Title

Safety and efficacy results of the Flow Redirection Endoluminal Device (FRED) stent system in the treatment of intracranial aneurysms: US pivotal trial.

Journal

Journal of neurointerventional surgery, 14(6)

ISSN

1759-8478

Authors

McDougall, Cameron G
Diaz, Orlando
Boulos, Alan
et al.

Publication Date

2022-06-01

DOI

10.1136/neurintsurg-2021-017469

Peer reviewed

OPEN ACCESS

Original research

Safety and efficacy results of the Flow Redirection Endoluminal Device (FRED) stent system in the treatment of intracranial aneurysms: US pivotal trial

Cameron G McDougall ,[1] Orlando Diaz,[2] Alan Boulos,[3] Adnan H Siddiqui ,[4,5] Justin Caplan,[1] Johanna T Fifi,[6] Aquilla S Turk,[7] Yasha Kayan ,[8] Pascal Jabbour ,[9] Louis J Kim,[10] Steven W Hetts,[11] Daniel L Cooke,[11] Christopher F Dowd[11]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/neurintsurg-2021-017469).

For numbered affiliations see end of article.

Correspondence to
Dr Cameron G McDougall, Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MD 21287, USA; cgm@jhmi.edu

Received 26 February 2021
Accepted 25 June 2021
Published Online First 19 July 2021

ABSTRACT

Objective To evaluate the safety and effectiveness of the Flow Redirection Endoluminal Device (FRED) flow diverter in support of an application for Food and Drug Administration approval in the USA.

Methods 145 patients were enrolled in a prospective, single-arm multicenter trial. Patients with aneurysms of unfavorable morphology for traditional endovascular therapies (large, wide-necked, fusiform, etc) were included. The trial was designed to demonstrate non-inferiority in both safety and effectiveness, comparing trial results with performance goals (PGs) established from peer-reviewed published literature. The primary safety endpoint was death or major stroke (National Institutes of Health Stroke Scale score ≥4 points) within 30 days of the procedure, or any major ipsilateral stroke or neurological death within the first year. The primary effectiveness endpoint was complete occlusion of the target aneurysm with ≤50% stenosis of the parent artery at 12 months after treatment, and in which an alternative treatment of the target intracranial aneurysm had not been performed.

Results 145 patients underwent attempted placement of a FRED device, and one or more devices were placed in all 145 patients. 135/145 (93%) had a single device placed. Core laboratory adjudication deemed 106 (73.1%) of the aneurysms large or giant. A safety endpoint was experienced by 9/145 (6.2%) patients, successfully achieving the safety PG of <15%. The effectiveness PG of >46% aneurysm occlusion was also achieved, with the effectiveness endpoint being met in 80/139 (57.6%)

Conclusion As compared with historically derived performance benchmarks, the FRED flow diverter is both safe and effective for the treatment of appropriately selected intracranial aneurysms.

Clinical registration number NCT01801007

To cite: McDougall CG, Diaz O, Boulos A, *et al*. *J NeuroIntervent Surg* 2022;**14**:577–584.

INTRODUCTION

Flow diverters have had a major impact on the treatment of intracranial aneurysms. Multiple flow diverters are approved outside the United States, but until recently only two such devices have been approved for use within the United States. The Flow Redirection Endoluminal Device (FRED) system received regulatory approval for use in Europe in 2013 and detailed descriptions of the device have been previously published.[1–3] The flow-diverting portion of the system is a self-expanding nitinol stent comprising two integrated layers, with the inner layer being composed of a low porosity, 36 or 48 nitinol wire braid.

This paper reports the results of the US pivotal trial of the FRED Stent System in the Treatment of Intracranial Aneurysms, a multicenter, prospective, single arm, investigational device exemption clinical study conducted to evaluate the safety and efficacy of the FRED system. Based on the results of this trial the US Food and Drug Administration (FDA) recently granted premarket approval of the FRED system.

METHODS

Study design

The US pivotal trial of the FRED Stent System in the Treatment of Intracranial Aneurysms was a prospective, multicenter, single-arm study initiated in 25 US centers and one additional Japanese site. One hundred and forty-five patients were treated at 23 centers with enrollment taking place between July 2013 and December 2016. The last subject visit was in January 2018. The study protocol was approved by each center's institutional review board, and all patients submitted written informed consent prior to enrollment. The study was conducted under good clinical practices and included independent adjudication of all adverse events. An independent core laboratory evaluated all angiographic data and adjudicated effectiveness outcomes. An independent Clinical Events Committee (CEC) adjudicated all endpoints. An independent Data Safety Monitoring Board conducted study safety reviews. Funding for this study was provided by Microvention Inc.

A detailed set of inclusion and exclusion criteria are included in the online supplementary materials (online supplemental appendix 1). Key inclusion criteria stipulated that the target aneurysm arise proximal to the anterior communicating segment, the middle cerebral artery M1/M2 junction, or the basilar artery bifurcation, that the parent artery be 2.0–5.0 mm in diameter, and that the aneurysm be wide necked or otherwise unfavorable in morphology as defined in online supplemental appendix 1. For the purposes of enrollment, the location of the aneurysm was determined by the

enrolling investigator, but ultimately adjudicated by the core laboratory. Discrepancies—for example, an aneurysm enrolled as an A1 segment aneurysm but later adjudicated as an anterior communicating artery aneurysm, were not considered to be major protocol violations. Exclusion criteria included recent (<60 days) subarachnoid hemorrhage, proximal arterial stenosis >50%, dolichoectatic aneurysms, bifurcation aneurysms, and prior stenting of the target aneurysm.

The study was designed to demonstrate non-inferiority in safety and effectiveness results as compared with performance goals (PGs) identified from a comprehensive analysis of the peer-reviewed published literature. The PGs were based on the results of prior studies reporting the safety and effectiveness of endovascular treatment of intracranial aneurysms with flow-diverter devices for patient populations that are directly comparable to this study's subject population (online supplemental appendix 2).

The safety and efficacy goals were a priori determined and prespecified at <15% and >46%, respectively.

Patients were evaluated clinically, including National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score preprocedure, and then re-evaluated after treatment at the time of discharge, and subsequently at follow-up around 30 days, 180 days, and 1 year. Ophthalmic evaluations were done at baseline and as needed subsequently for any patients with new visual symptoms. Mandatory 6-month and 1-year follow-up digital subtraction angiographic studies were core laboratory adjudicated.

Device characteristics

FRED stents are available in diameters 2.5 to 5.5 mm, with the 2.5 and 3.0 mm devices being deliverable through a Headway 21, 0.021" internal diameter microcatheter, and the larger sizes requiring a Headway 27, 0.027" internal diameter microcatheter. The flow diverting or 'working length' of the devices available are from 7 to 39 mm.

Procedures

All treated patients underwent a standard neuroendovascular procedure with the intention of delivering and implanting a FRED device across the aneurysm neck. Patients were treated with both aspirin and clopidogrel prior to the procedure with either a loading dose the day before or daily doses for 7 days before. All patients were treated with two antiplatelet agents for a minimum of 6 months after the procedure and then were maintained on monotherapy (American Stroke Association recommended) for the remainder of the study period (if no contraindication). Testing of antiplatelet medication effectiveness was not required.

Safety assessment

The primary safety endpoint of the study was the proportion of subjects who experienced death or major stroke (≥4 more points on the NIHSS) within 30 days of the procedure, or had any major ipsilateral stroke or neurological death within 12 months of the procedure. All adverse events reported by the investigational sites were adjudicated by an independent blinded CEC. In addition, a blinded independent Data Safety Monitoring Board provided oversight. Study site visits by clinical monitors were conducted, as needed, to achieve 100% verification of source data. Patient evaluations including, mRS and NIHSS scores, were conducted at baseline and hospital discharge and then within defined follow-up windows at the 30-, 90-, 180-day, and 12-month time points. Screening for adverse events occurred at each time point from the procedure forward.

Effectiveness assessment

The study primary effectiveness endpoint was the proportion of subjects with complete occlusion of the target aneurysm and ≤50% stenosis of the parent artery at the target intracranial aneurysm at 12 months after treatment as assessed by angiography, and without re-treatment of the target intracranial aneurysm within 1 year post-FRED placement. Any re-treatment was considered an endpoint failure for effectiveness. An independent core laboratory adjudicated the angiographic occlusion of the aneurysms using the Raymond scale,[4] reviewing images that were obtained immediately after the procedure, at 180 days and at 12 months. Parent artery stenosis was assessed by the core laboratory, with significant stenosis being defined as greater than 50% luminal loss using the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) method.[5] Multiple additional secondary safety and efficacy endpoints were also studied as noted in the results section.

Statistical methods

The study was designed to compare primary effectiveness success with an independently derived performance goal (a summary of the derivation and literature supporting the performance goals used as developed by Microvention and agreed to by the FDA is provided in online supplemental appendix 2). The trial is considered successful if the two-sided 95% credible interval, lower bound of the effectiveness rate exceeds the 46% PG and the two-sided 95% credible interval upper bound of the safety rate is below the 15% PG. The use of two-sided testing is consistent with the Pipeline premarket approval and FDA guidance.

Three patient populations were used for statistical analysis. The intention-to-treat (ITT) population, which consisted of all patients for whom the FRED system had been introduced into the bloodstream, was used for all effectiveness analyses to test the effectiveness hypothesis for the performance goal. The safety population consisted of all subjects in whom the investigational device was implanted as well as deaths due to technical failure during the index procedure, and was used to test the safety hypothesis of the performance goal. The third population was the per protocol population, consisting of all subjects in the ITT population for whom there were no major protocol deviations.

Study analyses for primary effectiveness and safety endpoints were conducted using Bayesian methods, consistent with other medical device submissions to the FDA's Center for Devices and Radiological Health to allow the computation of equitail 95% credible limits for assessment of the statistical hypotheses. This decision was made in advance of any data assessments for either effectiveness or safety. Other outcomes, including secondary endpoints for which formal hypothesis testing was not prespecified, are presented descriptively.

RESULTS

One hundred and sixty-seven patients consented to take part in the study, of whom 145 underwent attempted treatment with a FRED system. All these 145 patients had a FRED device implanted, and thus the same 145 patients comprised both the ITT and safety analysis populations. Subject and aneurysm characteristics are summarized in table 1 and subject accountability is presented in figure 1.

Table 1 Subject and aneurysm baseline characteristics

Characteristics	Mean±SD or N (%) (n=145)	(Median) (min, max)	
Age (years)	59.1±11.5	(60.1) (23.9, 82.9)	
Female	129 (89%)		
Race			
White	104 (71.7%)		
Black	24 (16.6%)		
Asian	7 (4.8%)		
Native American	1 (0.7%)		
Other	9 (6.2%)		
Prior Stroke	5 (3.4%)		
Hypertension	90 (62.1%)		
Hyperlipidemia	64 (44.1%)		
Diabetes mellitus	14 (9.7%)		
Multiple aneurysms	36 (24.8%)		
Family history of aneurysm	34 (23.4%)		
Tobacco use	48 (33.1%)		
mRS score			
0	103 (71.0%)		
1	31 (21.4%)		
2	9 (6.2%)		
3	2 (1.4%)		
Aneurysm location	Total	Fusiform	Saccular
Cavernous carotid	41 (28.3%)	10	31
Ophthalmic	50 (34.5%)	2	48
Supraclinoid carotid	10 (6.9%)	2	8
Superior hypophyseal	14 (9.7%)	1	13
PComA segment	20 (13.8%)	20	0
Anterior cerebral	2 (1.4%)	1	1
Anterior communicating	2 (1.4%)	0	2
Vertebral	2 (1.4%)	1	1
PICA	2 (1.4%)	1	1
Basilar	2 (1.4%)	0	2
Previously ruptured	8 (5.5%)		
Prior treatment			
Clipped	2 (1.4%)		
Coiled	23 (15.9%)		
Aneurysm dome height	11.5±4.7	(10.2)(3.7, 29.0)	
No >10 mm	106 (73.1%)		

mRS, modified Rankin Scale; PComA, posterior communicating artery; PICA, posterior inferior cerebellar artery.

The majority of subjects (135/145, 93.1%) had a single device deployed at the index aneurysm, while nine subjects (6.2%) had two devices deployed, and one subject (0.7%) had three FRED devices deployed. Of the total 155 devices implanted to deal with the target aneurysm in 145 patients, three were placed during reintervention procedures. These reinterventions were considered as treatment failures for the purposes of the study. Aneurysm sizes were reported by the sites: 102 aneurysms were large (>10 mm) and four were giant (≥25 mm), yielding a total of 73.1% large or giant aneurysms (table 1). Twenty-five aneurysms had undergone prior treatment with clips or coils, and eight of these had a history of rupture 76–2396 days prior to FRED treatment.

Protocol deviations

There were 10 major protocol deviations resulting in a per protocol population that consisted of 135 patients. Major deviations were adjudicated by the CEC and included five patients who missed a follow-up visit, two patients who did not have the required imaging performed, and one each of assessment not completed per protocol, stent used in addition to the FRED system, and enrollment of a patient with atrial fibrillation, which was an exclusion criterion.

Safety

After 1-year of follow-up (within 425 days), 9/145 (6.2%) patients met the composite primary safety endpoint of major stroke/death within 30 days or major ipsilateral stroke/neurological death after 30 days. The performance goal of <15% was therefore met. These nine events resulted in death or disabling stroke in four patients. Six had a major stroke within 30 days of treatment (four of these strokes occurred between 3 and 24 hours after the procedure, and the remaining two on postprocedure days 18 and 27). Two had a major ipsilateral stroke after 30 days and one patient fell at day 235 post treatment, sustaining an ipsilateral subdural hematoma (adjudicated as an ipsilateral stroke), which resulted in death. Enrollment of this patient was a protocol violation because of the pre-existing condition of atrial fibrillation, and at the time of the fall, the patient was taking warfarin in addition to aspirin and clopidogrel. The components of the primary safety endpoint and summary of events resulting in disabling stroke or death are given in table 2.

At last follow-up, among the nine patients who had met the safety endpoint, five had recovered to mRS score ≤2, leaving four patients who were dead or disabled defined as mRS score >2. The mean of the posterior distribution of the primary safety endpoint at 12 months after treatment is 6.8% with an equitailed 95% CI of 3.3% to 11.3%, meaning the safety endpoint performance goal of less than 15% was successfully met. The posterior probability of the alternative hypothesis is 0.999 therefore exceeding the predefined one-sided threshold of 0.975 (0.95 equitailed). Disabling strokes (including the patient that experience the subdural hematoma resulting in the sole neurological death in the series) occurred in 4/145 (2.8%) patients. In all, 11 patients had a deterioration in their mRS score as of their last follow-up, with two of these patients deteriorating for reasons unrelated to their aneurysm.

Safety outcomes were analyzed by prespecified subgroups, including study site, gender, ruptured versus unruptured, aneurysm size, aneurysm site, age, and comorbidities. With respect to the safety outcome across sites, no difference was seen between the pooled high volume (>4) versus low volume (<5) enrollers. Similarly, there was no difference in the safety endpoint events for anterior versus posterior circulation aneurysms, but a higher rate of major stroke was seen in the posterior communicating artery segment of the internal carotid artery—that is, 5/6 of the major strokes that occurred within 30 days of treatment ($p<0.001$) and 5/9 of the primary safety outcome endpoints overall ($p<0.005$) occurred in patients with the target aneurysm at this location. These adverse events were multifactorial in origin and no features specific to this location appeared to explain the higher rate of safety events at this site.

No significant differences in the rate of primary safety endpoint (or safety subcomponent) events were noted in relation

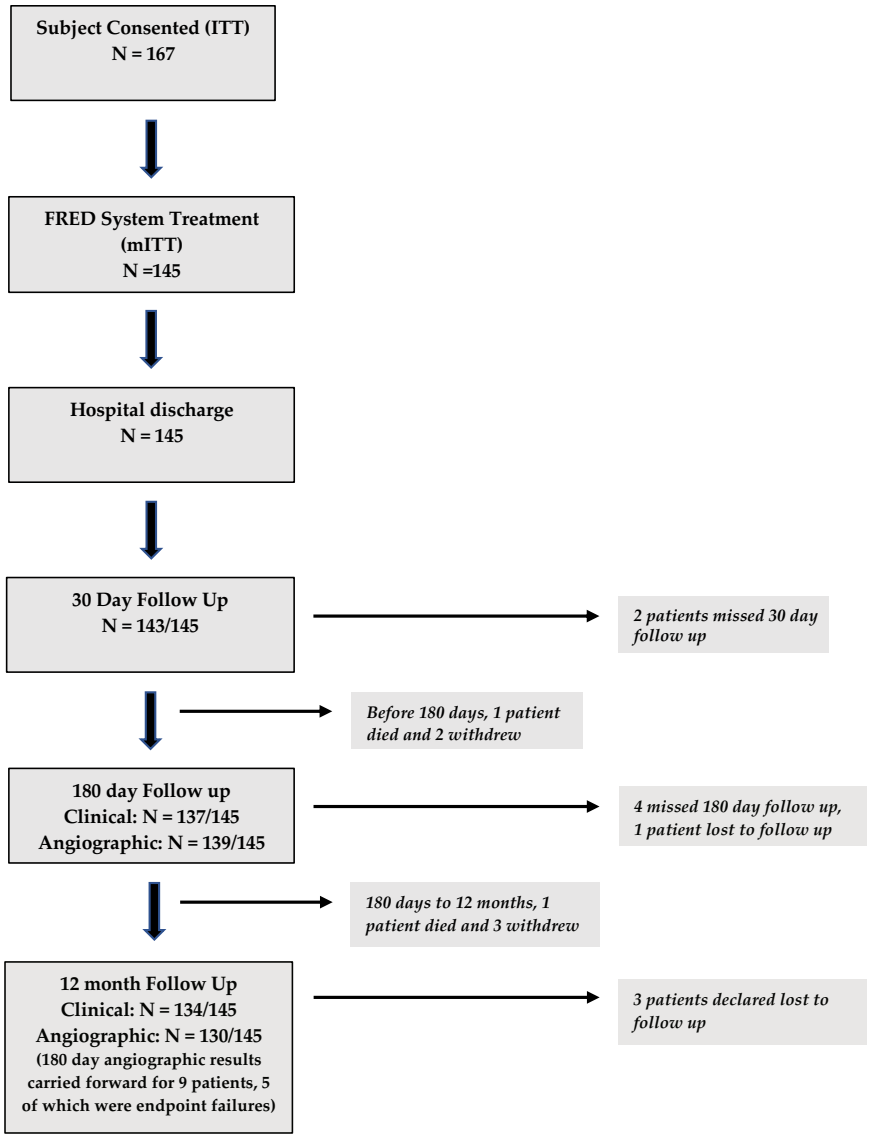

Figure 1 Patient accountability. FRED, Flow Redirection Endoluminal Device; ITT, intention-to-treat; mITT, modified intention-to-treat.

to patient age or gender, nor in relation to aneurysm size or rupture status. There were no unexpected adverse device effects during this trial.

As detailed above, a total of nine primary safety endpoint events occurred, resulting in death or permanent disability in four patients. An additional nine neurological events were adjudicated as minor strokes, for a total of 18 strokes occurring in 15 patients. The severity, timing, baseline mRS score, and mRS score at last follow-up of the patients with a stroke are shown in table 3.

As listed in table 2, four subjects experienced hemorrhagic events. Three of the events were adjudicated as primary safety endpoints, one of these, as described above, the result of a subdural hematoma secondary to a fall 235 days after treatment. The fourth event, 12 months after treatment of a small cavernous segment aneurysm, was a small sylvian fissure subarachnoid hemorrhage. This was adjudicated as a minor stroke but resulted in no new neurological deficit. The remaining two hemorrhagic events were adjudicated as primary safety endpoints secondary to delayed target aneurysmal hemorrhage. One of the delayed hemorrhages resulted from a previously unruptured 17 mm right carotid supraclinoid sidewall aneurysm. A second FRED was placed, and complete aneurysm occlusion was achieved. Twelve-month NIHSS and mRS scores were unchanged from their baseline values of 1 and 0, respectively. The final hemorrhagic event resulted from a previously unruptured 16 mm left posterior communicating segment aneurysm with a subarachnoid hemorrhage 18 days after treatment. A second FRED device was placed as was a ventricular drain. At the 12-month follow-up the aneurysm was completely occluded and mRS and NIHSS scores were 0. Although both of these patients achieved excellent outcomes, their treatment is reported as a failure with respect to both safety and efficacy. In total 9/145 (6.2%) patients experienced a device-related serious adverse event as adjudicated by the CEC (six strokes, one aneurysm rupture, two transient ischemic attacks).

Device thrombosis

There were 12 (8.3%) reports of 'device thrombosis'. Eight of these thrombosis events occurred on the day of the index procedure, and all eight were successfully treated with various

Table 2 Primary safety endpoint events through 12 months and primary safety analysis of neurological death and disabling stroke (CEC-adjudicated safety population)

Analysis using prespecified primary safety endpoint definition	n=145 n (%)	Posterior Mean (95% CI)	Posterior probability*
Primary safety†	9 (6.2%)	6.8% (3.3% to 11.3%)	0.999
Primary safety components:			
Major stroke within 30 days	6 (4.1%)	4.8% (1.9% to 8.7%)	
Death within 30 days	0	0.7% (0.0% to 2.5%)	
Major ipsilateral stroke 31–425 days	3 (2.1%)	2.7% (0.7% to 5.8%)	
Neurological death 31–425 days‡	1 (0.7%)	1.4% (0.2% to 3.7%)	
Additional primary safety analysis using composite rate of neurological death and any disabling stroke (mRS score ≥3)			
Primary safety	4 (2.8%)		
Primary safety components:			
Major stroke within 30 days	2 (1.4%)		
Death within 30 days	0		
Major ipsilateral stroke 31–425 days	2 (1.4%)		
Neurological death 31–425 days‡	1 (0.7%)		

*Posterior probability that the primary safety endpoint event rate is <15%.
†Primary safety endpoint defined as rate of death or major stroke within 30 days or neurologic death or major ipsilateral stroke within 12 months.
‡One subject fell and had a major ipsilateral stroke (subdural hematoma) at day 235 postoperatively with subsequent neurological death 1 day later and is listed under both stroke and death 31–425 days for this event.
CEC, Clinical Events Committee; mRS, modified Rankin Scale.

combinations of IIb/IIIa inhibitors and mechanical means. The remaining four events were identified on post-treatment days 1, 3, 5 and 345. Three of these four delayed events were thought to be due to technical problems, including carotid dissection and kinking of the device, and the fourth, noted on day 345, was seen in the setting of multiple territory thrombo-embolic infarcts. Two of these four patients with delayed events had complete occlusion of the parent artery at follow-up (both included as 'stenosis' below) and an additional patient did not undergo follow-up angiography. These 12 events resulted in two subjects experiencing major strokes, three subjects minor strokes, and two subjects with transient ischemic attacks.

Table 3 Listing of all patients with strokes (ischemic and hemorrhagic): CEC-adjudicated, Safety population and outcome by mRS score at last follow-up

Patient	Postoperative day	SAE	mRS at baseline	mRS at last assessment
Deaths (major and minor stroke)				
1	235	SDH (major)	1	6
1	Index	Stroke (minor)		
Major and minor strokes				
2	1	Stroke (major)	0	4
2	311	Visual impairment (minor)	–	
3	27	Stroke (major)	2	6
3	25	Stroke (minor)	–	
Major strokes				
4	345	Stroke (major)	0	3
5	76	Aneurysm rupture (major)	0	0
6	Index	Stroke (major)	0	1
7	1	Stroke (major)	0	0
8	18	Aneurysm rupture (major)	0	0
9	Index	Stroke (major)	1	1
Minor strokes				
10	Index	Stroke (minor)	1	1
11	Index	Stroke (minor)	0	1
12	298	Stroke (minor)	0	0
13	5	Stroke (minor)	0	2
14	1	Stroke (minor)	0	0
15	356	SAH (minor)	0	0

CEC, Clinical Events Committee; mRS, modified Rankin Scale; SAE, serious adverse event; SAH, subarachnoid hemorrhage; SDH, subdural hematoma.

Stenosis

Stenosis of ≥50% at the 12-month follow-up was observed in six patients. Two of the six patients with stenosis were symptomatic, and three of the six had complete parent artery occlusions. The symptomatic patient with complete occlusion was the one described above, who presented at day 345 with multiple territory thromboembolic strokes. The second patient with symptomatic stenosis had embolic strokes on the day of treatment but recovered to NIHSS and mRS scores of 0 by day 30, although kinking and severe stenosis of the device was noted at angiographic follow-up. The four remaining patients were asymptomatic, although two of these patients had complete parent artery occlusions thought to be due to carotid artery dissections.

Effectiveness

Of the 145 patients comprising the ITT population, 139 had follow-up angiograms interpretable by the core laboratory. In nine of these 139 patients angiograms from earlier than 1 year were carried forward as 1-year angiograms were not available. Five of these nine patients were adjudicated as endpoint failures. Eighty of 139 (57.6%) patients met the criteria for primary effectiveness—that is, complete aneurysm occlusion without stenosis >50% and no re-treatment (table 4).

To account for the six patients without follow-up imaging, a tipping point analysis was done. Assuming a worst-case scenario with none of the six missing patients meeting the effectiveness criteria, the primary effectiveness would be reduced to 80/145 yielding a posterior mean (95% CI) of 55.1% (47.0% to 63.0%). This worst-case scenario exceeds the predefined primary effectiveness endpoint

Table 4 Primary effectiveness (complete aneurysm occlusion with no significant stenosis and no re-treatment) and alternative definition of effectiveness (near-complete aneurysm occlusion with no significant stenosis and no re-treatment) intention-to-treat population

Endpoint	n=139 n (%)	Posterior mean (95% CI)	Posterior probability*
Primary effectiveness	80 (57.6%)	57.4% (49.2% to 65.5%)	0.997
Primary effectiveness components:			
Aneurysm occlusion (Raymond 1) (n=140)†	88 (62.9%)	62.7% (54.6% to 70.4%)	
Absence of clinically significant stenosis of parent artery (≥50%) (n=139)	133 (95.7%)	95.0% (90.9% to 98.0%)	
No re-treatment (n=140)†	132 (94.3%)	93.7% (89.1% to, 97.0%)	
Primary effectiveness, alternative definition	100 (71.9%)	71.6% (63.9% to 78.7%)	>0.999
Primary effectiveness components:			
Aneurysm occlusion (90% occlusion or greater) (n=140)†	112 (80.0%)	79.6% (72.6% to 85.8%)	
Absence of clinically significant stenosis of parent artery (≥50%) (n=139)	133 (95.7%)	95.0% (90.9% to 98.0%)	
No re-treatment (n=140)†	132 (94.3%)	93.7% (89.1% to 97.0%)	

*Posterior probability that the primary efficacy endpoint success rate is >46%.
†One subject was assessed for aneurysm occlusion but not stenosis of the parent artery.

success of >46%, yielding a favorable primary effectiveness result for the trial.

Primary effectiveness of prespecified subgroups of the intention-to-treat population was analyzed by aneurysm site, patient gender, age, aneurysm rupture status, size, and location. No statistically significant differences were seen among these groups for either the composite primary effectiveness measure or any of its subcomponents. There was a trend towards a higher occlusion rate for patients under age 60, but this did not reach statistical significance.

Target aneurysm re-treatment

Re-treatment occurred in eight subjects: four were carried out to deal with complications of aneurysm rupture or thrombosis, and four because of continued aneurysm filling. Three of these treatment failures were due, at least in part, to device migration (or foreshortening). All eight subjects were re-treated by placement of additional flow diverters.

Prespecified secondary endpoints

A summary of the secondary endpoints is included in table 5.

One of the prespecified secondary endpoints was an alternative definition of occlusion, defined as the number of patients with clinically acceptable (90–100%) occlusion, <50% stenosis of the parent artery, and without unplanned alternative treatment. This alternative definition of successful occlusion was seen in 100/139 (71.9%) patients. The subcomponents of this endpoint are shown in table 5.

DISCUSSION

The performance goals of the trial for safety and efficacy were both met, and as a result FDA approval of the FRED system

Table 5 Summary of secondary endpoints

Endpoint	% (n/N)
Proportion of subjects with clinically acceptable (90–100%) occlusion of the target aneurysm, ≤50% stenosis of the parent artery at the target IA at 12 months as assessed by angiography, and in whom an unplanned alternative treatment of the target IA had not been performed within 12 months	71.9% (100/139)
Proportion of subjects in whom an unplanned alternative treatment of the target IA had not been performed within 12 months	94.3% (132/140)
Proportion of subjects with clinically acceptable aneurysm occlusion (90–100%) of the target aneurysm at 12 months	80.0% (112/140)
Incidence of ≥50% in-stent stenosis at the target IA at 12 months as assessed by angiography at the independent core laboratory	4.3% (6/139)
Proportion of subjects with complete occlusion of the target aneurysm on 12 month angiography (Raymond 1)	62.9% (88/140)
Incidence of FRED system procedure-related serious adverse events	27.6% (40/145)
Incidence of FRED system device-related serious adverse events	18.6% (27/145)
Incidence of unsuccessful delivery of the FRED	1.4% (2/145)
Incidence of unsuccessful deployment of the FRED	2.8% (4/145)
Incidence of migration of the FRED system implant at 12 months	2.8% (4/145)
Unplanned alternative treatment on the target IA within 12 months, defined as re-treatment of the target aneurysm with an alternative treatment modality, including open repair, endovascular placement of an additional stent, or treatment of in-stent stenosis observed at the 180-day or 12-month follow-up time-points or at an unscheduled study follow-up visit	5.7% (8/140)
Change in clinical and functional outcomes at 180-day follow-up, as measured by an increase in the modified Rankin Scale score compared with baseline	13.9% (19/137)
Change in clinical and functional outcomes at 1-year follow-up, as measured by an increase in the modified Rankin Scale score compared with baseline	11.9% (16/135)
Incidence of major stroke, as measured by NIHSS score at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate)	6.2% (9/145)
Incidence of minor stroke, as measured by NIHSS score at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate)	6.2% (9/145)

FRED, Flow Redirection Endoluminal Device; IA, intracranial aneurysm; NIHSS, National Institutes of Health Stroke Scale.

was granted. The primary safety endpoint was met in 9/145 (6.2%) patients and the primary effectiveness endpoint in 80/139 (57.6%) patients. Disabling or fatal neurological events occurred in 4/145 (2.8%) patients. The goal of this trial—that is, to gain regulatory approval with the US FDA, can be compared with the Pipeline for Uncoilable or Failed Aneurysms (PUFS) and Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT) trials, which were similarly carried out to gain US FDA approval for the Pipeline and Surpass devices, respectively.[6 7] With respect to the PUFS trial, major differences from this trial include the larger mean size of the aneurysms included in PUFS, the more restricted locations of aneurysms included (proximal carotid only), and the use of multiple devices in the majority of patients (median three devices per patient). The 6 month safety outcome in PUFS of major stroke or neurological death was met in 5.8% of patients, similar to the rate of 6.2% seen at 1 year in the current study, but the rate of complete aneurysm occlusion seen at 6 months in PUFS was higher at 73.6%. It is possible that the location of aneurysms being primarily within the carotid siphon favored a higher rate of occlusion in PUFS as it has been shown that the straightening effect of a flow diverter in a curved segment of the artery correlates with complete aneurysm occlusion, an effect that would be less frequently seen in straighter segments of the carotid, such as the posterior communicating artery segment.[8] The corresponding safety and efficacy figures for the more recent SCENT trial are 8.3% and 62.8%, not meaningfully different from the current study results. Permanently disabling or fatal stroke events in SCENT were 6.1% vs 2.8% in the FRED Pivotal Trial.

Although the FRED system is a relative newcomer to the flow diversion field, a growing body of high-quality evidence consistently shows it provides satisfactory safety and efficacy results.[9–12] Some caution must be exercised in comparing the results of these trials as they vary in definitions of adverse safety outcome, the proportion of large versus small aneurysms, proportion of anterior versus posterior aneurysm locations, duration of follow-up, and number of aneurysms concomitantly treated with adjuvant devices such as coils. Additionally, the rate of complete aneurysm occlusion in these trials is generally higher than reported in the current study, perhaps, at least in part, because they did not employ the composite endpoint we used in this study where parent artery occlusion, stenosis >50%, use of adjuvant treatment, or re-treatment of target aneurysm would all be adjudicated as failures of efficacy.

Without losing sight of the fact that these differences exist, it is reassuring to note that the very low 2.8% rate of disabling stroke (mRS score >2) or death seen in this trial is consistently reflected in the other recent major trials of the FRED system, where combined permanent morbidity and mortality was reported as ranging from 2.3% to 4.8%.[9–12] As was seen with the Pipeline device,[6 13 14] these same studies of the FRED system report improving rates of complete aneurysm occlusion over time, with occlusion at 1 year ranging from 73.3% to 91.3%.

These results in aggregate are similar to the results reported in prior pooled analyses of treatment with the Pipeline flow diverters, specifically the International Retrospective Study of the Pipeline Embolization Device (IntrePED) study, and the pooled analysis of the PUFS, IntrePED, and ASPIRe data.[15 16] In the pooled analysis the combined major neurologic morbidity and mortality was 7.1% versus 2.8% in this trial and 2.3% in the EuroFRED registry.[9] Complete aneurysm occlusion at 1 year was 85.5% in the pooled Pipeline analysis, 57.6% in the current study, and 91.3% in EuroFRED, although EuroFRED occlusion results were not adjudicated by a core laboratory. It should be recognized that the pooled Pipeline analysis represents an earlier experience with flow diverters, and an aneurysm population that may be significantly different from more recent trials where aneurysm sizes tend to be smaller. These differences may account in some part for the more favorable results reported in the recent PREMIER trial.[17]

Study limitations

The chief limitation of the current study is the lack of a control group. Comparison with other trials is difficult because of significant differences in key features, such as allowed anatomical sites of included aneurysms, aneurysm characteristics such as size, and treatment-related issues such as the number of devices used.

CONCLUSIONS

As compared with historically derived performance benchmarks, the USA FRED pivotal trial successfully achieved favorable outcomes for the primary endpoints of both safety and efficacy in the treatment of intracranial aneurysms.

Author affiliations
[1]Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, Maryland, USA
[2]Cerebrovascular Center, Houston Methodist, Houston, Texas, USA
[3]Department of Neurosurgery, Albany Medical Center, Albany, New York, USA
[4]Department of Neurosurgery and Radiology and Canon Stroke and Vascular Research Center, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York, USA
[5]Department of Neurosurgery, Gates Vascular Institute, Buffalo, New York, USA
[6]Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[7]Department of Neurosurgery, Prisma Health, Greenville, South Carolina, USA
[8]Department of Neurointerventional Radiology, Abbott Northwestern Hospital, Minneapolis, Minnesota, USA
[9]Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania, USA
[10]Department of Neurosurgery, University of Washington, Seattle, WA, USA
[11]Department of Radiology and Biomedical Imaging, UCSF, San Francisco, CA, USA

Correction notice Since this article was first published online, the following authors have been added to the author group Louis J Kim, Steven W Hetts, Daniel L Cooke and Christopher F Dowd.

Twitter Yasha Kayan @yashakayan and Pascal Jabbour @PascalJabbourMD

Acknowledgements The investigators wish to recognize Jennifer Jelf, Ryan Chakra and Lucie Thibault for their integral role in the planning, design, and oversight of the FRED pivotal trial.

Contributors CGM acted as primary author for this manuscript. All other authors contributed substantially to the conception or design of the work, or the acquisition, analysis or interpretation of data.All authors participated in revising or reviewing critically for important intellectual content and gave final approval of the version published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This work was funded by Microvention-Terumo Inc.

Competing interests CGM: consultant to Microvention and Medtronic OOD: proctor for FRED/Microvention. AB: consultant to Microvention and Vesalio. AHS:SNIS Board of Directors; current research grants: co-investigator: NIH/NINDS 1R01NS091075 Virtual intervention of intracranial aneurysms; role: co-principal investigator NIH-NINDS R21 NS109575-01 Optimizing approaches to endovascular therapy of acute ischemic stroke; financial interest: Adona Medical, Inc., Amnis Therapeutics, Bend IT Technologies, Ltd., BlinkTBI, Inc, Boston Scientific Corp (for purchase of Claret Medical), Buffalo Technology Partners, Inc., Cardinal Consultants, LLC, Cerebrotech Medical Systems, Inc, Cognition Medical, Endostream Medical, Ltd, Imperative Care, Inc., Instylla, Inc., International Medical Distribution Partners, IRRAS, LaunchNY Seed Fund Management, LLC, NeuroRadial Technologies, Inc., Neurovascular Diagnostics, Inc., Perflow Medical, Ltd., Q'Apel Medical, Inc., Radical

Catheter Technologies, Inc., Rebound Therapeutics Corp. (purchased 2019 by Integra Lifesciences, Corp), Rist Neurovascular, Inc., Sense Diagnostics, Inc., Serenity Medical, Inc., Silk Road Medical, Spinnaker Medical, Inc., StimMed, Synchron, Three Rivers Medical, Inc., Truvic Medical, Inc, Vastrax, LLC, VICIS, Inc., Viseon, Inc., Viz.ai, Inc; consultant/advisory board: Amnis Therapeutics, Apellis Pharmaceuticals, Inc., Boston Scientific, Canon Medical Systems USA, Inc., Cerebrotech Medical Systems, Inc., Cerenovus, Corindus, Inc., Endostream Medical, Ltd, Imperative Care, Inc., Integra LifeSciences Corp., IRRAS, Medtronic, MicroVention, Minnetronix Neuro, Inc., Northwest University – Data Safety Monitoring Board chair for HEAT Trial, Penumbra, Perflow Medical, Ltd., Q'Apel Medical, Inc., Rapid Medical, Rebound Therapeutics Corp., Serenity Medical, Inc., Silk Road Medical, StimMed, Stryker, Three Rivers Medical, Inc., VasSol, Viz.ai, Inc., W.L. Gore & Associates; national PI/steering committees: Cerenovus NAPA Trial and ARISE II Trial; Medtronic SWIFT PRIME and SWIFT DIRECT Trials; MicroVention FRED Trial and CONFIDENCE Study; MUSC POSITIVE Trial; Penumbra 3D Separator Trial, COMPASS Trial, INVEST Trial;• No consulting salary arrangements. All consulting is per project and/or per hour. JC: No disclosures. JTF: SNIS Board of Directors; consultant to Microvention and Stryker. AST: consultant to Microvention, Medtronic, Viz AI, Siemens;.chief medical officer Imperative Care. YK: consultant to Microvention, Penumbra, Medtronic. PJ: consultant to Microvention

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Cameron G McDougall http://orcid.org/0000-0001-7372-7049
Adnan H Siddiqui http://orcid.org/0000-0002-9519-0059
Yasha Kayan http://orcid.org/0000-0002-7747-0188
Pascal Jabbour http://orcid.org/0000-0002-1544-4910

REFERENCES

1 Kocer N, Islak C, Kizilkilic O, *et al*. Flow Re-direction Endoluminal Device in treatment of cerebral aneurysms: initial experience with short-term follow-up results. *J Neurosurg* 2014;120:1158–71.
2 Ding YH, Tieu T, Kallmes DF. Experimental testing of a new generation of flow diverters in sidewall aneurysms in rabbits. *AJNR Am J Neuroradiol* 2015;36:732–6.
3 Möhlenbruch MA, Herweh C, Jestaedt L, *et al*. The FRED flow-diverter stent for intracranial aneurysms: clinical study to assess safety and efficacy. *AJNR Am J Neuroradiol* 2015;36:1155–61.
4 Raymond J, Guilbert François, Weill A, *et al*. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke* 2003;34:1398–403.
5 Chimowitz MI, Lynn MJ, Derdeyn CP, *et al*. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365:993–1003.
6 Becske T, Kallmes DF, Saatci I, *et al*. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. *Radiology* 2013;267:858–68.
7 Meyers PM, Coon AL, Kan PT, *et al*. SCENT trial. *Stroke* 2019;50:1473–9.
8 Awad AW, Kilburg C, Karsy M, *et al*. Change in the angle of the anterior genu is associated with occlusion rate after Pipeline flow diversion. *J Neurosurg* 2019:1–5.
9 Killer-Oberpfalzer M, Kocer N, Griessenauer CJ, *et al*. European multicenter study for the evaluation of a dual-layer flow-diverting stent for treatment of wide-neck intracranial aneurysms: the European Flow-Redirection Intraluminal Device study. *Am J Neuroradiol* 2018;39:841–7.
10 Pierot L, Spelle L, Berge J, *et al*. Safe study (safety and efficacy analysis of FRED embolic device in aneurysm treatment): 1-year clinical and anatomical results. *J Neurointerv Surg* 2019;11:184–9.
11 Piano M, Valvassori L, Lozupone E, *et al*. FRED Italian registry: a multicenter experience with the flow re-direction endoluminal device for intracranial aneurysms. *J Neurosurg* 2019:174–81.
12 Guimaraens L, Vivas E, Saldaña J, *et al*. Efficacy and safety of the dual-layer flow-diverting stent (FRED) for the treatment of intracranial aneurysms. *J Neurointerv Surg* 2020;12:521–5.
13 Becske T, Potts MB, Shapiro M, *et al*. Pipeline for uncoilable or failed aneurysms: 3-year follow-up results. *J Neurosurg* 2017;127:81–8.
14 Becske T, Brinjikji W, Potts MB, *et al*. Long-term clinical and angiographic outcomes following Pipeline embolization device treatment of complex internal carotid artery aneurysms: five-year results of the Pipeline for Uncoilable or Failed Aneurysms trial. *Neurosurgery* 2017;80:40–8.
15 Kallmes DF, Hanel R, Lopes D, *et al*. International retrospective study of the Pipeline embolization device: a multicenter aneurysm treatment study. *American Journal of Neuroradiology* 2015;36:108–15.
16 Kallmes DF, Brinjikji W, Cekirge S, *et al*. Safety and efficacy of the Pipeline embolization device for treatment of intracranial aneurysms: a pooled analysis of 3 large studies. *J Neurosurg* 2017;127:1–6.
17 Hanel RA, Kallmes DF, Lopes DK, *et al*. Prospective study on embolization of intracranial aneurysms with the Pipeline device: the PREMIER study 1 year results. *J Neurointerv Surg* 2020;12:62–6.