

FDA Executive Summary

Prepared for the
September 20, 2018 meeting of the
FDA's Pediatric Advisory Committee

H160002

**PulseRider Aneurysm Neck Reconstruction
Device**

Table of Contents

I.	INTRODUCTION	3
II.	DEVICE DESCRIPTION	3
III.	REGULATORY HISTORY	4
IV.	INDICATIONS FOR USE.....	4
V.	SUMMARY OF CLINICAL DATA.....	5
VI.	ANNUAL DISTRIBUTION NUMBER (ADN) AND US DEVICE DISTRIBUTION DATA	6
VII.	POST MARKET DATA: POST APPROVAL STUDY	6
VIII.	POST-MARKET DATA: MEDICAL DEVICE REPORTS (MDRs).....	8
	Overview of the MDR Database	8
	MDRs Associated with the Pulsar Vascular PulseRider Aneurysm Neck Reconstruction Device .	9
	MDR Conclusions.....	9
IX.	LITERATURE REVIEW	10
	Screening	1
	Identification.....	1
	Eligibility.....	1
	Included	1
X.	SUMMARY.....	2

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) 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 is a permanent self-expanding nitinol (nickel titanium) implant for the treatment of wide-necked aneurysms located at or near artery branch points 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 aneurysm) and holding them in place inside the aneurysm (Figure 1). The coils remain inside the aneurysm and a clot will form around them, preventing blood from entering the aneurysm. The PulseRider 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 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, and implant (see Figures 1 and 2).

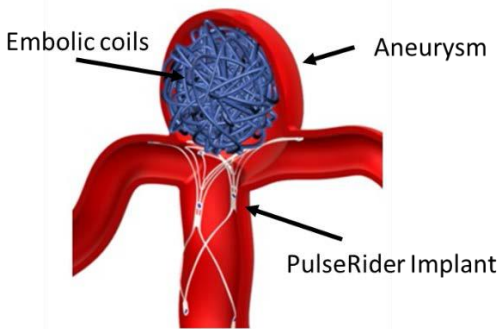


Figure 1: Treatment of an intracranial aneurysm at a vessel branch point using the PulseRider Implant and embolic coils.

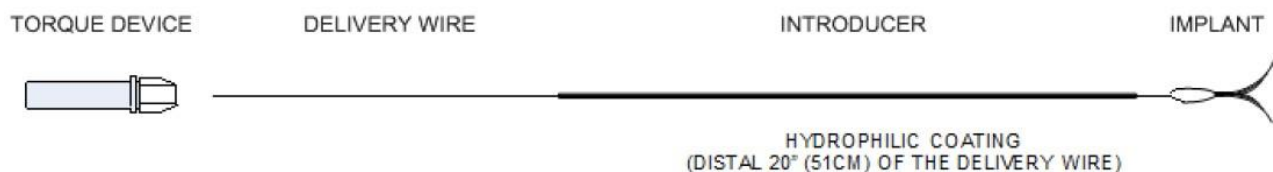


Figure 2: PulseRider Device (not to scale)

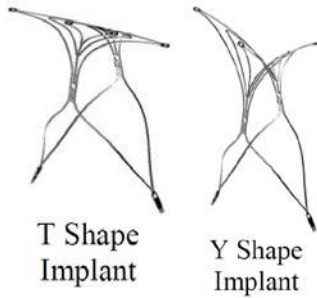


Figure 3: PulseRider Implants, T and Y shapes

The PulseRider is contraindicated in patients with:

- 1) vascular anatomy or dimensions at the targeted treatment site for which the available PulseRider® sizes are not appropriate (refer to package label for sizing information),.
- 2) 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) preoperative coagulation disorder, or with contraindications to antiplatelet or anticoagulant therapy.
- 4) known hypersensitivity to nickel..

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
H160002/S002	Location change	Approved
H160002/S003	30 day notice Process change	OK30
H160002/(b)	PAS report (6 month)	(b) (4)
H160002/(b)	PAS report (12 month)	
H160002/(b)	Annual report	

(4)

IV. INDICATIONS FOR USE

This 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.

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 (ANSWER study) 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 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 PulseRider 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, aneurysm occlusion assessed as Raymond 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 near complete occlusion of their unruptured wide-neck intracranial aneurysm originating near or at a vessel bifurcation of the basilar tip or carotid terminus immediately post-procedure. This combined aneurysm occlusion rate of Raymond I or II assessed at 180-days post-procedure increased to 87.9% ($n/N = 29/33$ patients), which was adjudicated by a blinded core laboratory. 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 aneurysm, deploy the device accurately, and detach the device successfully. Therefore, the PulseRider Aneurysm Neck Reconstruction 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 to retain the neurovascular embolization coils within the aneurysm sac to achieve 100% or near complete 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 Score (mRS) 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 aneurysm unrelated to stroke. 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, there is a low rate of peri-procedural complications (8.8% 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 is reasonable to include the Transitional Adolescent (18 to 21 year olds but treated as an adult).

Limitations to the clinical study design are 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 an unblinded 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 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 I and II scores. In addition, the PulseRider 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 Aneurysm Reconstruction 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 number of devices distributed in US between June 19, 2017 and May 1, 2018 is 174.

VII. POST MARKET DATA: POST APPROVAL STUDY

The clinical study used to support the original HDE approval studied subject out to six months (180 days). Longer term clinical data is 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.

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

Study Objective: The Post Approval Study is a continuation of the ANSWER study, collecting longer term data in the original patient cohort out to one year. The primary objective of the study is to evaluate the safety and probable benefit of the PulseRider when used in conjunction with embolic coils in the treatment of wide-neck 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 cohorts up to 365 days without any new enrollment.

Primary Endpoints:

- Safety – neurological death or major ipsilateral stroke or downstream stroke 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) of the patient by greater than or equal to 4.

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 years of age who presented with a wide neck (≥ 4 mm or dome to neck ratio <2) basilar or carotid terminus aneurysm located at a bifurcation. Subjects with acutely ruptured aneurysms were excluded from the study. The 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 antiplatelets therapy starting prior to the procedure.

Sample Size: 34 patients that were enrolled in pre-market cohort.

Results from the PAS are not yet available to be disclosed publicly and will be made available in the labeling once reviewed .

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

Overview of the MDR Database

Each year, the FDA receives over several hundred thousand 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
 - 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 Pulsar Vascular PulseRider Aneurysm Neck Reconstruction Device

The Agency searched the MDR database to identify reports associated with the PulseRider Aneurysm Neck Reconstruction Device entered between January 1, 2015 and May 30th, 2018. The search identified 39 MDRs (associated with 27 unique events), all of which were submitted by the manufacturer, Pulsar Vascular, or the manufacturer of a concomitantly used device, including 21 injury reports and 18 malfunction reports. No patient deaths were reported. Patient age was reported in 14 MDRs. The minimum age was 43 years old, the maximum age was 74 years old and the median patient age was 57 years old. There were no MDRs reported to be associated with pediatric patients (age less than 22 years old). Patient gender information was reported in 18 of the MDRs with 13 MDRs associated with female patients and 5 MDRs associated with male patients. The reporting country was available in all 39 MDRs and included the United States (N=32 MDRs), France (N=3 MDRs), the United Kingdom (N=3 MDRs), and Germany (N=1 MDR).

All MDRs were individually reviewed to identify the most frequently reported patient and device problems. Please note that more than one patient or device problem may be reported within a single MDR. The reported patient problems included stroke (N=7 MDRs, 6 unique events), hemorrhage (N=4 MDRs, 4 unique events), aneurysm rupture (N=4 MDRs, 4 unique events), headache (N=4 MDRs, 4 unique events), thrombosis/emboli (N=3 MDRs, 3 unique events), transient ischemic attack (N=1 MDR), and vasospasm (N=1 MDR). The Time to Event (TTE) for aneurysm rupture, thrombosis/emboli, transient ischemic attack, and vasospasm was 0 to 1 days with events occurring either during the procedure, or the day of the procedure. Stroke TTE ranged from 0 to 234 days with a median of 2.5 days. Hemorrhage TTE ranged from 0 to 4 days with a median of 0 days. Headache TTE ranged from 0 to 7 days with a median of 2 days. The reported device problems were primarily deployment and device placement related (N=25 MDRs, 15 unique events) and included issues such as device advancement/positioning difficulty (N=12 MDRs, 9 unique events), device not retaining coils within the treated aneurysm (N=7 MDRs, 3 unique events), and device detachment difficulty (N=2 MDRs, 2 unique events). There were eight MDRs (6 unique events) associated with use of the device in tortuous anatomy, which is warned against in the device labeling.

MDR Conclusions

A total of 39 MDRs, reporting 27 unique events, were associated with use of the PulseRider Aneurysm Neck Reconstruction Device. There were no known MDRs associated with pediatric patients and no patient deaths were reported. The most frequently reported patient problems included stroke, hemorrhage, aneurysm rupture and headache. The most frequently reported device problems were deployment related and included issues such as device advancement/positioning difficulty, the device not retaining coils within the treated aneurysm, and detachment difficulty. 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.

X. LITERATURE REVIEW

PulseRider Systematic Literature Review

Methods

This systematic literature review aimed to examine the current body of literature on the use of PulseRider in the pediatric population following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The following search was initially conducted in PubMed and Embase:

('pulserider'/exp OR pulserider) AND ('pediatric'/exp OR pediatric OR newborn* OR infant* OR child* OR adolescent*)

For Embase, this search identified 31 articles; and for PubMed, this search identified zero articles. Thus, a more general search using only “pulserider” in all fields was also conducted in both databases to ensure that all pertinent articles were captured (14 articles were found in PubMed and 26 additional articles were found in Embase).

Exclusion Criteria and Accountability of Publications

After conducting these searches, a review of titles and abstracts was performed followed by full-text assessment. All articles were reviewed independently by two reviewers and then discrepancies were discussed and resolved through group discussions. 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 pediatric 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.

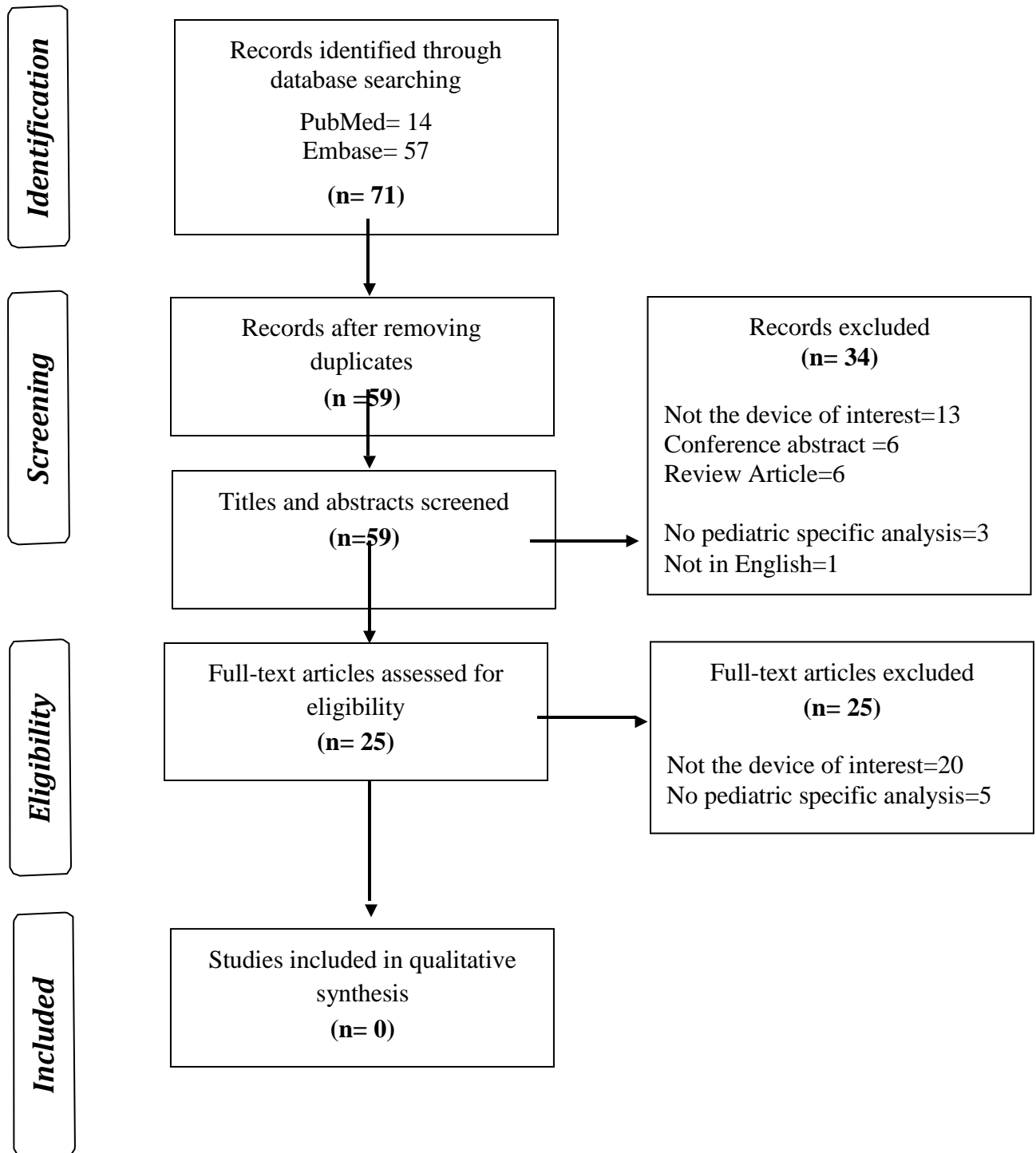
Overall from PubMed, 14 articles were identified and 57 were identified from Embase. After removal of duplicates (n=12), there were 59 articles identified for title and abstract review. Of these, 25 articles were included for full-text review and 34 were excluded for the following reasons: not the device of interest (n=13), conference abstract/oral presentation (n=6), review article (n=6), letter to the editor/editorial/commentary (n=5), no pediatric specific analysis (n=3), and not in English (n=1).

We conducted full-text review of the remaining 25 articles, all were found to be ineligible for quantitative synthesis because 20 were not on the device of interest and 5 did not have pediatric specific analysis.

Literature Review Conclusions

Given the current search of the literature, we did not find any studies published on PulseRider that report results for the use of this device in the pediatric population. Consequently, conclusions regarding the safety and probable benefit of PulseRider in the pediatric population cannot be drawn using the current published literature alone.

Figure 1. Search Strategy based on PRISMA for Relevant Articles



XI. SUMMARY

The data support the reasonable assurance of safety and probable benefit for this device when used in accordance with the indications for use. The clinical data of the combined aneurysm occlusion rate of Raymond I or II assessed at 180-days post-procedure was 87.9% (n/N = 29/33 patients), which was adjudicated by a blinded core laboratory. This result demonstrates that the PulseRider is able to successfully assist in retaining neurovascular embolization coils within the aneurysm sac for unruptured, wide-necked, intracranial aneurysms originating on or near a vessel bifurcation of the basilar tip or carotid terminus arteries to achieve 100% or near complete occlusion of the intracranial aneurysm to prevent cerebral blood flow from entering the aneurysm sac for a majority of patients in the clinical study. In addition, the observed adverse events and associated rates of adverse events were similar compared to marketed HDE neurovascular stents. After treatment with the PulseRider, the majority of patients had a favorable clinical outcome assessed using the mRS of 0-2 (i.e., 94.1% (n/N = 32/34 patients)) at the 180 day follow-up visit, which measures functional independence and disability.

Considering the 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 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 I and II scores. In addition, the PulseRider is specifically designed to be implanted at a vessel bifurcation.

FDA's Review Team has identified no new safety concerns compared to what was known/anticipated at the time of HDE approval in June 2017. Based on the available data, and taking into account the probable benefits and risks, FDA concludes that the HDE remains appropriately approved for patients 18 years or older. FDA will continue routine surveillance including MDR, literature reviews and oversight of the post approval study.

Therefore, FDA recommends:

- Continued surveillance and will report the following to the PAC in 2019:
 - Annual distribution number
 - PAS follow-up results
 - Updated MDR surveillance
 - Updated literature review