FDA Executive Summary

Prepared for the
Fall 2022 review by the
FDA's Pediatric Advisory Committee

H160002
PulseRider Aneurysm Neck Reconstruction Device

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this annual report provides a safety update based on the post-market experience with the use of the PulseRider Aneurysm Neck Reconstruction Device ("PulseRider device") in pediatric patients since approval in 2017, with a focus on data acquired since the prior report presented to the Pediatric Advisory Committee (PAC) in 2021. The Food and Drug Administration (FDA) and the Federal Food, Drug, and Cosmetic (FD&C) Act defines pediatric patients as persons aged 21 or younger at the time of their diagnosis or treatment, and the age range identified in the indications for use of the PulseRider device overlaps with this definition of the pediatric population. Evaluation of the post-market safety data review and assessment provided in the report allows the PAC to review information available to the FDA, and advise the Agency regarding any new safety concerns and whether they believe that the Humanitarian Device Exemption (HDE) remains appropriate for pediatric use.

II. DEVICE DESCRIPTION

The PulseRider device is a permanent self-expanding nitinol (nickel titanium) implant for the treatment of wide-necked intracranial aneurysms located at or near artery branch points of the basilar tip or carotid terminus in the brain. The device's Y or T shape allows the device to be implanted within the vessel while providing support for the placement of neurovascular embolic coils (flexible strands of thin coiled wire that assist clot formation within an intracranial aneurysm) and holding them in place inside the intracranial aneurysm sac (Figure 1). The PulseRider device is intended to treat wide-necked intracranial aneurysms with neck widths ≥ 4 mm or dome-to-neck ratio < 2 originating on or near a vessel bifurcation of the basilar tip or carotid terminus with at least a portion of the intracranial aneurysm neck overlapping the lumen of the parent artery. The inflow vessels should have diameters from 2.7 mm to 4.5 mm.

The PulseRider Aneurysm Neck Reconstruction Device is comprised of a torque device, delivery wire, introducer, implant, and detachment system (see Figures 2, 3 and 4). The PulseRider Detachment System is designed to detach the PulseRider implant from the delivery wire once the PulseRider implant is fully deployed at the desired location. The PulseRider Detachment System is comprised of the Detachment Controller and Connection Cable.

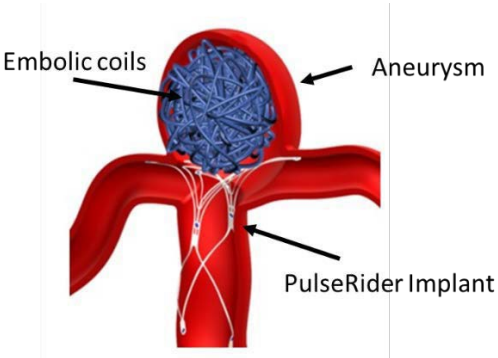


Figure 1: Treatment of an intracranial aneurysm at a vessel branch point using the PulseRider implant and neurovascular embolic coils.

Figure 2: PulseRider Device (not to scale)

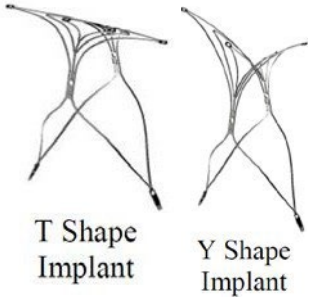


Figure 3: PulseRider Implants, T and Y Shapes

Figure 4: PulseRider Detachment System

The PulseRider device is contraindicated for:

1) Patients with vascular anatomy or dimensions at the targeted treatment site for which the available PulseRider device sizes are not appropriate (refer to package label for sizing information).
2) Patients with severe vascular tortuosity or anatomy that would preclude the safe introduction of the PulseRider device or the use of other devices involved with the procedure.
3) Patients with preoperative coagulation disorder, or with contraindications to antiplatelet or anticoagulant therapy.
4) Patients with known hypersensitivity to nickel.
5) Patients with active bacterial infection.

The PulseRider Detachment Controller is contraindicated for the magnetic resonance (MR) imaging environment and for exposure to known sources of electromagnetic interference such as computed tomography (CT), diathermy, radiofrequency identification (RFID), and electromagnetic security systems such as metal detectors.

III. REGULATORY HISTORY

The HUD designation (HUD #09-0223) was approved on March 11, 2010. HDE (H160002) was approved on June 19, 2017.

File	Content	Status
H160002/S001	30-Day Notice Process Change	OK30 (Approved)
H160002/S002	75-Day Supplement Location change	Approved (Approved)
H160002/S003	30-Day Notice Process Change	OK30 (Approved)
H160002/S004	75-Day Supplement Labeling Update	APGM (Approved)
H160002/S005	30-Day Notice Process Change	OK30(Approved)
H160002/S006	30-Day Notice Process Change	OK30 (Approved)
H160002/S007	30-Day Notice Process Change	OK30 (Approved)
H160002/S008	75-Day Supplement Add detachment accessory	APPR (Approved)
H160002/S009	30-Day Notice Process Change	OK30 (Approved)
H160002/S010	75-Day Supplement Location Change	APGM (Approved)
H160002/A	Post-approval Study (PAS) Report (6 month)	
H160002/B	PAS Report (12 month)	
H160002/C	Annual Report	
H160002/D	Annual Report	
H160002/E	Annual Report	
H160002/F	Annual Report	

IV. INDICATIONS FOR USE

PulseRider device is indicated for use with neurovascular embolic coils in patients ≥ 18 years of age for the treatment of unruptured wide-necked intracranial aneurysms with neck widths ≥ 4 mm or dome-to-neck ratio < 2 originating on or near a vessel bifurcation of the basilar tip or

carotid terminus with at least a portion of the aneurysm neck overlapping the lumen of the parent artery. The inflow vessels should have diameters from 2.7 mm to 4.5 mm.

The Detachment System, Detachment Controller, and Connection Cable are indicated for use to detach the PulseRider Aneurysm Neck Reconstruction Device permanent implant device from the delivery wire.

V. SUMMARY OF CLINICAL DATA USED TO SUPPORT HDE APPROVAL

A clinical study was performed to support the safety and probable benefit of the PulseRider device. The clinical study ["Adjunctive Neurovascular Support for Wide-Neck Aneurysm Embolization and Reconstruction (ANSWER)"] enrolled and treated 34 patients. The mean age was 60.9 years with a preponderance of women (85.3%) as is common in studies of intracranial aneurysms. The range of ages treated in the study was 26 to 86 years. The wide-necked intracranial aneurysms treated were located at the basilar artery bifurcation or the bifurcation of the carotid artery terminus. There were no reported neurological deaths or major ipsilateral/downstream strokes within 180 days of the procedure. The upper limit of a one-sided 95% confidence interval for neurological death or major ipsilateral/downstream stroke at 180-days post-procedure was 8.4% based on the observed rate of 0%. While not included in this primary safety outcome, there were 5 minor strokes or neurological deficits potentially due to strokes that occurred in 5 patients.

Immediately following the procedure with the PulseRider device, intracranial aneurysm occlusion assessed as Raymond-Roy I or II were obtained in the majority of cases (79.4% or n/N = 27/34). This result demonstrates that the majority of treated patients achieved 100% occlusion or stable, near complete, occlusion of their unruptured wide-necked intracranial aneurysm originating near or at a vessel bifurcation of the basilar tip or carotid terminus immediately post-procedure. This combined intracranial aneurysm occlusion rate of Raymond-Roy I or II assessed at 180-days post-procedure increased to 87.9% (n/N = 29/33 patients), which was adjudicated by a Core Lab. In addition, in 34/34 (100%) cases, the treating physicians viewed the procedure as a technical success if they were able to access the target intracranial aneurysm, deploy the device accurately, and detach the device successfully. Therefore, the PulseRider device demonstrated in the ANSWER clinical study that there is probable benefit in successfully stabilizing the intracranial aneurysm using endovascular embolization coiling assisted by the PulseRider device to achieve 100% or stable, near complete, intracranial aneurysm occlusion from cerebral blood flow.

The risks of the device are based on non-clinical laboratory and animal studies, as well as data collected in the ANSWER clinical study conducted to support HDE approval. The most common observed adverse event in the ANSWER clinical study was headache (29.4% (n/N = 10/34)) followed by respiratory problems (20.6% (n/N = 7/34)), stroke (14.7% (5/34)), nausea and/or vomiting (11.8% (n/N = 4/34)), hypotension (8.8% (n/N = 3/34)), shortness of breath (8.8% (n/N = 3/34)), and anemia or drop in hemoglobin (8.8% (n/N = 3/34)). The majority of these adverse events can be clinically managed shortly after symptom onset and will not result in long-term clinical sequelae. All of the 5 stroke patients recovered to a favorable clinical outcome of a modified Rankin Scale (mRS) score of 0-2 at 180-days post-procedure with minimal disabilities except for one patient who was wheelchair bound due to an ongoing mass effect of the intracranial aneurysm. There were no adverse events of neurological death caused by the device and/or procedure and no major debilitating strokes. For all 34 treated patients, the peri-

procedural complications rate was 8.8% with ongoing neurological events and a satisfactory outcome (mRS 0 – 2) was achieved in 94.1% of patients (n/N = 32/34) at the 180-day follow-up visit.

The youngest patient in the clinical study was 26 years old. The clinical study protocol was approved to treat patients as young as 18 years old. There are no differences between vascular anatomies (for sizing and placement of the device) between the 18-21-year-old group and older adults. Also, the incidence of intracranial aneurysms in this age group is much less than older adults (> 45 years old). Given the risk/benefit of this device in the population studied and the similarities between young adults and the 18-21 year old population with respect to target anatomies and intracranial aneurysm presentation and treatment, it was reasonable to include the transitional adolescent (18 to 21 years old but treated as an adult) population within the FDA-approved indications for use.

Limitations to the clinical study design were its single arm study design, which limits the ability to draw comparisons to alternative treatments, financial conflicts of interest as some of the investigators had a significant payment from Pulsar Vascular, Inc., the study was not statistically powered for hypothesis testing of the safety and probable benefit outcomes, and the mRS evaluations were not conducted by a blinded assessor at the 180-day follow-up visit.

Considering all of these limitations to the clinical study design and after a thorough review of all of the clinical data including the case report forms (CRFs), the results generally support that the risks of the PulseRider device are similar to marketed HDE neurovascular stents and the majority of patients in the study were able to achieve occlusion of their unruptured, wide-necked, intracranial aneurysm originating on or near a vessel bifurcation of the basilar tip and carotid terminus arteries as assessed by Raymond-Roy I and II scores. In addition, the PulseRider device is specifically designed to be implanted at a vessel bifurcation.

In conclusion, given the available information above, the data support that for patients ≥ 18 years of age, the PulseRider device used with neurovascular embolic coils for the treatment of unruptured wide-necked intracranial aneurysms with neck widths ≥ 4 mm or dome-to-neck ratio < 2 originating on or near a vessel bifurcation of the basilar tip or carotid terminus with at least a portion of the aneurysm neck overlapping the lumen of the parent artery and the inflow vessels should have diameters from 2.7 mm to 4.5 mm, the probable benefits outweigh the probable risks.

VI. ANNUAL DISTRIBUTION NUMBER (ADN) AND US DEVICE DISTRIBUTION DATA

Section 520(m)(6)(A)(ii) of the Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. The established ADN for this device is 8,000. The number of devices distributed in the US between May 2, 2021, and May 1, 2022, is 40. In addition, a total of 28 units of the PulseRider Detachment System, approved September 11, 2019, under H160002/S008, were distributed between May 2,

2021, and May 1, 2022.

VII. POST MARKET DATA: POST APPROVAL STUDY

The clinical study used to support the original HDE approval studied subjects out to six months (180 days). Longer term clinical data was necessary to confirm the benefit to risk profile of the device. Therefore, as a condition of approval, the following post-approval study (PAS) was requested to collect data on the original study cohort out to one-year post-operative.

Study Title: Adjunctive Neurovascular Support for Wide-Neck Aneurysm Embolization and Reconstruction (ANSWER)

Study Objective: The PAS is a continuation of the ANSWER study, collecting longer term data in the original patient cohort out to one-year post-operative. The primary objective of the study is to evaluate the safety and probable benefit of the PulseRider device when used in conjunction with neurovascular embolic coils in the treatment of wide-necked intracranial aneurysms originating at or near a vessel bifurcation of the basilar artery or carotid terminus.

Study Design: This study is a prospective, multi-center, single-arm, non-randomized study. It is continued follow-up of the pre-market cohort up to 365 days without any new enrollment.

Primary Outcome:

- Safety – Neurological death or major ipsilateral stroke or downstream stroke up to 365-days post-procedure. Major stroke is defined as a stroke, which is present after seven days and increases the National Institute of Health Stroke Scale (NIHSS) score of the patient by greater than or equal to 4 points.

Additional Evaluations:

- Incidence of new neurological deficits;
- Complication rate (neurological and non-neurological);
- Rate of occlusion at 365 days;
- Device movement or migration;
- Stenosis at implant site.

Study Population: The study population consists of both male and female subjects, aged 26 years and older who presented with a wide-necked ($\geq$ 4 mm or dome-to-neck ratio < 2) basilar or carotid terminus intracranial aneurysm located at a bifurcation. Subjects with acutely ruptured intracranial aneurysms were excluded from the study. The intracranial aneurysm parent vessel measurements were required to be between 2.7 mm and 4.5 mm to be suitable for the procedure. Patients were required to take dual antiplatelet therapy starting prior to the procedure.

Sample Size: Thirty-four (34) patients were enrolled in the pre-market cohort. These subjects are the PAS cohort. There were no adolescent subjects enrolled in the PAS.

The enrollment phase of the ANSWER study was completed in October 2015. The HDE for the PulseRider device was approved on June 19, 2017, based on 180-day post-operative data. The one-year follow-up was completed and results for the original 34 patients of the ANSWER study were summarized in an HDE annual report, the IDE final report, and the PAS final report.

In summary, no device migration or stenosis defined as greater than 50% at the implant site was reported at the 1-year follow-up visit. Clinical outcomes as measured by the mRS and the NIHSS were consistent with the reported 180-day outcomes. No unanticipated adverse device effects were reported out to 1 year. Therefore, it was concluded that the safety and risk profile of the PulseRider device approved under H160002 remain unchanged. Tabulated results from the PAS were incorporated into the device labeling and submitted for FDA approval under H160002/S004. This supplement was approved by FDA on March 25, 2020. The PAS is officially closed.

VIII. POST-MARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of the MDR Database

Each year, the FDA receives over 1.4 million medical device reports of suspected device-associated deaths, serious injuries, and malfunctions. The database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters, such as health care professionals, patients, and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type.
- Detect actual or potential device problems used in a clinical practice setting, including:
  - rare, serious, or unexpected adverse events;
  - adverse events that occur during long-term device use;
  - adverse events associated with vulnerable populations; or
  - use error.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important post-market surveillance data sources.

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.

- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the PulseRider Device

The FDA searched the MDR database to identify MDR reports associated with the PulseRider device entered into the MDR database between May 2, 2021, and May 1, 2022. The search identified 38 MDRs, all of which were submitted by the manufacturer and originated in Japan. None of the 38 MDRs were from published literature. The 38 MDRs included 14 malfunction reports and 24 injury reports. No patient deaths were reported. Eight of the 38 MDRs reported patient age and were associated with adult patients (age range 49-73 years old). There were no MDRs reported to be associated with pediatric patients (age 21 years or younger). Patient sex was reported as female in eight MDRs and male in five MDRs. The remaining 25 MDRs did not report patient sex.

All MDRs were individually reviewed to identify the most frequently reported patient and device problems. More than one patient or device problem, or no problems at all, may be reported within a single MDR. The reported patient problem codes included no clinical signs, symptoms or conditions (N =14 MDRs), ischemic stroke (N = 11 MDRs), hemorrhage/bleeding (N = 6 MDRs), thrombo-embolism/thrombosis (N = 6 MDRs), vessel perforation (N = 3 MDRs) and intracranial aneurysm recanalization (N = 1 MDR).

The reported device problems were primarily no identified device or use problem (N = 19 MDRs), and deployment and device placement related issues (N = 18 MDRs), such as separation failure, unstable positioning, and positioning failure. There were three MDRs associated with use of the device in tortuous anatomy.

MDR Conclusions

A total of 38 MDRs were associated with use of the PulseRider device, including 14 malfunction reports and 24 injury reports. No patient deaths were reported. There were no known MDRs associated with pediatric patients. The reported patient problems included no clinical signs, symptoms or conditions, ischemic stroke, hemorrhage/bleeding, thrombo-embolism/thrombosis, vessel perforation, and intracranial aneurysm recanalization. The most frequently reported device problems were deployment related. None of the 38 MDRs originated in the United States. The patient and device problems reported in the MDRs are either noted in the device labeling or are known risks associated with interventional treatment of intracranial aneurysms. Based on the information provided in the MDRs, no new patient or device problems, or reports associated with pediatric patients were identified.

IX. LITERATURE REVIEW

Methods

This systematic literature review update aimed to examine the current body of literature on the use of the PulseRider device in the adolescent population following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The publication date eligibility ranged from May 2021 to May 2022. This range was utilized to identify articles published since the previous PulseRider device literature review update using PubMed and EMBASE that was performed in 2021 by CDRH.

To ensure that all articles pertinent to the device of interest are captured, the initial general searches were based on the term "pulserider" for all search fields in two databases, PubMed and EMBASE.

In PubMed, the initial search resulted in a total of 37 articles; after limiting the publication date from May 2021 to May 2022, the PubMed findings were reduced to 9 articles.

In EMBASE, the initial search identified 2,422 records; after applying the EMBASE "Device Trade Name" filter for "PulseRider", a total of 42 records were identified including 7 articles published from May 2021 to May 2022. However, none of these records included pediatric or adolescent study subjects according to the "Age" filter. To confirm the absence of published PulseRider records on the population of interest, the initial EMBASE findings (N = 2,422) were first subjected to the "Age" filter which identified a total of 121 records referring to pediatric or adolescent subjects; however, none of these records included "PulseRider" as a "Device Trade Name."

Thus, PubMed and EMBASE searches yielded a total of 16 PulseRider related records (N = 9 and 7, respectively) published since the previous systematic literature review update in 2021 by CDRH.

Exclusion Criteria and Accountability of Publications

After identifying one record as a duplicate found in both EMBASE and PubMed searches, the remaining 15 records were subjected to a title and abstract screening followed by a full-text assessment as needed. The main inclusion criteria were presented by the PulseRider as a device of interest and the pediatric and adolescent study subjects as a population of interest. Main exclusion criteria were as follows: duplicates, non-English language, article types other than original clinical studies, the lack of the PulseRider device, and not the population of interest.

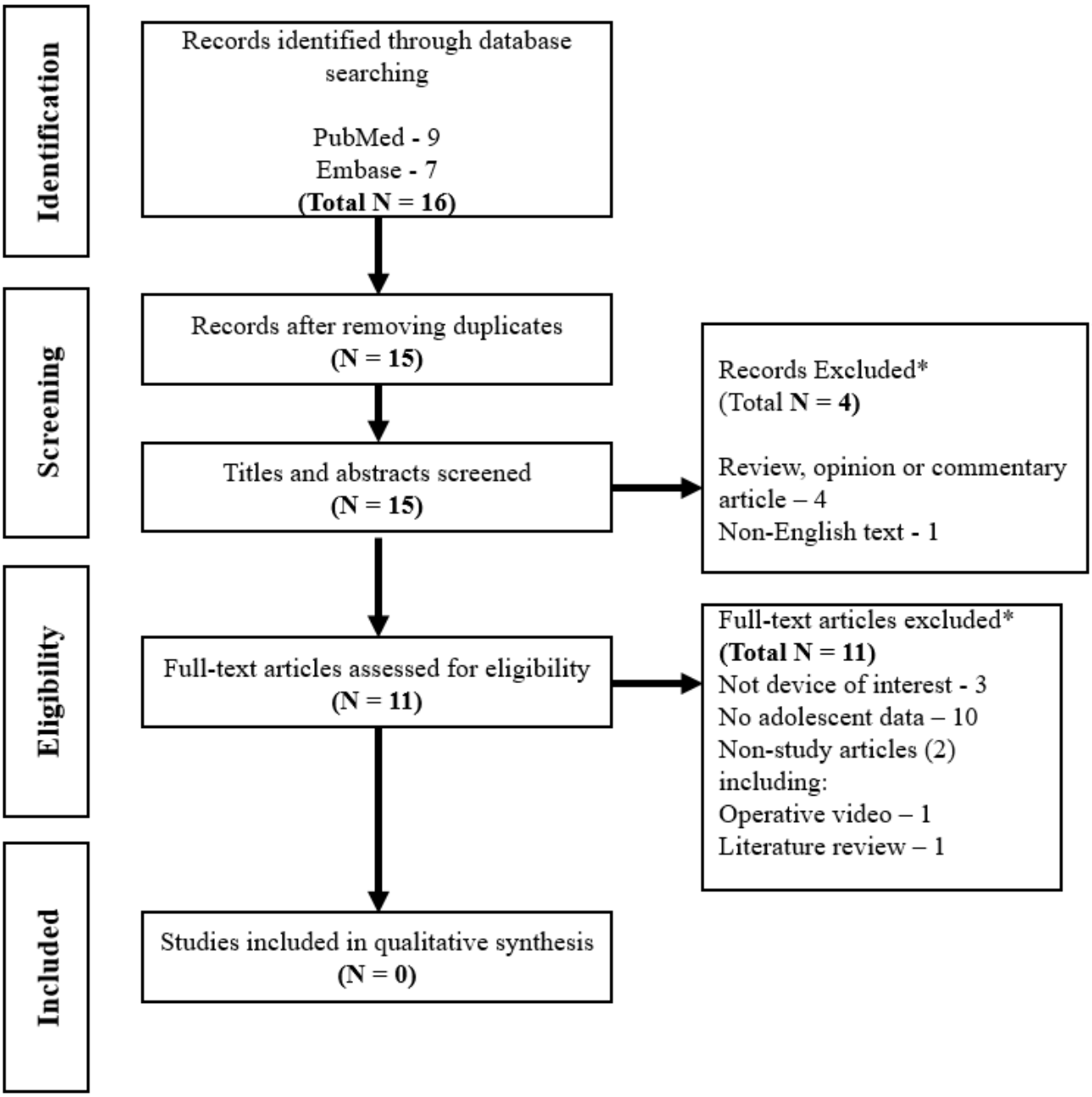
After the title and abstract screening of 15 unique records from both searches, a total of 4 publications were excluded due to non-original study article types such as reviews, expert opinions, and commentaries or non-English language. After the full-text review, the remaining eleven articles were excluded due to the following reasons: non-study article formats; case reports and case series with adult or elderly subjects; and clinical studies with adult or elderly subjects, and no mention of the device of interest used or device-related outcomes reported.

Figure 5 presents the article screening and review process. Note that the number of exclusion reasons exceeds the number of reviewed articles since some articles had more than one reason for exclusion. All identified case reports and case series were subjected to a full text review to ensure that no data regarding potential pediatric and adolescent subjects are missed. All articles are individually examined for inclusion or exclusion by the same reviewer; no potential issues regarding the selection criteria used were identified.

Literature Review Update Conclusions

Given the current systematic searches of the literature, we did not find any studies published between May 2021 and May 2022 that report results for the use of the PulseRider device in the pediatric and adolescent population. Therefore, conclusions regarding the benefit-risk profile of the use of the PulseRider device in the pediatric and adolescent population cannot be obtained from the published literature.

Figure 5. PRISMA-based Search and Selection in PulseRider
Systematic Literature Review Update 2022



* Note that the number of exclusion reasons exceeds the number of reviewed articles since some of the articles had more than one reason for exclusion.

X. SUMMARY

FDA recommends continued surveillance of the safety and probable benefit of the PulseRider device and will report the following to the PAC in 2023:

- Annual distribution number;
- Systematic literature review update; and
- MDR review update.