FDA Executive Summary

Prepared for the
Fall 2021 Meeting of 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 review 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. The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-market safety data so the committee can advise the Food and Drug Administration (FDA) on whether they have any new safety concerns and whether they believe that the 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.

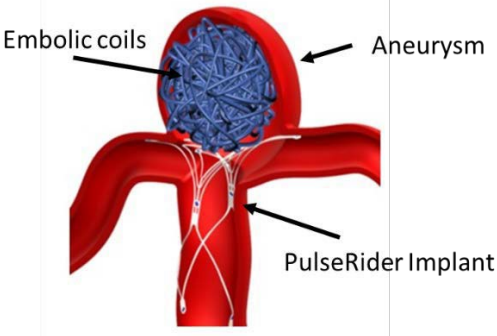


Figure 1: Treatment of an intracranial aneurysm at a vessel branch point using the PulseRider Implant and Embolic Coils.

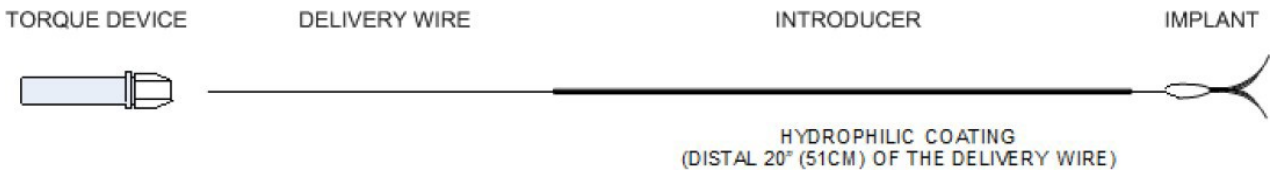


Figure 2: PulseRider Device (not to scale)

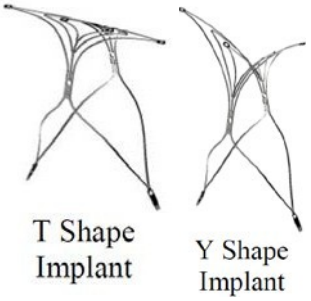


Figure 3: PulseRider Implants, T and Y Shapes

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	

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 CLINCAL 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 endpoint, 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 nonclinical 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 endpoints, 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) 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 8000. The number of devices distributed in the US between May 2, 2020, and May 1, 2021, is 75. In addition, a total of 35 units of the PulseRider Detachment System, approved September 11, 2019, under H160002/S008, were distributed between May 1, 2020, and May 2, 2021.

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 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 Endpoints:

- 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 (MDRs) 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 "real world" 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 Agency searched the MDR database to identify MDR reports associated with the PulseRider device entered into the MDR database between June 1, 2020, and May 31, 2021. The search identified 19 MDRs, all of which were submitted by the manufacturer. The 19 MDRs included five reports which were associated with published literature. These five literature-related MDRs were not included in the MDR analysis as published literature was reviewed in a separate section of this document. The 14 remaining MDRs were included in the analysis. The 14 MDRs included five malfunction reports and nine injury reports. No patient deaths were reported. One of the 14 MDRs originated from within the United States (a malfunction MDR), while the remaining 13 MDRs originated in Japan. Three of the 14 MDRs reported patient age and were associated with adult patients (age range 56-79 years old). There were no MDRs reported to be associated with pediatric patients (age less than 22 years old). Patient gender was reported as female in six MDRs and was not reported in the remaining eight MDRs.

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 impact or consequence to patient (N=6 MDRs), ischemic stroke (N=5 MDRs), hemorrhage/bleeding (N=5 MDRs), vessel perforation/dissection (N=4 MDRs) and thromboembolism (N=1 MDR).

The reported device problems were primarily deployment and device placement related, 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 14 MDRs were associated with use of the PulseRider device, including five malfunction reports and nine injury reports. No patient deaths were reported. There were no known MDRs associated with pediatric patients. The reported patient problems included no impact or consequence to patient, ischemic stroke, hemorrhage/bleeding, vessel perforation/dissection, and thromboembolism. The most frequently reported device problems were deployment related. Only one of the 14 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 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 years of publication eligibility ranged from January 1, 2020, to June 30, 2021. This range was utilized to identify articles published since the previous PulseRider device literature review that was performed in 2020 by CDRH. The following search was conducted in PubMed and Embase:

Embase search criteria: ('pulserider'/exp OR pulserider) AND ('pediatric'/exp OR pediatric OR newborn* OR infant* OR child* OR adolescent*) AND [2020-2021]/py. Search performed on June 11, 2021.

PubMed search criteria: PubMed (search performed on 6/11/2021, ('pulserider') and 2020/01/01:2021/06/30:[dp]). Search performed on June 11, 2021.

A more general search was used in PubMed, analogous to the search performed in 2020, to ensure that all pertinent articles were captured.

For Embase, this search identified 43 articles; and for PubMed, this search identified 9 articles.

Exclusion Criteria and Accountability of Publications

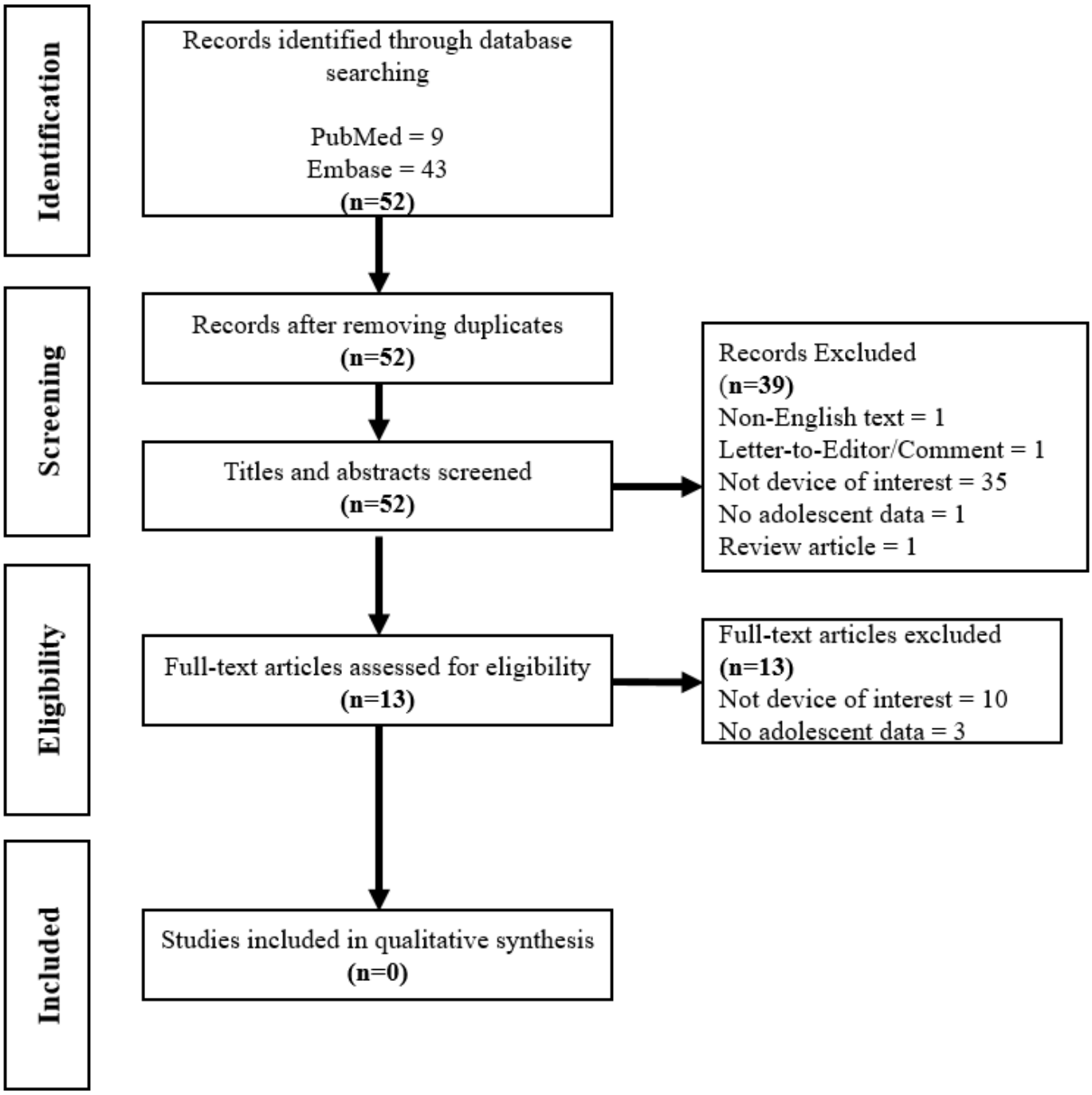
After conducting these searches, a review of titles and abstracts was performed followed by full-text assessment. The full exclusion criteria included the following: duplicates, conference abstracts/oral presentations, letters to the editor/commentaries/editorials, review articles, not the device of interest, no adolescent specific analysis, no humans in the study (e.g., animal study), not written in English, and unrelated topic. Review articles were individually examined to check for other potential articles for inclusion.

Figure 5 presents the article screening process. All 52 articles were excluded for the following reasons: review article (1), letter-to-editor/response (1), non-English text (1), not the device of interest (45), and no adolescent data (4).

Literature Review Conclusions

Given the current searches of the literature, including the MDRs reported in the literature, we did not find any studies published on the PulseRider device that report results for the use of this device in the adolescent population. Therefore, there are no new safety concerns relevant to the use of the PulseRider device in an adolescent population. Conclusions regarding the benefit-risk profile of the use of the PulseRider device in the adolescent population cannot be obtained from the published literature.

Figure 5. Search Strategy based on PRISMA for Relevant Articles



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 2022:

- Annual distribution number;
- Literature review; and
- MDR review.