, S. V., & Razak, F. (2018). A demographic, clinical, and behavioral typology of obesity in the United States: an analysis of National Health and Nutrition Examination Survey 2011-2012. *Annals of epidemiology*, 28(3), 175–181.e4.

[20] Waxman A. WHO Global Strategy on Diet, Physical Activity and Health. Food and Nutrition Bulletin. 2004;25(3):292-302.

[21] This applies to data from clinical investigations that began on or after February 21, 2019 and are submitted to support a premarket submission, including IDEs, PMAs, and 510(k)s.

[22] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked.

For additional information on principles for the design of premarket clinical studies, refer to FDA's guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices."[23]

B. Study Duration and Follow-up Schedule

The study should be designed to include adequate follow up to support the indications for use. The follow-up period should also account for the risk posed by device use.

To support device effectiveness, study duration and the follow-up schedule should be selected with the proposed indication in mind.

- For a proposed indication of "weight loss," the duration of device use and primary endpoint should typically demonstrate weight loss at 12 months or more.
- A proposed indication of "short term weight loss" can typically be supported with a duration of device use and primary endpoint demonstrating weight loss at six months or more, but less than 12 months.
- Weight loss measured at, or a device that is used for, less than six months could be supportive of a proposed "weight management" indication.
- Additional follow-up may also be warranted to understand the durability of weight loss. Sometimes a supplemental marketing submission is submitted after these additional follow-up data are collected, for example, to update labeling. Consequently, we recommend consenting patients long enough for any anticipated additional follow-up which may be necessary to support such labeling (or other) modifications.

To support device safety, study duration and follow-up should be adequate to collect sufficient adverse event information depending on the device design and how it is used. The duration of follow-up needed to support device safety may be longer than that to support effectiveness if warranted due to the risk that the device may pose to patients.

C. Inclusion/Exclusion Criteria

As body mass index (BMI) increases, risk of weight-related morbidity and mortality increases. The BMI range for inclusion in a clinical study should be the result of a risk-based decision to ensure that study patients will have an appropriate level of anticipated benefit to offset the risks associated with the device.

In general, clinical trials of implanted or surgically-placed devices should enroll individuals with a BMI greater than or equal to 35 kg/m^2, or greater than or equal to 30 kg/m^2 if accompanied by

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.

weight-related comorbidities (e.g., type 2 diabetes mellitus (T2DM)).[24] In studies of lower risk devices, patients with a BMI of 27 kg/m^2 with weight-related comorbidities may be included. Higher-risk device studies may warrant additional specification of the BMI range and/or weight-related comorbidities, to ensure that the anticipated benefit outweighs the probable risks.

Given the risks associated with implanted or surgically-placed devices, patients in studies of such devices should have failed more conservative, first-line weight loss methods such as diet, exercise, and behavior modification.

Treatment with these medical devices in a clinical study may not be appropriate for certain patients. We recommend that submitters consider the following for the exclusion criteria as applicable:

- Patients who are unable or unwilling to follow the dietary restrictions specified by the clinical protocol;
- Altered anatomy (e.g., sleeve gastrectomy);
- History of dysmotility or delayed gastric emptying;
- Pregnancy or breastfeeding;
- Current smokers, because of the contribution of smoking to obesity-linked comorbidities and increased risk of complications;
- Persons with a history of eating disorder(s), or a serious or uncontrolled psychiatric illness that could compromise understanding or compliance with visits and device maintenance/removal;
- Active substance abuse;
- Untreated endocrine or metabolic cause for obesity;
- Previous gastrointestinal surgery (e.g., bowel resection); and
- Older patients for whom the risks of the procedure are not acceptable and/or the anticipated lifespan conflicts with the expected period of benefit.

D. Patient Demographics

We recommend that submitters include in their study a representative sample of patients from various demographic groups (e.g., sex, gender, age, ethnic, and racial) in which the prevalence of obesity is highest. FDA recommends that clinical studies for these devices enroll participants that reflect the demographics for clinically relevant populations.

[24] This recommendation is consistent with the 2018 position statement of the American Society of Metabolic and Bariatric Surgery (ASMBS): Aminian, A., Chang, J., Brethauer, S. A., Kim, J. J. (2018). ASMBS updated position statement on bariatric surgery in class I obesity (BMI 30–35 kg/m^2), *Surgery for Obesity and Related Diseases*, 14(8), 1071-1087.

For more information regarding the evaluation and reporting of age, race, ethnicity and sex-specific data in medical device clinical studies, see FDA's guidances "Evaluation of Sex-Specific Data in Medical Device Clinical Studies"[25] and "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies."[26]

E. Treatment Parameters/Protocol

The study-specific treatment protocol should minimize risk to patients. The protocol should not only consider the risks associated with the device and device placement, but any additional risk that may be applicable to all patient populations included in the study. For example, if submitters choose to include patients with certain comorbidities (e.g., T2DM), the protocol should explain how these patients will be protected from complications that may arise due to their disease.

Specifically, when designing trials that include patients with T2DM, we recommend that a safety monitoring plan be included in the protocol to detect and manage hypoglycemia or continued uncontrolled hyperglycemia. The management plan should consider an algorithm for the lowering or elimination of oral hypoglycemics or insulin based on fasting glucose levels and/or glycated hemoglobin (HbA1c)[27] (for patients who lose clinically significant amounts of weight).

For a device with novel technology and/or with an undefined risk profile, it may also be appropriate to prospectively define stopping rules in the study protocol and/or initially enroll a limited number of patients in a phased manner to better manage risk.

If the device is a permanent implant, the study design should include considerations for how a device should be explanted if warranted or requested during or at termination of the study. Considerations should include, at a minimum, removal instructions and a plan for tracking reasons for device explant, including association with any adverse events as noted in Section IV.F below. There should also be evidence that removal instructions in device labeling are sufficient to safely remove the device if explant is warranted. Removal instructions should be evaluated during the course of the clinical study if devices are explanted from patients.

Throughout the study, participants should receive the standard of care, including medication and monitoring for comorbidities such as hypertension, dyslipidemia, and glycemic control.

F. Safety Endpoints and Data

The primary safety endpoint should be reporting of all device- and procedure-related adverse events, as FDA intends to consider all adverse events in our assessment of the premarket

[25] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-specific-data-medical-device-clinical-studies-guidance-industry-and-food-and-drug.

[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-age-race-and-ethnicity-specific-data-medical-device-clinical-studies.

[27] HbA1c (glycated hemoglobin) is a term commonly used in relation to diabetes - the higher the HbA1c, the greater the risk of developing diabetes-related complications.

submission. Additional safety assessments may be warranted based on the design and principles of operation of the specific device.

G. Effectiveness Endpoints and Data

Demonstrated weight loss should be based on percent total body weight loss (% TBWL),[28] which is typically captured in a clinical study with co-primary effectiveness endpoints that include:

- a hypothesis with a pre-specified superiority margin of the mean % TBWL over control; and
- a performance goal for a responder rate based on individual subject success.

FDA recommends a pre-specified superiority margin for mean % TBWL be included in the clinical protocol depending on the indication being sought in the premarket submission:

- For an indication of "weight loss," we recommend at least a 5% superiority margin of the mean % TBWL over the control. However, the minimum value over the control arm should be appropriate for the risk associated with device use and any device-related procedures.
- For an indication of "limited weight loss," we recommend at least a 2% superiority margin of the mean % TBWL over the control. However, the minimum value over the control arm should be appropriate for the risk associated with device use and any device-related procedures.
- For an indication of "weight management," a superiority margin of less than 2% may be supportive if additional benefit is measured (i.e., responder rate endpoint is met). However, the benefit should be appropriate for the risk associated with device use and any device-related procedures.

For the responder rate, we recommend that at least 50% of treated patients achieve at least 5% TBWL for any indication associated with weight loss (i.e., weight loss, limited weight loss, weight reduction, weight management, or obesity treatment).

For an indication of "obesity treatment," we recommend endpoint(s) demonstrating clinical benefits in addition to weight loss alone. Support for additional benefits should be appropriately powered in the study design.

We recommend submitters consider the following secondary effectiveness endpoints:

- Percent excess weight loss (% EWL);[29]
- Change in weight;

[28] For the purposes of this guidance, FDA defines % TBWL = [(initial weight − final weight)/initial weight] × 100%.

[29] For the purposes of this guidance, FDA defines % EWL = [(initial weight − weight to be at a BMI of 25)/initial weight] × 100%.

- Change in BMI; and
- Change in waist circumference.

We also recommend that submitters consider including patient-reported outcomes (PROs)[30] and patient preference information (PPI)[31]. The value patients associate with the treatment, their willingness to accept the risk of this treatment to achieve the benefit, the treatment's ability to improve the patient's overall quality of life, and the patient's ability to understand the benefits and risks of the treatments are important factors in evaluating device benefit.

Changes in common weight-related comorbidities are often secondary endpoints in studies of devices with indications associated with weight loss. If any of the secondary endpoint analyses are intended to support the indications for use or to describe device performance in the labeling (e.g., comparing treatment and control groups using p-values or confidence intervals), we recommend pre-specifying this intention in the study protocol and providing a detailed description of the statistical methods planned to follow. The study should be powered appropriately to evaluate such changes, if comparative statements are intended to be made in the labeling.

H. Adverse Events

We recommend that all adverse event data be collected during the study and that events be adjudicated as to whether they are device- and/or procedure- related. In general, we recommend that studies have a data safety monitoring board (DSMB) and establish an endpoint assessment/adjudication committee. We refer the submitter to the FDA guidance "Establishment and Operation of Clinical Trial Data Monitoring Committees"[32] for more information. Independent data monitoring committees help to ensure the safety of enrolled participants as follows:

- The committee can provide a comparative assessment of accumulating safety and effectiveness data to inform recommendations to the study sponsor whether to continue, modify, or stop the study;
- Potential complications may warrant robust study oversight from a third party that is advisory to the study sponsor; and

[30] See FDA guidances "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use, and "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.

[31] See FDA guidance "Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.

[32] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees.

- Unbiased adjudication of adverse events reduces the uncertainty in study safety outcome data.

We recommend an adverse event classification modeled after the Clavien-Dindo Classification of Surgical Complications,[33] shown in Table 2, where the severity of each adverse event is graded based on the treatment used to address the event.

Table 2. Adverse event classification for clinical studies

Grade	Definition
Grade I	Any deviation from the normal treatment course without the need for surgical, endoscopic, and radiological interventions. Includes all over-the-counter pharmacological interventions and non-narcotic prescription pain medications (including anti-emetics, antipyretics, analgesics, diuretics, electrolytes, physiotherapy, and bedside wound care)
Grade II	Requiring pharmacological treatment with prescription drugs (excluding non-narcotic pain medications in Grade I), the administration of intravenous fluids, blood transfusions, or total parenteral nutrition
Grade III	Requiring surgical, endoscopic, or radiological interventions
Grade IV	Life-threatening complications requiring intensive care/intensive care unit management (including single and multiorgan dysfunction, and central nervous system complications)
Grade V	Death

The classification scheme identified in Table 2 focuses on deviations from the normal treatment course for a device. For example, the normal treatment course for a device may include use of concomitant medications, and additional therapy (e.g., anti-emetics, pain medication) typically provided as part of the practicing physician's treatment plan. While concomitant medications are not considered as adverse events per this classification scheme, FDA does consider such as part of the overall benefit-risk determination for a device, as described in Table 4 in Section V.A.

A single type of adverse event can be categorized into different grades, depending on the treatment required for resolution. For example, vomiting can be resolved with over-the-counter medication (Grade I), or vomiting can require administration of intravenous fluids (Grade II). The grades are to be considered mutually exclusive, and together the grades should cover all event outcomes. All events that fit into a single grade are of approximately equal severity/risk to the patient.

[33] Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery*, 240(2), 205.

We recommend submitters present adverse event information to FDA in their premarket submission as follows:[34]

- Tabulate all adverse events and categorize as device-related, procedure-related, or not related to the device or procedure and categorize all adverse events as explained in Table 2;
- Tabulate all serious adverse events (SAEs) and categorize as device-related, procedure-related, or not related to the device or procedure and categorize all SAEs as explained in Table 2;
- Identify any and all unanticipated adverse device effects;
- Provide the time to onset as well as duration for all gastrointestinal-associated device- and/or procedure-related adverse events, including resolution status; and
- Tabulate all unanticipated device removals and the reason for removal.

We recommend the use of PRO instruments to assess non-serious adverse events using validated tools such as the gastrointestinal symptom scales included in the National Institutes of Health (NIH) PRO Measurement Information System (PROMIS).[35]

I. Statistical Analysis Considerations

(1) Sample Size

For pivotal studies, we recommend that co-primary effectiveness endpoints include a hypothesis with a pre-specified superiority margin for percent total body weight loss and a performance goal for a responder rate. The number of patients should be the maximum of sample sizes calculated based on the co-primary endpoints considering anticipated loss to follow-up; however, additional patients should be enrolled to assess device safety to support premarket submission. In general, calculations should be based on two-sided tests of significance at the 5% level and at least 80% power. Effect sizes for the calculations should represent clinically meaningful differences.

(2) Analysis Methods

Endpoints should be analyzed based on the intent-to-treat (ITT) population, defined as patients that were enrolled and randomized into the study, regardless of whether the patients received the treatment to which they were randomized.

[34] As described in Section III.B.(4), of FDA's draft guidance, "Medical Devices with Indications Associated with Weight Loss - Non-Clinical Recommendations," FDA recommends that the adverse event information in this list also be included in the device's labeling. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-indications-associated-weight-loss-non-clinical-recommendations.

[35] Spiegel, B. M., Hays, R. D., Bolus, R., Melmed, G. Y., Chang, L., Whitman, C., ... & Khanna, D. (2014). Development of the NIH patient-reported outcomes measurement information system (PROMIS) gastrointestinal symptom scales. *The American journal of gastroenterology*, 109(11), 1804.

The analysis of % TBWL should use analysis of variance (ANOVA) or analysis of covariance (ANCOVA) with baseline weight as a covariate in the model.

Response rates should be compared between the treatment and control groups using statistical methods appropriate for categorical data. A sensitivity analysis should be conducted that considers patients who are treated, drop out, and do not have complete post-baseline data as treatment failures. Additionally, a tipping point analysis for binary response variables should be considered.

Type I error should be controlled across all clinically relevant secondary effectiveness endpoints intended for product labeling.

(3) Missing Data

a. Efforts to reduce missing data

We recommend you describe the efforts that will be used during the course of the study to monitor and minimize the incidence of patient dropouts, such as monitoring activities, special incentives to patients for study compliance, methods to remind patients of scheduled visits, and specific efforts to contact patients who miss their visit (e.g., telephone calls, postcards, contact next-of-kin).

b. Document reasons for missing data

We recommend you identify the steps to document:

- the reason for each missed visit, e.g., complications, difficulty getting transportation to the site; and
- the reason for each dropout, e.g., seeking alternate therapy, complications or intolerance to the device, dissatisfaction with the device, moved away.

To permit a complete and detailed accounting of all study patients, we recommend you collect complete information during the study because loss to follow-up jeopardizes the conclusions that can be made about the long-term safety and effectiveness of a device.

c. Handling missing primary endpoint data

To allow for a true ITT analysis, we recommend obtaining body weight measurements in all patients who prematurely withdraw from studies near the calendar date at which they were scheduled. This will reduce uncertainty in the ultimate outcome of the study by having a data measurement at the primary effectiveness endpoint rather than imputing the measurement. For example, a patient who withdraws from a 12-month study after six months of treatment should have a body weight measurement at the time he or she would have completed 12 months of study participation. If this is not possible, we recommend conducting sensitivity analyses to determine the best mechanism to account for missing data.

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d. Sensitivity analyses

Sensitivity analyses employing imputation strategies should assess the effect of dropouts on the results. The imputation strategy should be prespecified and should consider the expected dropout patterns and the time-course of weight changes in the treatment group. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. We recommend multiple imputation when a "missing at random" assumption is plausible. For early exit due to adverse events or ineffectiveness of the device, we recommend you use "unfavorable clinical outcome" to impute missing data.

(4) Subgroup Analyses

We recommend submitters conduct gender and sex-based subgroup analyses. We recommend submitters conduct subgroup analyses based on race and ethnicity as the prevalence of obesity varies among these groups in the U.S. population.[36] If the study includes sites O.U.S. then we recommend conducting a U.S. subgroup analysis.

J. Pediatric Studies

Planning clinical trials for pediatric patients includes additional considerations beyond those of adult patients, such as ethical issues of studying a more vulnerable patient population and an altered benefit-risk profile because of potential interference of a medical device with physical growth and maturation. Consistent with the FDA guidance "Premarket Assessment of Pediatric Medical Devices,"[37] FDA considers patients below 22 years of age to be pediatric (that is, from birth up to but not including the 22nd birthday) for medical device studies.

The increased prevalence of children being overweight or having obesity, emphasizes an unmet need to provide therapy to children who have a disease that impacts their health, quality of life, and psychosocial factors. FDA remains open to considering risk-based clinical study designs and intends to consider both the benefits and risks to adolescent study participants when determining the amount of benefit-risk evidence needed before initiation of an adolescent weight-loss device study.

We recommend using the U.S. Centers for Disease Control and Prevention (CDC) National Center for Health Statistics definitions for classifying pediatric-aged patients as overweight or

[36] https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity.

[37] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-assessment-pediatric-medical-devices.

obese and the American Heart Association recommendation for severe obesity based on age- and sex-matched BMI cutoffs as follows:[38, 39, 40, 41]

- BMI-for-age between the 85th and 95th percentile is overweight;
- BMI-for-age at or above the 95th percentile is obesity; and
- BMI ≥120% of the 95th percentile or an absolute BMI ≥35 kg/m^2, whichever is lower based on age and sex is severe obesity.

FDA developed the following recommendations considering outcomes from the 2005 FDA Pediatric Advisory Committee (PAC) meeting on weight loss device clinical trial designs for pediatric patients,[42] changes in the field of childhood obesity since the PAC's recommendations,[43] and input from external experts, including clinicians. Additionally, the following recommendations are intended to supplement and not supersede those discussed in the FDA guidance "Premarket Assessment of Pediatric Medical Devices."[44] These recommendations are in addition to those discussed elsewhere in this document for adult patients.

Recommendations specific for pediatric patients include:

1. In general, the device should not be studied in the pediatric population until enough data has been obtained to show that the study does not involve greater than minimal risk.[45,46] Additionally, if the device is a permanent implant, sufficient data should exist to support anticipated benefit in the pediatric population.[47] Other sources of data, including animal

[38] Kelly, A. S., Barlow, S. E., Rao, G., Inge, T. H., Hayman, L. L., Steinberger, J., ... & Daniels, S. R. (2013). Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation*, 128(15), 1689-1712.
[39] Gulati, A. K., Kaplan, D. W., & Daniels, S. R. (2012). Clinical tracking of severely obese children: a new growth chart. *Pediatrics*, 130(6), 1136-1140.
[40] Ogden, C. L., & Flegal, K. M. (2010). Changes in terminology for childhood overweight and obesity. *Age*, 12(12).
[41] Flegal, K. M., Wei, R., Ogden, C. L., Freedman, D. S., Johnson, C. L., & Curtin, L. R. (2009). Characterizing extreme values of body mass index-for-age by using the 2000 Centers for Disease Control and Prevention growth charts. *The American journal of clinical nutrition*, 90(5), 1314-1320.
[42] FDA Pediatric Advisory Committee, Development of Trials to Assess the Safety and Efficacy Relevant to Scientific and Ethical Issues Surrounding Trials for Pediatric Devices for Weight Loss. Gaithersburg, MD. Meeting materials can be accessed at https://wayback.archive-it.org/7993/20170403222257/https://www.fda.gov/ohrms/dockets/ac/oc05.html#Pediatric.
[43] Marrone A.K., Venkataraman-Rao P., Gottschalk L. (2021). Food and Drug Administration insights on clinical study of weight-loss devices intended for adolescent patients. *Pediatric Obesity,* e12768.
[44] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-assessment-pediatric-medical-devices.
[45] In general, the 2005 FDA PAC recommended that "devices, especially implants, should not be studied in the pediatric population until enough data has been gained from adult study and use." For more information, see https://wayback.archive-it.org/7993/20170404062450/https://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4179m_summary.pdf.
[46] In general, the 2005 FDA PAC recommended that "A staged introduction should be used when studying devices for obesity in the pediatric population. Namely, after adequate information is available in adult populations, the device can be studied in the older adolescent group (12 or 14 to 17). Sufficient experience and data should be collected before studying the device in patients younger than this." *Ibid.*
[47] In general, the 2005 FDA PAC recommended that "post-approval data should be collected through 5 years" and "parties should be encouraged to have registries for long-term implants, which follow patients for 5-10 years." *Ibid.*

or other relevant modeling and simulation data, may preclude or mitigate the need to preliminarily collect data on older populations. This may be especially relevant when designing clinical investigations to meet the more immediate needs of patients, such as younger adolescents, experiencing co-morbidities associated with the severe end of the obesity spectrum.

2. If the device is a permanent implant, risk associated with potential explantation of the permanent implant should be well defined.
3. Pediatric patients should have a documented history of failing to achieve weight-loss goals with lifestyle modification before enrollment into a clinical study for these devices. In general, patients should have participated in a comprehensive, multi-disciplinary pediatric weight management program for at least six months without adequate results.
4. Studies should have a lead-in period that allows for adequate time for the clinical team to get to know the patient, for the failure of adequate therapy programs to be documented, for the patient to understand the therapy and its impact, and for the patient's ability to comply with diet, protocol, and other considerations (e.g., psychosocial comorbidities) to be assessed.[48]
5. FDA considers the risk profile of the device for the appropriate study population in a pediatric clinical study. Table 3 illustrates recommended percentiles for BMI-for-age for inclusion of adolescent patients into a study for a device with indications associated with weight loss. Generally, higher risk devices should have the potential for greater benefit, as indicated by the percentiles for BMI-for-age in Table 3. If the submitter believes that the device is low-risk, FDA encourages discussion of a risk-based justification for inclusion of study patients with lower BMI-for-age percentiles.

Table 3. Recommended percentiles (%ile) for BMI-for-age values for inclusion of adolescent patients into a study for a device with an indication associated with weight loss. Risk-dependent value should fall within specified ranges.

	Comorbidity	**No comorbidity**
Temporary[49] device	≥85th %ile BMI	≥95th %ile BMI
Permanent[50] device	≥85th %ile to 120% of the 95th %ile BMI	≥95th %ile to 140% of the 95th %ile BMI

[48] In general, the 2005 FDA PAC recommended that "studies should have a lead-in period during which the physician team got to know the patient and it could be documented that the patient had failed adequate conservative therapy programs and to ensure the patient's ability to comply with diet, protocol, etc." *Ibid.*

[49] For the purposes of interpreting this table, a temporary device is intended to be implanted or used for a pre-determined, limited amount of time (for example: a six-month intragastric balloon). A permanent device is one that is implanted without intention to remove or one that permanently alters the patient's anatomy and/or physiology. For the purposes of device classification procedures, the definition of an implant is provided in 21 CFR 860.3.

[50] *Ibid.*

6. A study endpoint of less than 12 months is likely not appropriate to evaluate a permanent device in the pediatric population, as these patients are still growing and maturing.[51]
7. Obesity-related comorbidities that should be considered for inclusion include:[52]
    - Obstructive sleep apnea;
    - Prediabetes;
    - T2DM;
    - Uncontrolled hypertension;
    - Orthopedic complications;
    - Pseudotumor cerebri;
    - Non-alcoholic steatohepatitis (NASH);
    - Polycystic ovary syndrome (PCOS); and
    - Hyperlipidemia/dyslipidemia.
8. Exclusion criteria should include:
    - Uncontrolled psychiatric conditions;
    - Patients that are ill-equipped or unwilling to change behavior;
    - Patients who are unwilling to undergo the intervention themselves;
    - Patients with anatomical issues that may put them at unreasonable risk;
    - Patients with connective tissue disorders that may result in tissue breakdown, if the device is an implant or changes anatomy; and
    - Developmentally disabled patients who cannot follow recommendations.
9. To determine suitability for participating in a clinical study, maturity level and psychosocial comorbidities should be assessed by a specialist trained in psychology and in discussing mental health issues, stigma, bias, bullying, binge-purge behaviors, readiness for change, and other related considerations.
10. Patients should be screened for known genetic causes of obesity such as Prader-Willi Syndrome.[53] For these patients, as well as those with hypothalamic obesity related to

[51] In general, the 2005 FDA PAC recommended that "Premarket data should be collected for 2 years although patients should be consented/assented for 5 years." For more information, see https://wayback.archive-it.org/7993/20170404062450/https://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4179m_summary.pdf.

[52] Obesity-related comorbidities listed are also applicable to adult study populations. These comorbidities are listed in this section of this guidance document due to the relevant general recommendations from the 2005 FDA PAC: 1) Long-term implant devices should be studied in patients with significant disease, i.e., those who are in the 99th percentile for BMI-for-age, and have at least one significant comorbidity, such as sleep apnea, diabetes, pseudotumor cerebri, or NASH (Non-Alcoholic Steatohepatitis); and 2) Comorbidity reduction or resolution would be an important secondary effectiveness endpoint although the study would need to be powered appropriately to evaluate such changes. *Ibid.*

[53] In general, the 2005 FDA PAC recommended that "patients should be screened for known genetic causes of obesity and for Prader Willi, and if included in the study, should be evaluated separately." *Ibid.*

craniopharyngioma surgery that are about eight years old and above, inclusion into a study could be considered, though FDA recommends that the submitter consider separately evaluating the data for this subpopulation.

11. As for adult studies, clinically meaningful weight loss may be defined by % TBWL that should be linked to the health risk in the desired pediatric patient population. Consistent with clinical guidelines based on cardiometabolic risk,[54] we consider at least a 5-10 % TBWL clinically meaningful, and these values could be applicable to the pediatric population. However, linear growth should be considered when assessing changes in body weight of children and adolescents. Thus, the primary effectiveness parameter could be a function of the change in %BMI-for-age and/or % TBWL. This should depend on what is most clinically meaningful in the desired patient population considering age, BMI range, and any additional disease factors (e.g., associated comorbidities). Additionally, endpoint(s) should be able to demonstrate a positive outcome on the disease status (e.g., change in class of obesity).
12. If applicable, comorbidity reduction or resolution should be a secondary effectiveness endpoint.
13. The overall clinical study duration and follow-up should be justified considering the anticipated benefit and device risk. However, for devices that result in the modification of anatomy or involve a permanent implant, we recommend that premarket evaluation include follow-up for two years to account for weight loss durability. Patients should be consented or assented, as applicable, for five years to allow for longer-term follow-up post-marketing. Parental permission should be obtained when applicable.
14. For a device that is temporary, durability of device-effect should be measured at least six months post device use unless a shorter assessment period is justified.
15. Height measurements should be obtained from a wall-mounted stadiometer by study personnel trained in its use. A bone age study to obtain radiographic imaging of the growth plates can also be considered.

Other clinically relevant issues to consider when designing a pediatric study include endocrinologic causes of obesity, assessing neuropsychiatric symptoms and/or psychosocial environment, compliance, nutritional issues, and reproduction issues. We recommend addressing and/or monitoring these issues as appropriate.

We encourage submitters to utilize FDA's Q-Submission Program to ensure that the pediatric study protocol addresses safety concerns depending on the facts and circumstances of the device and study.

[54] Jensen, M. D., Ryan, D. H., Apovian, C. M., Ard, J. D., Comuzzie, A. G., Donato, K. A., & Yanovski, M. (2014). AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*, 129(25 Suppl 2), S102-138.

V. Benefit-Risk Considerations

A. Benefit-Risk

FDA evaluates whether a device has a reasonable assurance of safety and effectiveness during the PMA review, or whether general or general and special controls provide such assurance for a device in a De Novo classification, or whether it is substantially equivalent to a valid predicate in 510(k) review, by weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,[55] or assessing the benefit-risk profile of a device as compared to a valid predicate,[56] among other relevant factors. To aid in this process, submitters include valid scientific evidence, including one or more clinical investigations, where appropriate, and/or non-clinical information, which FDA reviews to determine, among other things, whether the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device.[57]

When assessing the benefits of devices, FDA considers the types of benefits, the magnitude of benefits, the probability of patients experiencing one or more benefits, and the duration of effects.[58] When assessing the risks of devices, FDA considers severity, type, number, and rate of harmful events associated with use of the device or procedure associated with the device, probability of harmful events, and duration of harmful events. Additional factors considered when assessing the probable benefits and risks of devices include uncertainty[59] surrounding the benefit and risk, patient-centric assessments and PROs, characterization of the disease or condition, patient preferences,[60] availability of alternate treatments, risk mitigation, device-type post-market data, and novel technology for addressing unmet medical needs.

Specific to devices with indications associated with weight loss, important considerations include the factors listed in Table 4.

[55] The criteria for determining the safety and effectiveness of a device are set forth in section 513(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 860.7.

[56] See FDA guidance "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.

[57] Section 513(a)(3)(A) of the FD&C Act.

[58] See FDA guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de.

[59] See FDA guidance "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de.

[60] See FDA guidance "Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.

650
651 **Table 4.** Factors considered as part of the benefit-risk evaluation for devices with indications
652 associated with weight loss

Factor	Example(s)
Assessment of Benefits from a Clinical Study	
Weight loss	amount of weight loss attributed to the device, proportion of patients experiencing weight loss, and durability of weight loss
Changes in comorbidities	improvements in cardiometabolic risk factors, as well as other obesity-related comorbidities (e.g., clinically significant reduction in HbA1c, hypertension, and/or dyslipidemia), reduction in medication(s)
Other benefit	improvement in quality of life
Assessment of Risks from a Clinical Study	
Device- and procedure-related adverse events	seriousness, severity, types, numbers, rates, duration, resolution of adverse events and exacerbation of pre-existing conditions
Effects of the device	permanent implantation, anatomic changes, restriction of future treatment options, reversibility limitations, effect on drug and/or nutrient absorption
Clinical treatments/procedures related to the device	risk associated with expected concomitant medications or therapies, rate of early device removal due to patient request, risks related to placement/removal procedures, risks related to procedures necessary to diagnose adverse events, hospitalization (need, duration, and reason for)
Additional Factors	
Evaluation matrices decision aid[61]	extent of weight loss and duration of device use versus prevalence and severity of adverse events reported in a clinical study
Uncertainty	uncertainty resulting from study design, study conduct, potential for sham effect, and range of confidence intervals
Additional clinical data	studies from outside the United States, feasibility studies, real-world evidence, use of the device repeatedly or in sequence
Additional considerations	availability of alternative therapies, risk mitigation measures, patient preferences

653
654 There is a wide range of technology and techniques being attempted for devices with indications
655 associated with weight loss. These different approaches can translate into different impacts or
656 outcomes, such as duration of device implantation, adverse event profiles, and different amounts
657 of weight loss. As innovators conceive and develop the next generation of devices with plans to
658 market such devices in the U.S., the recommendations below explain how FDA intends to

[61] The evaluation matrices are applicable to devices with indications outlined in Table 5.

consider, in the context of premarket submission decision, adverse events in light of varying degrees of benefit (specifically extent of weight loss and duration of device use).

B. Use of Modified Clavien-Dindo to Assess Risk

As described in Section IV.HH, we recommend an adverse event classification modeled after the Clavien-Dindo Classification of Surgical Complications,[62] where the severity of each device- and procedure-related adverse event is graded based on the treatment used to address the event (*See* Table 2). The Clavien-Dindo Classification was chosen due to its wide use among physicians as a reliable and reproducible system for reporting surgical complications. Modifications to the Classification system were adapted to make it more relevant for weight loss device-related complications.

We highlight the differences from the original Clavien-Dindo Classification as well as relevant considerations in the following summation:

- Grade I was adapted to include over-the-counter medications and non-narcotic prescription pain medications.
- Grade II includes all other prescription medications and the administration of intravenous fluids.
- Like the original Clavien-Dindo Classification scheme, length of hospital stay is not included, since practices vary between medical centers and unexpected hospitalization typically occurs in combination with other therapies that are captured by the classification. However, FDA intends to consider seriousness and the need, duration of, and reason for hospitalization when making our overall benefit-risk determination for these devices.
- Diagnostic procedures, such as diagnostic endoscopies, are not included, because an adverse event discovered by a diagnostic procedure would be classified by the treatment needed for the adverse event. However, FDA intends to consider the risk of diagnostic procedures that may be used to diagnose device- or procedure-related adverse events when making our overall benefit-risk determination for these devices.
- Regarding Grade II, a patient's need for blood transfusions and total parenteral nutrition (TPN) would be indicative of more serious adverse events in comparison to prescription medication use; however, the associated adverse events are likely to include additional treatments defined as Grade III or Grade IV, and the grades of those additional treatments would also be captured.
- Devices can electively be removed prior to the end of their intended course of therapy for reasons other than adverse events included in the Adverse Event Classification described in Table 2. These reasons could be at patient request. These events are not captured in the Adverse Event Classification, but FDA intends to consider early device removal when making our overall benefit-risk determination for these devices.

[62] Dindo, D., Demartines N., Clavien P.A. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 240:205–213.

C. Balancing Weight Loss and Adverse Events for an Indication of Weight Loss

FDA's assessment of tolerability of adverse events in light of varying degrees of weight loss for devices specifically with a weight loss indication have been developed considering:

- Outcomes from the 2012 Gastroenterology-Urology Devices Panel on general issues related to obesity treatment devices;[63]
- Feedback from external experts, including clinicians; and
- The public comments submitted to Docket No. FDA-2019-N-4060 in response to a discussion paper outlining concepts discussed below.

As described in Sections IV.GB and IV.G, indications for weight loss depend on the extent and duration of weight loss demonstrated in a clinical study. For devices used for less than six months, or having less benefit than that outlined in Table 5, a weight management indication may be appropriate. An obesity treatment indication should be supported by clinical benefits in addition to weight loss alone.

Table 5 summarizes four weight loss indication categories based on the amount of weight loss observed in a clinical study and the duration of device use.

Table 5. Weight loss indication categories

Indication	Demonstrated Weight Loss		Duration of Device Use
	Superiority Margin **% TBWL Over Control**	**Responder Rate** **% patients achieving ≥5% TBWL**	
Short-Term Limited Weight Loss	≥2% and <5%	50%	6 months to <12 months
Limited Weight Loss	≥2% and <5%	50%	≥12 months
Short-Term Weight Loss	≥5%	50%	6 months to <12 months
Weight Loss	≥5%	50%	≥12 months

For the categories in Table 5, the duration of device use depends on the characteristics of device use. It may depend on the time period over which the device is used and/or the time period over which weight loss is measured, as follows:

[63] 2012 Materials of the Gastroenterology-Urology Devices Panel can be accessed at https://wayback.archive-it.org/7993/20170113191551/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm286235.htm.

- For an implantable device, the duration of device use is the total time that the device is inside the body. For example, for an intragastric balloon that is in the stomach for 6 months and then removed, the duration of device use would be 6 months.
- If the device is used transiently and results in changes to the anatomy and/or physiology that persist after use, the duration of device use is the terminal time point at which weight loss is measured. For example, for a device that is used temporarily but permanently reduces the size of the stomach, if the change in total body weight was assessed at 12 months post-device use, then the duration would be 12 months.
- For devices that are used on a recurring basis, the duration of device use is the course of time the device is used before measuring the results. For example, for a device that is used daily, if the change in total body weight is assessed after eight months of daily use, then the duration would be eight months.

In a hypothetical example, a device was temporarily placed in the stomach. A clinical investigation included two groups: a treatment group that had the device placed via an endoscopic procedure; and a sham group for the control arm, which underwent an endoscopic procedure, but no device was placed. After six months, devices were removed from the treatment group and the change in weight was measured for both groups, so the duration of this device use is six months. The results showed that at least half (50%) of the treatment group lost at least 5% of their starting body weight. The results also showed that the treatment group lost more of their starting body weight than the sham group did, with a superiority margin of 3% more weight lost. Thus, the device successfully met co-primary effectiveness endpoints of 50% responder rate and at least 2% TBWL over sham when measured at device removal 6 months post implant. Based on the recommendations in Table 5, this weight loss would be considered "short-term limited weight loss."

FDA intends to use the weight loss indication categories (Table 5), the Adverse Event classification (Table 2), and the Evaluation Matrices decision aid (Figure 1) to compare the weight loss demonstrated with the adverse event classification profile as part of the benefit-risk assessment of a weight loss device (Table 4).

1. There are four proposed Evaluation Matrices (numbered 1-4 in Figure 1). There is one Evaluation Matrix corresponding with each of the four weight loss indication categories described in Table 5. An Evaluation Matrix is selected for a device based on the amount of weight loss demonstrated in a clinical study and the duration of device use, consistent with Table 5.
2. Within each Evaluation Matrix, there are five columns for the five grades of adverse events described in Table 2. For each grade of adverse event, if there is a patient in the clinical study with that adverse event, then a lettered cell is intended to be selected based on the percentage of patients who experienced that grade of adverse event. The letter of the cells is for reference purposes only.
3. The shading of each cell indicates the possible consideration for the device based on the corresponding grade of adverse events (the column the cell is in). White indicates that the

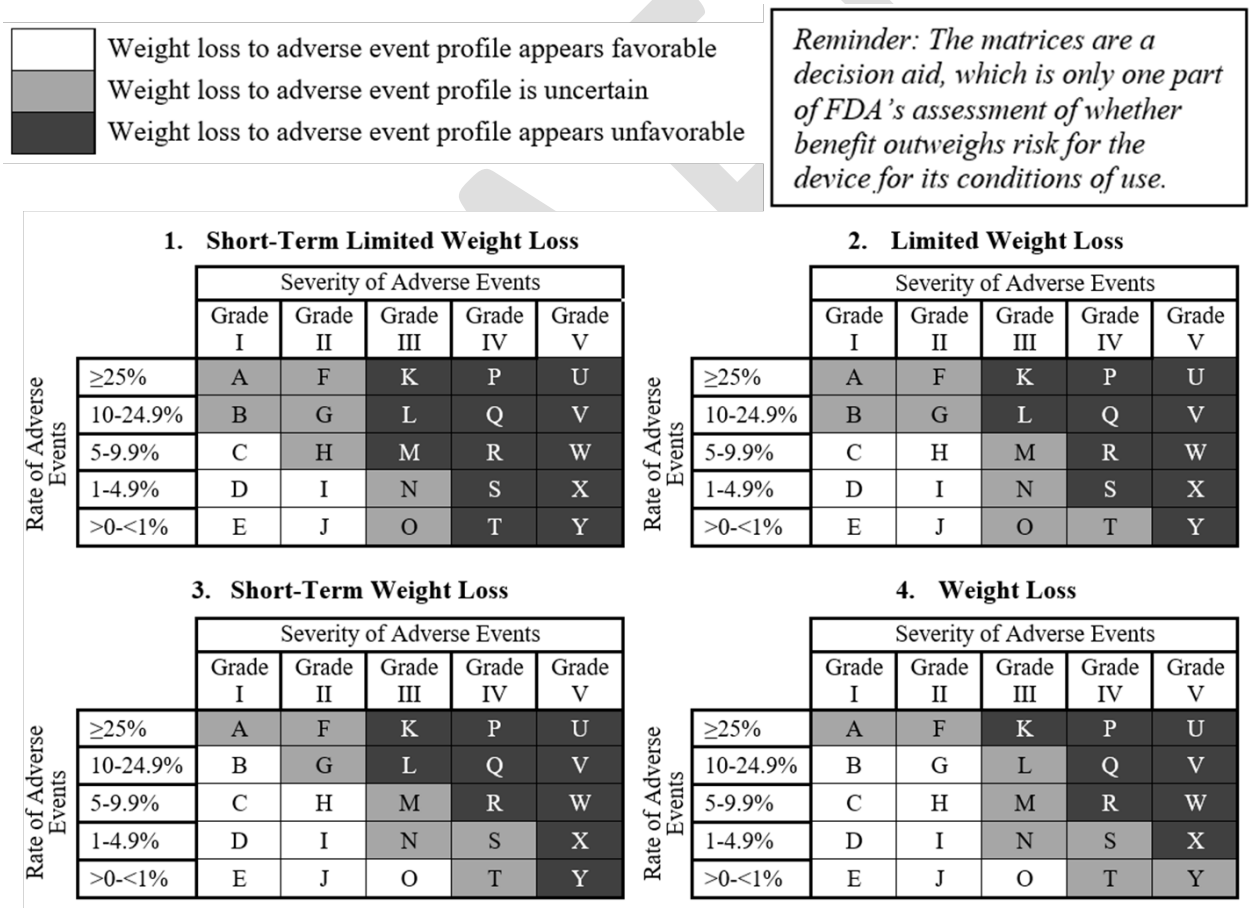
766 weight loss to adverse event profile appears favorable. Light gray shading indicates that
767 the weight loss to adverse event profile is uncertain. Dark gray shading indicates that the
768 weight loss to adverse event profile appears unfavorable.

769 4. The Evaluation Matrix for a specific device may include some combination of cells with
770 different shading. The overall risk of the device depends on the cell of greatest risk; thus,
771 the cell with the darkest shading suggests the outcome of the decision aid.

772 5. The outcome from the Evaluation Matrix is considered as part of the totality of the
773 benefit-risk determination (Table 4).

774 6. The matrices are provided as a decision aid, which is only one part of FDA's assessment
775 when evaluating whether probable benefit outweighs probable risk for the device for its
776 conditions of use.

777



778
779
780 **Figure 1.** Evaluation Matrices for comparing weight loss indication categories (Table 5) and
781 adverse events classification.[64]

[64] Lettering within the matrices is included for reference purposes only. For example, the cell corresponding to a Grade IV adverse event occurring at a rate of more than 25% of the time is lettered "P."

In a hypothetical example, suppose that in a clinical investigation, a device successfully met co-primary effectiveness endpoints of 50% responder rate and a superiority margin of 3% TBWL over sham control when measured at device removal six months post implant. Based on Table 5, the weight loss indication category would be "short-term limited weight loss," so the device would be evaluated via Evaluation Matrix 1 in Figure 1. In the assessment of the clinical study:

- 50% of patients had Grade I adverse events, which corresponds to the light gray cell A in Matrix 1 of Figure 1;
- 3% of patients had Grade II adverse events, which corresponds to the white cell I in Matrix 1 of Figure 1;
- 0% of patients had Grade III adverse events; and
- 1% of patients had Grade IV adverse events, which corresponds to the dark gray cell S in Matrix 1 of Figure 1.

Overall, the risk of the device is characterized by the prevalence of greatest risk observed in the study, i.e., the 1% Grade IV adverse event rate, where the dark gray cell indicates that the weight loss to adverse event profile may not be favorable for the given amount of weight loss as part of the overall benefit-risk assessment. The low rate of adverse events in Grade II (the white cell) and Grade I (the light gray cell) may not negate the risk associated with the rate of adverse events in Grade IV (the dark gray cell).

In another hypothetical example, suppose that in a clinical investigation, a device successfully met co-primary effectiveness endpoints of 50% responder rate and a superiority margin of 10% TBWL over sham control when measured at device removal 12 months post implant. Based on Table 5, the weight loss indication category would be "weight loss," so the device would be evaluated via Evaluation Matrix 4 in Figure 1. In the assessment of the clinical study:

- 70% of patients had Grade I adverse events, which corresponds to the light gray cell A in Matrix 4 of Figure 1;
- 10% of patients had Grade II adverse events, which corresponds to the white cell G in Matrix 4 of Figure 1;
- 0.5% of patients had Grade III adverse events, which corresponds to the white cell O in Matrix 4 of Figure 1; and
- 2% of patients had Grade IV adverse events, which corresponds to the light gray cell S in Matrix 4 of Figure 1.

Overall, the risk of the device is characterized by the prevalence of greatest risk observed in the study, i.e., the 2% Grade IV adverse event rate and 70% Grade I adverse event rate, where the light gray cells indicate that the weight loss to adverse event profile is uncertain given the amount of weight loss as part of the overall benefit-risk assessment. The low rate of adverse events in Grade II and Grade III (the white cells) may not negate the risk associated with the rate of adverse events in Grade I and Grade IV (the light gray cells).

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During the review of a marketing submission, FDA intends to consider information from the proposed Evaluation Matrices, along with all other applicable factors identified in Table 4, to make a final determination regarding whether the probable benefits of the device outweigh the probable risks of the device.

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