



August 15, 2023

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Attn: Saikat Bhuiyan, Lead Reviewer

Re: Supplement to Q211873, Breakthrough Device Designation Request

Device Name: Openwater LVO Stroke Alert

Indications for Use:

Openwater LVO Stroke Alert is indicated for use as an early notification system to identify patients suspected of large vessel occlusion (LVO) in the anterior circulation. This software as a medical device (SaMD) utilizes data from Openwater Headset in adult patients. Openwater LVO Stroke Alert is intended to be used in hospitals, clinics, and in pre-hospital settings.

Type of Q-Sub	Breakthrough Device Designation Request
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Subject: Breakthrough Device designation request for Openwater LVO Stroke Alert

Dear Mr. Bhuiyan,

Openwater is seeking FDA review to designate its device, Openwater LVO Stroke Alert as a Breakthrough Device as defined in 515B(b) of the FD&C Act (21 U.S.C. 360e-3(b)). Openwater LVO Stroke Alert is intended for use as an early notification system to aid in the pre-hospital

assessment of acute stroke patients with suspected large vessel occlusion of the internal carotid artery or proximal middle cerebral artery in need of emergent transport to an endovascular-capable center. Openwater believes that the device satisfies the two criteria set forth in 515B(b) of the FD&C Act and would request FDA to designate Openwater LVO Stroke Alert as a Breakthrough Device.

Openwater had previously requested this designation in Q211873. After this Q-Submission was reviewed by the FDA, the Agency noted in a letter dated November 12, 2021 that the information provided by Openwater did not “*demonstrate a reasonable expectation that the proposed device could function as intended thereby demonstrating technical success and could provide for more effective diagnosis or treatment of the target condition compared to current available methods.*”

In this Q-Submission supplement, Openwater is providing information to address the deficiencies noted by the FDA. Specifically, to demonstrate technical feasibility, Openwater conducted a new feasibility clinical study (Section **Error! Reference source not found.**) and collected data from 158 subjects with a stroke code (68 with LVO and 90 non-LVO including other ischemic strokes, hemorrhagic strokes and stroke mimics). Openwater analyzed this data and noted that the Openwater LVO Stroke Alert algorithm had a sensitivity of 81% and a specificity of 80%. Openwater believes that with this feasibility data, there is a reasonable expectation that the Openwater LVO Stroke Alert could function as intended and could provide for more effective diagnosis or treatment of the target condition compared to current available methods.

Openwater is submitting herein supporting documentation per FDA guidance “Breakthrough Device Program: Guidance for Industry and Food and Drug Administration Staff”, issued in December 2018. Per the guidance, this request package includes the following material:

- Background Information:
 - Summary of clinical context and currently available technologies,
- Device Description including the principles of operations,
- Intended Use / Indications for Use,
- Regulatory history including a discussion on how Openwater addressed deficiencies previously raised by the Agency on Nov 12, 2021,
- Current feasibility clinical data,

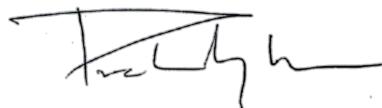
- Rationale for satisfying the designation criteria, and
- Data Development Plan.

Enclosed is an eCopy of this Q-Submission. The eCopy of this submission is provided on a DVD in accordance with FDA Guidance, “eCopy Program for Medical Device Submissions” issued April 27, 2020. The electronic PDF copy can be searched using standard PDF reader programs and includes bookmarks to the appropriate section of the submission.

Openwater considers the information in this submission to be confidential commercial information, and we have taken precautions to protect the confidentiality of this information under 21 CFR§807.95, Confidentiality of Information. We respectfully request that this submission and proprietary information herein be treated as confidential in accordance with the Freedom of Information Act.

Thank you in advance for your review of this application. If you have any questions, you may contact me by phone at 408-316-5707 (mobile), or by email at prabhu@mdqr.solutions.

Sincerely,



Prabhu Raghavan
Regulatory Consultant to Openwater
Principal, MDQR, LLC.

Cc: Carolyn Shelton

Enclosures.

Breakthrough Device Designation Request

for

Openwater LVO Stroke Alert

Q211873 – Supplement 002

August 15, 2023



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1 Background

In Q211873, Openwater had requested the Breakthrough Device designation for its device, the Openwater LVO Stroke Alert. This device is intended for use as an early notification system to aid in the pre-hospital assessment of acute stroke patients with suspected large vessel occlusion of the internal carotid artery or proximal middle cerebral artery in need of emergent transport to an endovascular-capable center. After this Q-Submission was reviewed by the FDA, the Agency noted in a letter dated November 12, 2021 that the information provided by Openwater did not *“demonstrate a reasonable expectation that the proposed device could function as intended thereby demonstrating technical success and could provide for more effective diagnosis or treatment of the target condition compared to current available methods.”*

In this Q-Submission supplement, Openwater is providing information to address the deficiencies noted by the FDA. Specifically, to demonstrate technical feasibility, Openwater conducted a new feasibility clinical study (Section 3) and collected data from 158 subjects with a stroke code (68 with LVO and 90 non-LVO including other ischemic strokes, hemorrhagic strokes and stroke mimics). Openwater analyzed this data and noted that the Openwater LVO Stroke Alert algorithm had a sensitivity of 81% and a specificity of 80%. Openwater believes that with this feasibility data, there is a reasonable expectation that the Openwater LVO Stroke Alert could function as intended and could provide for more effective diagnosis or treatment of the target condition compared to current available methods.

1.1 Clinical Problem: Current State of Pre-hospital LVO Detection

As noted previously in Q211873, large vessel occlusions (LVOs) due to acute blockages of the proximal intracranial anterior and posterior circulation account for up to 46% of acute ischemic stroke (AIS) and are considered refractory to intravenous tissue plasminogen activator (tPA) [Rennert et al., 2019]. Emergent transport for endovascular therapy has now become the standard of care for anterior LVO resulting in AIS, with five randomized clinical trials (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT) demonstrating significant clinical improvements in both recanalization rates and clinical outcomes when comparing endovascular treatment to medical therapy alone [McCarthy et al., 2019]. Anterior LVO is defined as proximal occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) at the first segment branching off the ICA, which is called the M1 segment. Importantly, thrombectomy is only indicated for ICA and M1 occlusions, and therefore identification of the specific subtype of AIS being caused by anterior LVO from an ICA or M1 occlusion is of greatest importance for thrombectomy workflows.

Clinical trials have demonstrated that the average time from hospital arrival to arterial access to begin endovascular treatment (“door to groin” time) can be improved by 50 minutes when there is a pre-hospital notification that the patient is being transferred [Goyal et al., 2016]. The need to better detect large vessel occlusions in the prehospital setting in order to reduce the time to thrombectomy [Noorian 2021, Adeoye et al. 2022, Pajor et al. 2023] has led to active research in several areas.

Prehospital stroke scales designed to enable EMS personnel to detect stroke have been compared in several recent studies [Duvekot et al. 2021, Nguyen et al. 2020]. While these scales tend to have high specificity (80%-93%), their sensitivity is low (38%-62%). Furthermore, a recent

analysis shows that while the scales are good at identifying subjects with severe symptoms, there is a need for methods that can better identify LVO in subjects with moderate symptoms, as these subjects are more common and the performance of the stroke scales in this population is worse [Goyal et al. 2022].

Mobile stroke units (MSUs) with CT scanners are another possible approach [Fassbender 2003]. Two recent studies (B_PROUD, BEST-MSU) have shown the dispatch of MSUs results in lower global disability at 3 months primarily by enabling earlier thrombolysis [Grotta et al. 2021, Ebinger et al. 2021, Rohmann et al. 2023]. There is interest in using MSUs to improve routing decisions to enable earlier thrombectomy as well, since endovascular therapy using mechanical thrombectomy has been shown to outperform intravenous thrombolysis. However, in both studies MSUs did not change frequency of or time to mechanical thrombectomy [Navi et al. 2022]. In addition, significant concerns remain with MSUs including cost-effectiveness, financing, and their benefit in nonurban settings [Navi et al. 2022].

Several portable diagnostic devices at various stages of development are currently under investigation for prehospital LVO detection [Chennardreddy et al. 2022, Patrick et al. 2021]. A recent multicenter study using a combination of electroencephalography (EEG) and somatosensory evoked potentials (SSEPs) showed 80% sensitivity and specificity in hospital emergency departments and has led to a breakthrough designation for this technology [Sergot et al. 2021]. Other studies have included the analysis of robot assisted transcranial doppler (TCD) waveforms [Dorn et al. 2020, Thorpe et al. 2020], cranial accelerometry [Smith et al. 2020, Keenan et al. 2020], and volumetric impedance phase-shift spectroscopy (VIPS) [Walsh et al. 2019, Kellner et al. 2018]. While some of these studies show promising results, none have been validated in the prehospital setting, and significant work remains to demonstrate their efficacy.

Openwater is proposing to introduce the Openwater LVO Stroke Alert, which a noninvasive early notification system to quickly identify patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery.

2 Device Description

In Q211873, Openwater provided a detailed device description of Openwater LVO Stroke Alert. Please refer to Q211873 for details as the proposed device is largely identical. The following is a brief summary of the key aspects of the subject device. The notable differences between the version submitted in Q211873 and the current version used in clinical studies is also discussed below (Section 2.1).

Openwater LVO Stroke Alert is indicated for use as an early notification system to identify specific patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery (i.e., anterior LVO). In prehospital acute settings, this alert can help improve post-hospital arrival time workflows via advanced notification and parallel mobilization of staff and resources in anticipation of arrival, and in addition can help enable Emergency Medical Services (EMS) protocols to make better routing decisions for patients suspected of anterior LVO stroke in need of transport to advanced endovascular capable centers (ECCs), i.e. where direct transfer to closest ECC would be faster than inter-facility transfer delays from routing through the closest hospital.

The Openwater LVO Stroke Alert system consists of two separate devices working together to achieve this function, namely:

- Openwater Headset
 - The Openwater Headset is the base hardware platform that has the sensors to acquire laser speckle information used by Openwater LVO Stroke Alert. Openwater discussed this device previously with the FDA in Q212494. Please refer to Sections 2.1 for details. Note that the focus of this Breakthrough Designation request is the Openwater LVO Stroke Alert and not the Openwater Headset.
- Openwater LVO Stroke Alert
 - Openwater LVO Stroke Alert is a software as a medical device (SaMD) that analyzes the laser speckle data from Openwater Headset to identify specific patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery. Please refer to Sections 2.2 for details.

2.1 Openwater Headset

Openwater Headset is a head-mounted, wearable headset with built-in optical fibers for the delivery of low power laser light to the subject. CMOS (complementary metal oxide semiconductor) image sensors are utilized for the collection of light from the subject. The fibers and image sensors are positioned at symmetrically located positions on either side of the head on the surface directly overlying the vascular territories of the anterior circulation of the ICA and MCA. The electronics to drive the headset and process the signal are housed in a briefcase-sized box (console), which can be carried to the point of care. The Openwater Headset current design is shown in Figure 1.

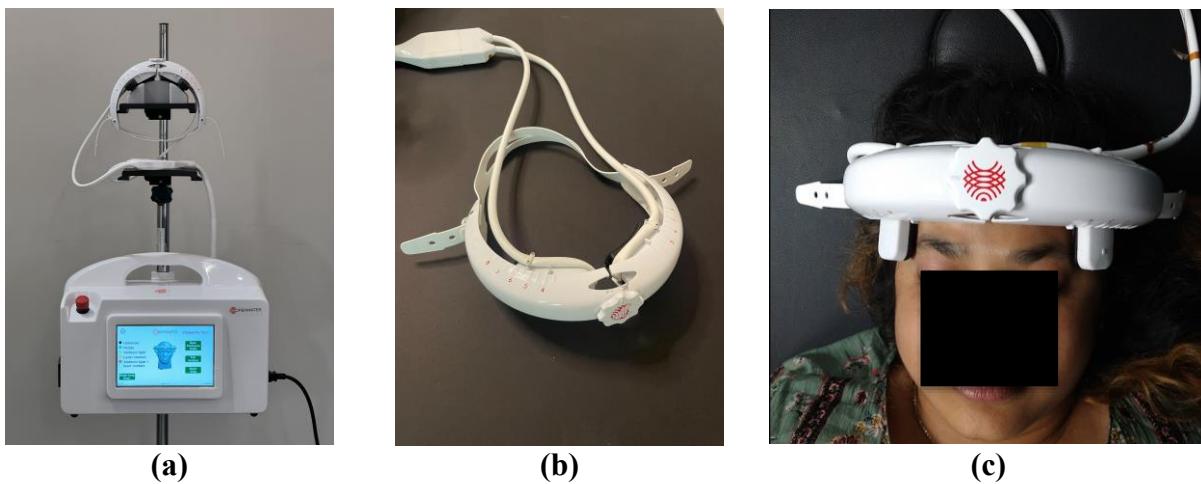


Figure 1: Openwater Headset consisting of (a) console containing the laser, electronics, and computer, (b) a wearable headset containing optical fibers and CMOS camera sensors. (c) Openwater Headset frame placed on a subject's head.

Note that in Q211873, Openwater had referenced a prototype version of the core technology housed in a cart and using a wand configuration (see Q211873, Figure 4). In contrast to the previous wand-based prototype design, the headset reduces motion artifacts and is more convenient to position and automate the measurements of multiple locations without the need to manually reposition to interrogate the locations of interest. In addition, the carrying case makes the device more portable than the previous cart configuration. In Q211873, Openwater discussed the handheld wand configuration to collect preliminary data and a headset version that was being planned to enable more repeatable and stable measurements. A portable handheld console was also proposed in Q211873 to replace the main processing unit, which was originally in a cart that connected to the wand configuration. Both the headset configuration and the portable mobile console have since been developed (see Figure 1) and the clinical study discussed in Section 3 uses this design. The portable console also includes an algorithm to detect and remove data artifacts generated by patient motion. The console also includes a prescan data quality check to ensure good contact with scalp by checking that enough light is detected when laser is on, and that almost no ambient light is detected when the laser is off.

The Openwater Headset consists of a structural frame that contains two sensor modules for detection. The sensor module houses all the optics and electronics for measurement. Both sensor modules have 4 contact points that are intended to touch the bare skin of the patient (see Figure 2, Figure 3, and Figure 4). These contacts points are:

1. The source exit window, which is where the laser to interrogate tissue below exits.
2. The near sensor, which is sensitive to blood flow at depths of up to 15 mm.
3. The far horizontal sensor, which is sensitive to blood flow at depths of up to 30 mm. This area is perfused through by the middle cerebral artery and the anterior cerebral artery.
4. The far vertical sensor, which is sensitive to blood flow at depths of up to 30 mm. This area is perfused through by the middle cerebral artery.

As noted above, each sensor within the Openwater Headset extracts laser speckle information, as described in Q211873. This laser speckle information is used by the Openwater Headset to compute blood flow and blood volume information in an Openwater proprietary format.

However, the laser speckle information is the key input used by the Openwater LVO Stroke Alert.

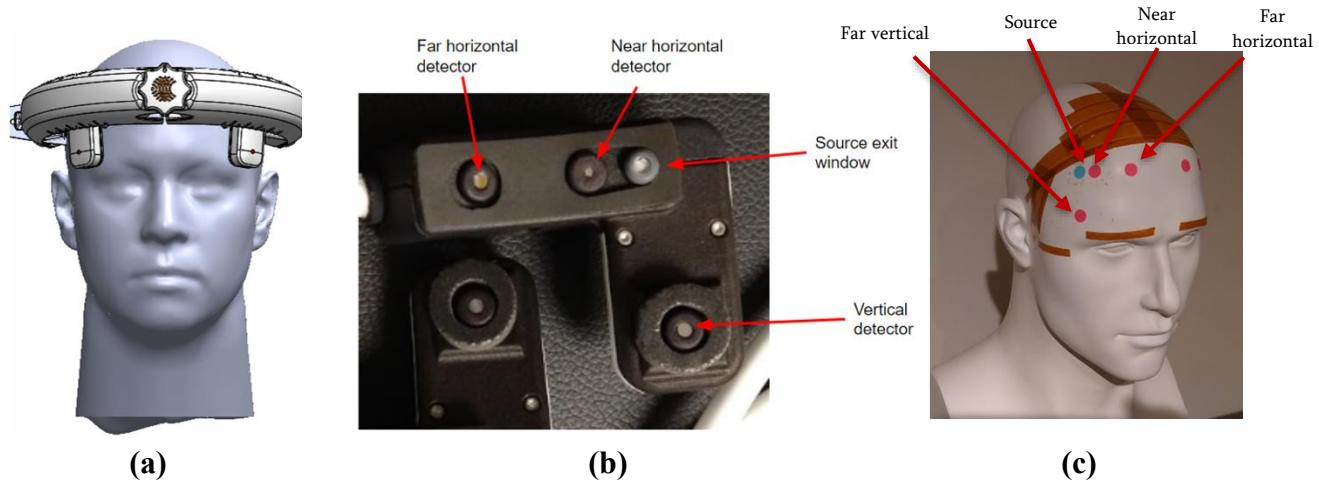


Figure 2: (a) Headset placed on a subject model, (b) Openwater Headset sensor module, (c) placement location of sensor module.

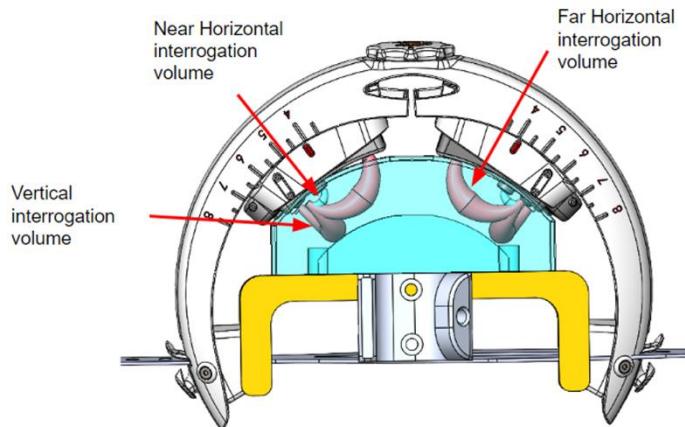


Figure 3: Openwater Headset shown sitting on the calibrated test phantom, the optical paths or interrogation volumes and depths are depicted in the solid model representation.



Figure 4: Openwater Headset sensor module (a) CAD model of the sensor module, (b) view of the module within the headset frame.

2.2 Openwater LVO Stroke Alert

Openwater LVO Stroke Alert is an SaMD that operates within the console of Openwater Headset and does not require any external communication or internet connection. This software as a medical device analyzes the laser speckle information data from each of the Openwater Headset's sensors. Openwater LVO Stroke Alert applies a proprietary machine learning algorithm to identify if a large vessel occlusion of the internal carotid artery or proximal middle cerebral artery is suspected. This machine learning model is described further in Section 2.4.

The device provides a dichotomous output of either a positive finding, resulting in an “*LVO Stroke Alert*,” or a negative finding, resulting in an output of “*Does not meet criteria for LVO Stroke Alert*.” The EMS reviewing this notification on screen of the Openwater Headset’s console would interpret the “LVO Stroke Alert” finding to route the patient to an EVT capable center or would follow normal routing workflows with the “Does not meet criteria for LVO Stroke Alert” finding. Interpretation of the output of Openwater Headset is not necessary to utilize the findings by Openwater LVO Stroke Alert.

A block diagram of the various elements of Openwater Headset including Openwater LVO Alert is shown in Figure 5. As shown in the figure, the two devices are located in the shared platform of the Openwater Headset console and the interface between the two devices is in software only. When the Openwater LVO Stroke Alert software package is installed, the Openwater Headset automatically shares the recorded blood flow data with Openwater LVO Stroke Alert and the subsequent LVO stroke alert finding will be displayed on the LCD screen of the console. There are no wireless or cellular paths of transmission for the data and all of the data is transmitted through physically wired means.

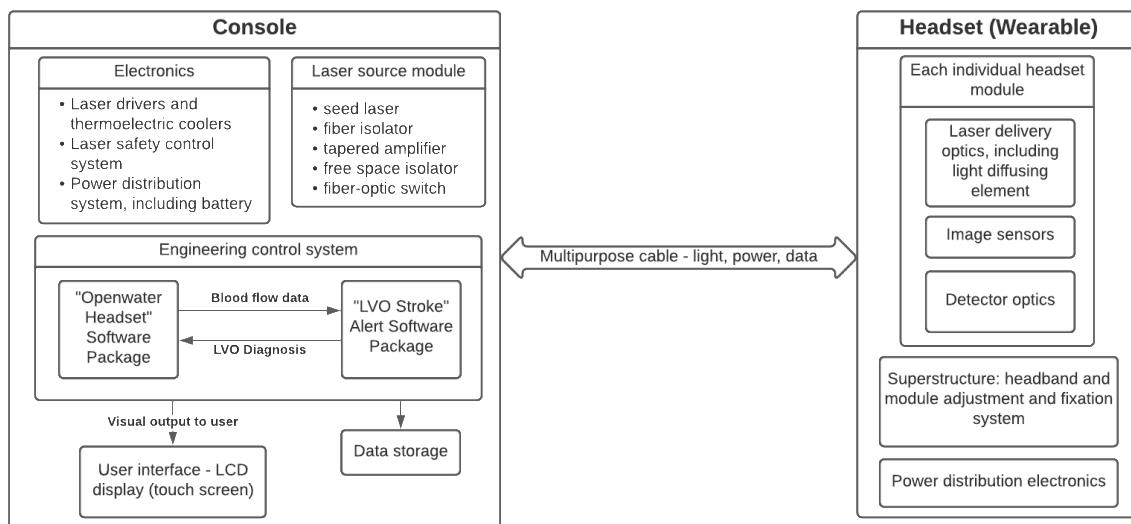


Figure 5: Block diagram showing Openwater Headset with Openwater LVO Alert installed as a package or module.

The sources of device failure are similar to that associated with such types of electronic devices, including hardware issues with the console, multipurpose cable, or wearable headset, software issues, and use errors. In addition, the device may fail to provide an alert if the device is not fitted correctly or is unable to perform its scan. A separate detailed discussion of the sources of variability in performance was previously discussed in Q211873/S001, Deficiency 1(c). The

sources of device failure are mitigated through design controls and the use of verification and validation testing as well as human factors testing that ensures that the device is robust. Proposed testing to assess the effectiveness of the mitigations and to support a planned marketing submission for this device was discussed in Section 8 of Q211873. A preliminary analysis of risks is provided in Section 2.6, Table 1 – this brief discussion on the proposed device risks and their mitigation was previously discussed in Q211873/S001, Deficiency 3(b). Additional details of the noted sources of failure and their risk assessment and risk mitigation strategy will be included as part of the premarket submission to support the Openwater Headset.

2.3 Device Operation, Use Model, Device Output

The steps for using the device to measure a new patient (total duration less than 5 minutes) are described below:

1. Power on the device.
2. Select “new patient”.
3. Place headset on the patient’s head, following the placement instructions. Device executes a test to check for full contact with the patient’s head.
4. If the headset is properly placed, initiate scan. If not, device will prompt for the user to address the placement issue.
5. Execution of the scan.
6. Scan finishes:
 - a. Once the scan is successful, data is saved onto the device and the following parameters are displayed for the underlying tissue beneath the sensors (this information is not in scope of this Breakthrough Device designation request):
 - i. **rCBFi** (relative cerebral blood flow index): a proprietary **Blood Flow Index**, measure of the flow rate of blood in the underlying tissue below the sensor.
 - ii. **rTHb** (relative total tissue hemoglobin concentration): a proprietary **Blood Volume Index** based on measurements of the concentration of absorbing chromophores within the underlying tissue below the sensor.
 - b. If the scan is not successful, the device prompts the user to review the headset placement and to maintain contact stability, and re-attempt the scan.
7. The laser speckle data is then processed by the Openwater LVO Stroke Alert SaMD. If the device detects a possible LVO, it sends an alert to the user regarding the probability of an underlying LVO.
 - a. With that information, the EMS users decide how best to route the patient for the fastest time for reperfusion and provide the receiving facility a pre-hospital alert to prepare LVO workflows ahead of time in anticipation of patient arrival time.

The scientific explanation for these outputs was previously provided in Q211873. A brief discussion on the principles of operation of the Openwater LVO Stroke Alert is provided in the next section.

2.4 Principles of Operation

The principles of operation are no different than what was previously provided in Q211873 except for the specifics of the detection algorithm. Please refer to Section 2.4, pages 11-17 in

Q211873 for details on the technology and methods. The stroke detection algorithm is described below in Section 2.4.1.

2.4.1 LVO Stroke Detection

Openwater LVO Stroke Alert uses a deep learning model [Natarajan 2020]. The model is based on a transformer architecture that learns discriminative feature representations from the raw blood flow waveform. Transformers are a type of neural network that are well-suited for natural language processing tasks, but they can also be used for other tasks, such as blood flow classification.

The Openwater LVO Stroke Alert's machine learning model uses the speckle contrast signal from the Openwater Headset as input. The Openwater Headset has two sensing modules, one on the left and one on the right. Each module has one laser source that interrogates structures below that module. Each module has three sensors to acquire the return signal. Source-sensor separation defines the depth of interrogation as discussed previously in Q211873. One of the three sensors in a module is closer to the source ("near sensor"), and the remaining two are farther away ("far sensor"). The location of the two far sensors are over the temple and forehead, and the near sensor is over the lateral portion of the forehead. For each image captured by each sensor, the speckle contrast signal is calculated by dividing the standard deviation of pixel values by the mean value of the pixels. Thus, the Openwater Headset outputs a 6 channel speckle contrast signal.

The Openwater LVO Stroke Alert algorithm processes the 6-channel speckle contrast signal through a neural network and provides a dichotomous output of either a positive finding, resulting in an "LVO Stroke Alert," or a negative finding, resulting in an output of "Does not meet criteria for LVO Stroke Alert."

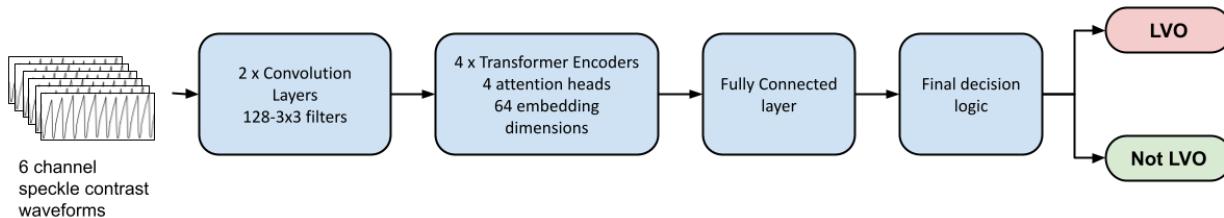


Figure 6: Flow of algorithm in Openwater LVO Stroke Alert

Please refer to Section 3 for methods used to train and assess performance to demonstrate feasibility.

2.5 Potential Sources of Measurement Variability

As part of product development, Openwater analyzed several factors that may affect device performance. Please refer to Q211872/S001, Table S-1 for details.

2.6 Analysis of Risks

The Openwater Headset is expected to take about 5 minutes from the start of set up to completion of the assessment. The 5 minute duration includes powering on the device, navigating to the proper LCD display screen, securing the headset onto the head, adjusting the headset location for accuracy, as well as the duration of the scan itself. As the scan duration itself

is expected to take 30 seconds or less, if the first attempt fails and a 30 second readjustment and rescan is needed, it should add no more than a minute. The LCD screen will have visual cues to help the user position the device successfully on the first attempt. Before the scan, the device will also run a test to evaluate if any of the headset modules are not properly flush with the patient's skin. There may be a learning curve for new users where the entire process takes longer than 5 minutes, but apart from that, Openwater expects the total duration to be less than 5 minutes.

Openwater's risk assessment for this procedure is summarized in Table 1 below and the typical risk is for a short delay in care due to device utilization of about 5-10 minutes.

Table 1: Summary of risks associated with device use

Hazard	Hazardous Situation	Harm	Mitigations
Device does not turn on or provide an analysis output	Patient with stroke needing immediate assessment of type of stroke to optimize routing decisions.	Delay in care	Labeling: Instruct HCP to revert to the current standard of care protocol if device analysis is not available. Design: Use of cGMP (specifically design controls and production/process controls) to ensure reliable operation of hardware and software in emergency situations.
User misinterprets the results of the displayed parameters	Misinterpretation leads to a false positive LVO diagnosis, causing incorrect routing to either an EVT-capable center or to the standard of care routing to the closest stroke center.	Delay in care	Design: Applying human factors and usability engineering to the design of the console user interface. Labeling: Instructions for use.
Interference between the headset and the head (e.g., hair) blocks light transmission and/or detection.	Patient with stroke needing immediate assessment of type of stroke to optimize routing decisions and the assessments are not available or delayed.	Delay in care	Design: Device includes algorithms to detect that the measurement is inappropriate for analysis and instructs user to address the issue and re-attempt the scan. If this repeatedly recurs the onscreen instructs HCP to revert to the current standard of care protocol. Labeling: Headset and labeling provide visual cues and instructions on how to properly situate the sensor modules for an effective scan. Please refer to Section 2.6.1 for additional details on analysis of placement.

Table 1: Summary of risks associated with device use

Hazard	Hazardous Situation	Harm	Mitigations
Improper headset fit or inaccurate headset installation	Inaccurate measurement leading to a false positive LVO alert, causing unnecessary routing to CSC	Patient without an LVO transferred to a comprehensive stroke center instead of the closest center leading to delay in care	Design: Headset is intended to fit most heads with an easy tightening feature. Headset and labeling provide visual cues and instructions on how to properly situate the sensor modules for an effective scan. Please refer to Section 2.6.1 for additional details on analysis of placement and fit.
System malfunction	Inaccurate LVO diagnosis, causing unnecessary routing to CSC	Patient without an LVO transferred to a comprehensive stroke center instead of the closest center leading to delay in care	Design: Design controls to ensure reliable operation of hardware and software in emergency situations
Laser power is too high	Laser light delivered to patient is over the MPE (maximum permissible energy)	Skin burns (minor or major) Eye damage (temporary or permanent)	Design: The device constantly verifies the correct laser parameters are being delivered (such as power, pulse width, etc.), otherwise an interlock will turn off the laser. The diffusing element on the laser delivery module is physically captured, and thus cannot fall out. Note that the device is a Class 1 laser device and the likelihood of skin or ocular eye risks are negligible.

2.6.1 Analysis of Headset Placement

The Openwater Headset's frame is designed to fit the range of head circumferences in the US population [Head and Face Anthropometry of Adult US Civilians (1993)]. The Openwater Headset's frame includes a rack and pinion gear left-right symmetric for adjustment, an elastic band for tightening around the patient. The design of the frame is optimized to fit the forehead possible area available for each patient that is free of hair in between the optical contact windows and the skin. The two modules (left and right) within the Openwater Headset are held in place with a spring loaded universal joint. The universal joint pivots the sensor module to the patient's forehead in such a way that the optical contact points are always in direct contact with the skin.

The Openwater Headset is placed on a patient by the operator using visual cues. A placement guide is provided on the user interface screen. A simplified version of this guide is provided as Attachment *A1 Headset Placement Guide* of this Q-Submission. Direct skin contact of all optical contact windows is important. When the operator has fit the Openwater Headset on the patient, the user interface performs a quick test before each measurement to ensure optical contact is

sufficient to make a good measurement. The test is based on both the minimum amount of laser light needed and the maximum amount of stray light permitted, to ensure a low noise measurement. The test analyzes the light level with the laser on to check that enough laser light is detected, and with the laser off to check if there is too much “stray” light detected from a source that is not the laser.

While the visual cues are currently the primary method to ensure fit, Openwater has performed some preliminary characterization of the repeatability of the placing the device and its effect on speckle contrast. In this preliminary analysis, Openwater assessed repeatability by analyzing the computed Coefficient of Variation (CoV). When the headset is static, an average CoV of 1.9% was observed and when the headset was removed and reapplied, an average CoV of 5.7% was observed. Additional methods to reduce the CoV are being explored. The analysis also characterized the effect of various levels of strap tightness and found minimal variation in the contrast signal.

Based on this preliminary analysis, the effect of placement and the resulting changes in the speckle contrast signal appear to be minimal. However, a more comprehensive analysis will need to be performed. Additionally, Openwater is working to design a simpler headset that is easier to locate and place repeatably.

3 Current Clinical Performance Data

3.1 Openwater LVO Stroke Alert – Feasibility

In order to assess feasibility of Openwater LVO Stroke Alert to detect an anterior LVO, Openwater conducted a clinical study. The study was conducted at the University of Pennsylvania and at Brown University. Both institutions approved the use of Openwater Headset as a nonsignificant risk device and utilized the abbreviated IDE per 21 CFR 812.2(b). The study sampled the intended use population and by recruiting subjects with a stroke code who came into the emergency room or the emergency transport helipad. All subjects followed the standard of care workflow for stroke at these institutions. The Openwater Headset recording was captured after initial imaging to determine the presence and type of stroke when the patient was waiting for this analysis to be complete. Informed consent was obtained proactively, if the patient was alert and was capable of providing consent, or retroactively, if the patient was not or to avoid interruption in care of the patient. The methods of obtaining informed consent were reviewed and approved by the overseeing IRB at both institutions.

The study included 158 subjects who completed the study, of which 135 subjects had analyzable data. Of the excluded subjects, 7 had poor Openwater Headset data either due to poor contact or incomplete data, and 16 had a pulse check failure from the device. The study population characteristics are shown in Table 2 below. The reference annotation for LVO or not LVO as well as the type of LVO was confirmed from hospital source data that included annotations by the attending radiologist using CT imaging as well as information from any procedures conducted (e.g., embolectomy). The study included 68 subjects with an anterior LVO, and 90 subjects suspected of a stroke but without an anterior LVO. The latter group included subjects with a non-LVO ischemic stroke, hemorrhagic stroke, and stroke mimics.

Table 2: Study Population Characteristics

Median Age (IQR)	72 (62-80)
Male	53.4%
Median Fitzpatrick Scale (IQR)	2 (2-5)
Median NIHSS (IQR)	9 (4-18)
Last known well (hours)	5.6 (3-14)
LVO	68
ICA	13
M1	28
M2	15
Tandem (M1/M2)	12
Ischemic Stroke (Non-LVO)	36
Hemorrhagic Stroke	15
Stroke Mimics	39

Openwater performed two types of performance assessments that are described further in Sections 3.1.1 and 3.1.2 below.

3.1.1 Feasibility Assessment 1 – Cross-Validation

A five-fold cross validation method was used to assess the ability to detect anterior LVO using the 6-channel speckle contrast signal acquired from the Openwater Headset. Cross validation is a resampling method that uses a portion of the available data to train a machine learning model and the remaining portion to assess performance. This process is repeated in several rounds to partition the data in different slices and the overall average performance is reported. At this stage in the development of Openwater LVO Stroke Alert, the use of cross validation methods helps Openwater identify feasibility of detecting LVO especially when data is limited to train and validate.

Table 3 below provides a summary of the performance of this method against the various standard scoring systems, such as NIH Stroke Score, LAMS, and RACE. Additionally, the Table 3 also provides the performance on various subgroups. Figure 8 shows the analysis of subjects as compared to the reference. Figure 7 shows the ROC curves for the Openwater algorithm as compared to RACE and LAMS.

As can be seen from this analysis, Openwater LVO Stroke Alert's algorithm showed a sensitivity of 81%, a specificity of 80%. The positive likelihood ratio was 3.7, a PPV of 67.8%, a negative likelihood ratio of 0.23, and an NPV of 86.8%. The balance of sensitivity and specificity well above current hospital stroke scores is encouraging and speaks to the potential of the proposed device in assessing patients in a prehospital setting. With additional training data, Openwater believes that this performance can be further improved. Additionally, the algorithm may be optimized to improve PPV or NPV, based on the situation such as distance to a comprehensive stroke center.

Openwater reviewed the performance of the algorithm across two types of subgroups, namely performance by gender and by skin tone. As can be seen in Table 3 below, there was negligible performance differences between male and female subjects as well as subjects with skin tone above and below 4 on the six-level Fitzpatrick scale [Fitzpatrick1975].

Table 3: Performance Characterization of Large Vessel Occlusion Detection

Type of method	Prediction Method	Sensitivity %	Specificity %	Positive Likelihood Ratio	Negative Likelihood Ratio
Hospital stroke scores	NIHSS ≥ 6	79	50	1.4	0.51
	NIHSS ≥ 10	53	76	2.1	0.67
	RACE ≥ 5	37	82	2.4	0.76
	LAMS ≥ 4	38	84	2.7	0.62
Openwater LVO Stroke Alert	Overall	81	80	3.7	0.23
	Fitzpatrick ≥ 4	82	80	3.9	0.23
	Fitzpatrick < 4	80	79	3.7	0.22
	Gender (M)	82	80	3.8	0.23
	Gender (F)	78	80	3.6	0.24

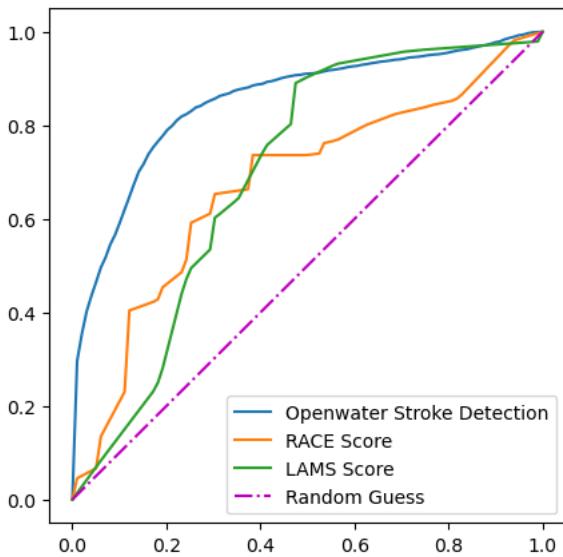


Figure 7: ROC curves for the various assessed methods

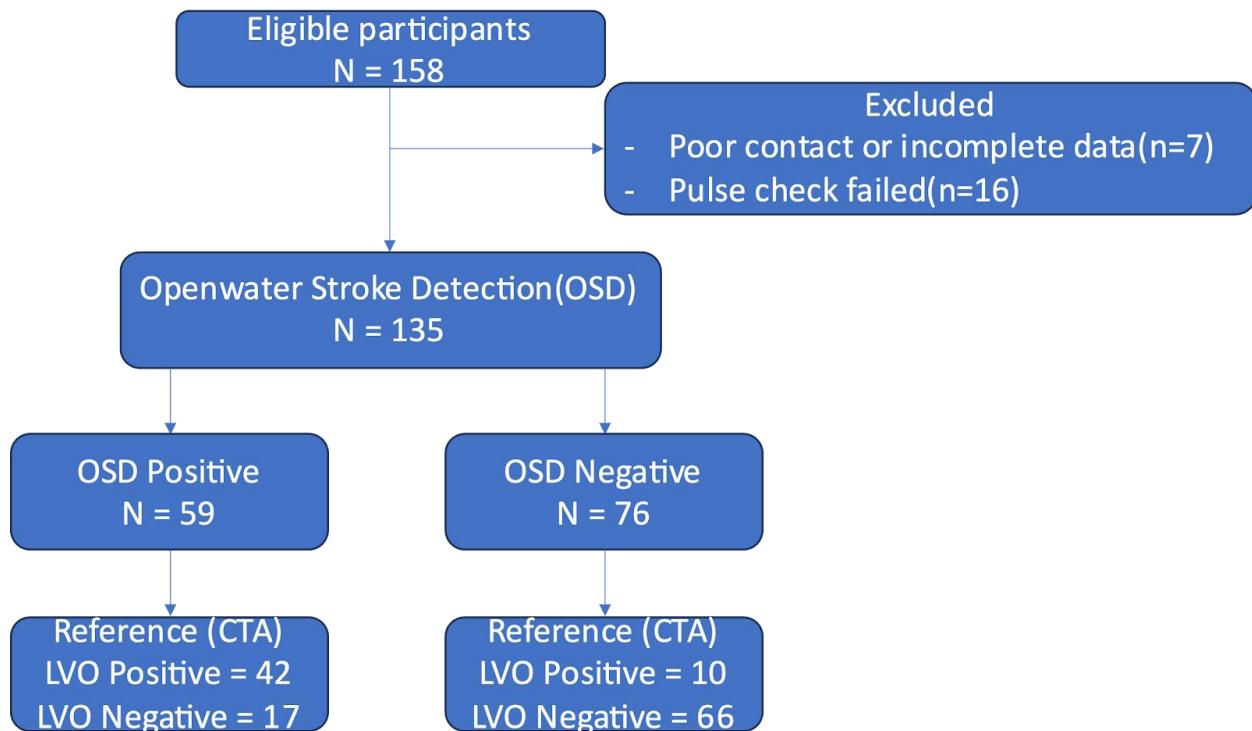


Figure 8: Subject flow and detection by Openwater LVO Stroke Alert

3.1.2 Feasibility assessment 2 – Holdout

In order to have an independent assessment of performance, the clinical dataset of 158 subjects was split into two parts, with one dataset of 128 subjects to train the model, and another dataset of 30 subjects (15 LVO and 15 non-LVO) to independently assess the model. The split was performed by selecting subjects randomly. Cross-validation methods were used to train a new model on 138 subject dataset and then the final model was then evaluated on the fresh dataset of

30 subjects. To address the problem of data insufficiency, Openwater pre-trained the network to reconstruct the waveforms from 80 Openwater Headset scans on healthy volunteers. Openwater then added a set of 4 transformer decoders to the network for reconstruction. After pre-training, the decoder stack was discarded from the network.

When evaluated with this sequence, the model demonstrated a sensitivity of 76% at 80% specificity. This assessment gave further confidence in the feasibility of the methodology as well as strongly indicated that the performance can be further improved with additional training data.

3.2 Openwater Headset – Feasibility

Openwater separately conducted a clinical study to evaluate that the speckle contrast waveforms, the underlying signals used by the Openwater LVO Stroke Alert, as generated by the Openwater Headset are correlated to cerebral blood flow velocity (CBFv). In the study, Openwater conducted optical measurements synchronized with transcranial doppler ultrasound (TCD) on healthy subjects performing hypercapnic breath holding exercises and compared the velocity waveforms to the speckle contrast waveforms.

Healthy individuals between the ages of 18 and 45 were eligible to participate. Subjects were excluded if they had a history of hypertension, type-2 diabetes, hyperlipidemia, heart failure, stroke, cerebrovascular abnormality, intracranial mass lesion, or skull defect which could interfere with TCD monitoring at the temporal region. The study protocol was approved by the University of Pennsylvania Institutional Review Board, and all study procedures were conducted in accordance with the ethical standard of the Helsinki Declaration. All study participants provided written informed consent prior to any study procedures.

CBFv was assessed using a Multigon Industries® TCD system (Elmsford, NY). The left middle cerebral artery (MCA) was insonated via the trans-temporal window at a depth of 40-65 mm. The vessel was confirmed by its characteristic depth range, Doppler signal, direction, and velocity. To ensure signal stability for the duration of the monitoring period, a 2 MHz TCD probe was secured directly to the Openwater Headset using a custom clamp designed to facilitate continuous vessel insonation, while minimizing motion induced artifacts or signal loss. MCA waveform and beat-to-beat mean CBFv was recorded at 125 Hz and synchronized with optical data.

Concurrently, speckle contrast waveforms were acquired by the left far horizontal sensor on the Openwater Headset. After 1-minute of baseline data, a 30-second breath hold was completed. The breath-hold was initiated at the end of expiration to avoid pre-oxygenation and elicit a more reliable hypercapnic response.

Figure 9 shows the relative change in speckle contrast signal from baseline (“rContrast”) compared to the relative change in CBFv to baseline for two subjects with large and small changes in waveform morphology in response to the breath hold. The figure’s panels show the following:

- Panel (a): Example rContrast waveform, in this case specifically the data used to generate Panel (b).
- Average waveforms from an individual with a large morphology change during the breath hold.

- Panel (b), (c): Average rContrast waveform from baseline and post hold, respectively.
- Panel (d), (e): Average rCBFv waveform from baseline and post hold, respectively.
- Average waveforms from an individual with a small morphology change during the breath hold.
 - Panel (f), (g): Average rContrast waveform from baseline and post hold, respectively.
 - Panel (h), (i): Average rCBFv waveform from baseline and post hold, respectively.

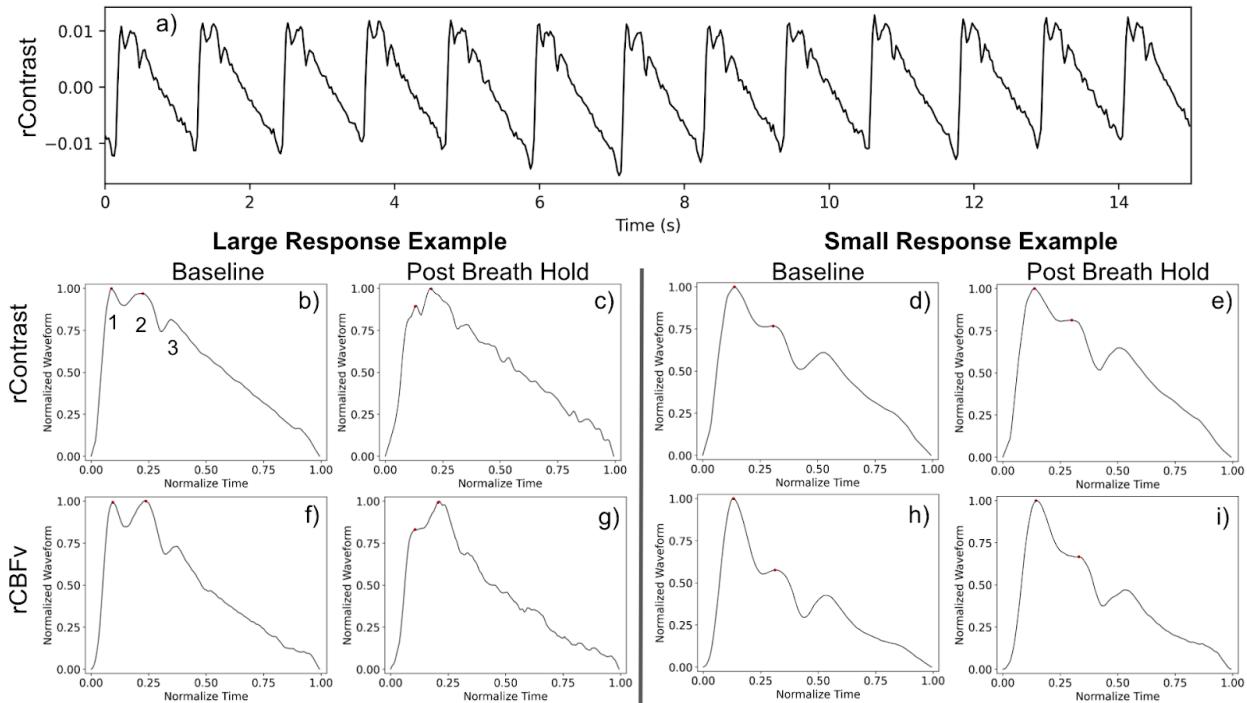


Figure 9: rContrast and rCBFv waveform morphology features change similarly before and after breath holds.

As can be seen from Figure 9, the waveforms are highly correlated. The study analyzed data from 22 subjects and the speckle contrast waveforms showed a high degree of correlation to the CBFv waveforms ($R > 0.8$). Details of the various comparisons are provided in *Attachment A2 Comparative Analysis of TCD to Speckle Contrast* of this Q-Submission.

4 Proposed Indications for Use/Intended Use

Openwater proposes an Indications for Use statement as follows:

- Intended use: Openwater LVO Stroke Alert is intended to identify specific patients suspected of large vessel occlusion (LVO) in the anterior circulation.
- Indications for Use:
Openwater LVO Stroke Alert is indicated for use as an early notification system to identify patients suspected of large vessel occlusion (LVO) in the anterior circulation. This software as a medical device (SaMD) utilizes data from Openwater Headset in adult patients. Openwater LVO Stroke Alert is intended to be used in hospitals, clinics, and in pre-hospital settings.

5 Regulatory History

In Q211873, Openwater had requested the Breakthrough Device designation for its device, the Openwater LVO Stroke Alert.

After Q211873 was reviewed by the FDA, the Agency noted in a letter dated November 12, 2021 that the information provided by Openwater did not “*demonstrate a reasonable expectation that the proposed device could function as intended thereby demonstrating technical success and could provide for more effective diagnosis or treatment of the target condition compared to current available methods.*” In the following section, Openwater is providing information to address the noted deficiencies.

5.1 Agency feedback in Q211873 dated November 12, 2021

In this document, the deficiencies noted in the Agency feedback letter dated November 12, 2021 are noted in bold italics followed by Openwater’s response in normal text.

1. *To meet Breakthrough Device designation criterion #1 as defined by section 515B(b)(1) of the Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 360e-3(b)(1)), you need to demonstrate a reasonable expectation that the proposed device could function as intended thereby demonstrating technical success and could provide for more effective diagnosis or treatment of the target condition compared to current available methods. In response to the October 13, 2021, request for additional information (AIRQ) letter, you clarified that the Openwater LVO Stroke Alert classified 100% of large vessel occlusion (LVO) strokes accurately (N=4), 100% of the non-LVO strokes accurately (N=3, with one intracranial hemorrhage (ICH) and two non-LVO ischemia), and 100% of controls as not LVO (N=30) based on a small human feasibility study comparing the blood volume index (BVI) and blood flow index (BFI) from the Openwater Headset and the Openwater LVO Stroke Alert output to computed tomography (CT) and magnetic resonance imaging (MRI) data. However, we believe that this sample size is too small and may not be generalizable to all suspected stroke patients in the United States (US) to understand the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the subject device and how this performance compares to alternative diagnostic methods to meet Breakthrough Device criterion #1. Therefore, we request that you submit additional clinical performance data to characterize the sensitivity, specificity, PPV, and NPV of the Openwater LVO Stroke Alert that is more representative of your device performance to be used in all suspected LVO stroke patients in the US that incorporates and addresses the following items:*
 - a. *Specify the demographics of the patient population enrolled and justify how the sample size is adequate to quantify the device performance that is representative of all suspected LVO stroke patients in the US based on stroke location, infarction size, and time from last known well. As part of the demographics of the patients enrolled, there should be a sufficient number of enrolled patients with varying degrees of skin pigmentation, including darker skin pigmentation to assess whether device performance can be affected by skin pigmentation due to the technological characteristics of the Openwater Headset. Although you state in the response to the October 13, 2021, AIRQ letter that “skin tone should have*

minimal effect on Openwater LVO Alert's algorithms for various reasons," the accompanying bench test of speckle contrast changes in response to varying light filtration and discussion of device design are insufficient justification to support this statement. While it is reasonable to state that measurements between left and right hemispheres will be affected equally by patient skin pigmentation, it is not clear how changes in the magnitude of the resulting difference would affect device performance. Furthermore, while the provided bench data may provide an initial assurance of potential resilience of the BFI to changes in skin pigmentation, we lack information about how the proprietary calculation of BVI is affected.

Please refer to Section 3 on page 14 for details on the preliminary feasibility data from 158 subjects that included 68 LVO and 90 non-LVO. Details of the population are provided in Table 2 within Section 3. The section also discusses methods used to train and validate performance. A discussion of performance by subject skin tone as well as gender is provided. As can be observed from Table 3, the performance of the Openwater model remained consistent within these subgroups.

- b. *Provide a risk assessment that evaluates how poor device placement and other technical issues may affect the interpretation of the data and all of the scenarios in which the device output could be misinterpreted by the end user. This assessment should include a targeted discussion of use of the Openwater LVO Stroke Alert in the intended clinical use environment, which can include the pre-hospital emergency medical services (EMS) setting. This is important because various environmental use factors can affect device performance, such as how the end user interprets the output and how the device is applied in a moving ambulance versus at a hospital.*

Please refer to Section 2.6 that discusses the risks related to placement as well as an analysis of how placement may affect performance.

- c. *The response (p.10) to deficiency #2.a. in the October 13, 2021, AIRQ letter mentioned that "stroke scales have shown poor sensitivity in actual practice, as low as 38% in some studies (Nguyen et al., 2021) and additionally suffer from particularly poor specificity as low as 20% in some studies (English et al., 2018)." However, the Los Angeles Motor Scale (LAMS) and other scales have good accuracy and predictive value for LVO strokes in the pre-hospital and emergency department settings ([Noorian et al., 2018](#)). Additionally, LAMS can be used for ischemic strokes in the posterior circulation as well. Provide additional information comparing the device safety and effectiveness when compared to pre-hospital stroke scales, such as LAMS using more updated performance data. Also, provide a discussion of the intended use of the device and whether it is intended to replace stroke scales or imaging modalities.*

Please refer to Section 3 on page 14 for details on the preliminary feasibility data from 158 subjects that included 68 LVO and 90 non-LVO. A discussion of performance of LAMS as compared to the proposed device is provided in Table 3.

Openwater LVO Stroke Alert is intended to guide prehospital workflows and not to replace any the current standard of care or any imaging modalities. The main goal is to quickly identify anterior LVO so that patients may be routed quickly to an endovascular capable stroke center. As discussed in Section 1.1 above, clinical trials have demonstrated that the average time from hospital arrival to arterial access to begin endovascular treatment (“door to groin” time) can be improved by 50 minutes when there is a pre-hospital notification that the patient is being transferred [Goyal et al., 2016]. Openwater is proposing to introduce the Openwater LVO Stroke Alert, which a noninvasive early notification system to quickly identify patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery

2. *The proposed indications for use (IFU) related to the Openwater Headset states:*

“The non-invasive Openwater Headset is intended for monitoring of blood flow in tissue, including the brain. The Openwater headset is intended for monitoring of adults. The prospective clinical value of data from Openwater Headset has not been demonstrated in disease states. Openwater Headset should not be used as the sole basis for diagnosis or therapy.”

The proposed IFU related to the Openwater LVO Stroke Alert states:

“Openwater LVO Stroke Alert is indicated for use as an early notification system to identify and communicate blood flow data on patients suspected of large vessel occlusion (LVO) of the internal carotid artery or proximal middle cerebral artery. This software as a medical device (SaMD) utilizes blood flow data from Openwater Headset in adult patients.”

The proposed IFU should include information specifying use of the device in the pre-hospital setting to align with its intended use. It should also mention information related to the triage and routing of patients to stroke facilities that are equipped to manage LVO vs. non-LVO patients, if applicable. Therefore, we request that you include these modifications to the IFU statement of the Openwater LVO Stroke Alert to better identify the patient population for which the device is intended to be used for and assist with effective diagnosis of LVO strokes to support the Breakthrough Device designation.

The proposed indications for the Openwater LVO Stroke Alert has been updated to include reference to prehospital settings. Please refer to Section 4 for the updated indications for use statement.

6 Breakthrough Designation Criteria

The two criteria, as noted in sections 515B(b) of the FD&C Act (21 USC 360e-3(b)) were discussed in detail in Q211873 to provide justification that the Openwater LVO Stroke Alert qualifies for the FDA Breakthrough Device program. For ease of review, the same information provided in Q211873 is provided below.

Criterion	Satisfies criterion?	Justification summary
<i>1. Device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions.</i>	Yes	Stroke is a life-threatening and irreversibly debilitating condition that meets all requirements for Criterion 1. The Openwater device provides the potential for more effective diagnosis and treatment of anterior LVO stroke because it quickly (within 5 minutes) can detect such strokes in a pre-hospital acute setting. Such detection can help speed up the patient's access to endovascular therapy, which is critical as delays of 50 minutes to >2 hours are often the difference between good functional neurological outcome and severe disability or death from LVO stroke.
<i>2. Device meets one of the components of the criterion, listed below:</i>		
<i>A. Device represents breakthrough technology;</i>	Yes	There are no prehospital technologies indicated for the accurate diagnosis of anterior LVO stroke. The proposed device can significantly improve the workflow in diagnosing and treating anterior LVO stroke and can help mitigate the life-threatening or irreversibly debilitating conditions by reducing the inherent delays in the current standard-of-care workflows.
<i>B. No approved or cleared alternatives exist;</i>	Yes	Efforts have been made to develop “mobile stroke units” that outfit ambulances with Computed Tomography (CT) imaging devices to detect the presence of LVO and the need for emergent transport for endovascular therapy but are limited due to cost and availability and thus are not standard of care (SOC).
<i>C. Device offers significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization,</i>	Yes	The standard of care requires routing to a closest hospital to get a CT scan often at a hospital not capable of providing endovascular therapy, which can result in >2hrs of transfer time delays. The Openwater solution provides significant advantages over these existing options in that it can be quickly and easily operated by EMS personnel in a pre-hospital acute setting. The device thereby enables notification of transport

Criterion	Satisfies criterion?	Justification summary
<i>improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long term clinical efficiencies; or</i>		for the receiving hospital to be able to prepare in advance for a potential LVO stroke patient in transport as well as improved EMS transport protocols to endovascular therapy capable stroke centers.
<i>D. Device availability is in the best interest of patients.</i>	Yes	Availability of the device is in the best interest of patients, as a prehospital notification can save 50 minutes on average in workflow times per SWIFT PRIME and better routing can potentially reduce significant delays to transfer patients to comprehensive stroke centers. Improving stroke-related workflow is critical, as delays of 50 minutes to >2 hours are often the difference between good functional neurological outcome and severe disability or death from LVO stroke.

6.1 Criterion 1

Per FDA Guidance Document, Criterion 1 requirement is that the “*device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions.*” An analysis of the how the Openwater LVO Stroke Alert satisfies this condition is provided considering the three factors that the Guidance notes, namely

1. *Whether a Device Provides for “More Effective” Treatment or Diagnosis:* FDA believes it is appropriate to consider whether there is a reasonable expectation that a device could provide for more effective treatment or diagnosis relative to the current standard of care (SOC) in the U.S.
2. *Whether a Disease or Condition is “Life-Threatening”:* FDA considers a disease or condition life-threatening if it is a disease or condition for which the likelihood of death is high unless the course of the disease is interrupted.
3. *Whether a Disease or Condition is “Irreversibly Debilitating”:* FDA considers a disease or condition associated with morbidity that has substantial impact on day-to-day functioning to be irreversibly debilitating. Factors such as survival, day-to-day functioning, and the likelihood that the disease or condition, if left untreated, will progress to a more serious disease or condition

Stroke is a life-threatening and irreversibly debilitating condition that meets all requirements for Criterion 1 above. According to the WHO, 2/3 of all stroke patients will die or have irreversible disability. Large vessel occlusions (LVOs) due to acute blockages of the proximal intracranial anterior and posterior circulation account for up to 46% of acute ischemic strokes [Rennert et al., 2019].

The Openwater device provides the potential for more effective diagnosis and treatment of LVO Stroke because it provides earlier detection in a pre-hospital setting that enables notification of transport for the receiving hospital to be able to prepare in advance for a potential LVO stroke patient in transport. A prehospital notification alone has been shown to improve the workflow times upon arrival by 50 minutes as staff and resources can be mobilized in parallel in anticipation of patient transport. In addition, accurate prehospital identification of anterior LVO stroke patients who would be eligible for direct to endovascular routing could support EMS transport protocols that avoid transporting patients to the closest hospital, which can result in >2 hours delay from interfacility transfer time delays. Addressing these workflow issues are critical, as delays of 50 minutes to >2 hours are often the difference between good functional neurological outcome and severe disability or death from LVO stroke.

6.2 Criterion 2

The following is the requirement from the FDA Guidance Document for Criterion 2:

Device meets at least one of the criterion's components below:

Criterion 2.A. *Device represents breakthrough technology.*

Guidance: FDA considers the potential for a device to lead to a clinical improvement in the diagnosis, treatment (including monitoring of treatment), cure, mitigation, or prevention of the life-threatening or irreversibly debilitating condition.

The Openwater device meets the criteria for breakthrough technology as there are no prehospital technologies that are indicated for the accurate diagnosis of anterior LVO stroke. The Openwater device utilize the pulsing of near-infrared laser source that detect changes in interference of the light waves produced (known as laser speckle) over time and utilizes an optimized source-detector separation for collecting the returning photons from the signal that is most sensitive to cerebral brain blood flow changes. Such a device can be quickly and safely used in acute pre-hospital settings to assess whether a patient has an anterior LVO.

Emergent transport for endovascular therapy has now become the standard of care for stroke resulting from anterior LVO, however >55% of LVO stroke patients undergoing thrombectomy are left with a poor outcome of death or severely disabled dependent state. If thrombectomy can be performed within 2.5 hours of LVO stroke onset, there is a >90% chance of a good neurological outcome, with minimal or no deficit. The median loss in net monetary benefit of thrombectomy is calculated to be \$1059 per minute, with every 10 min reduction in average workflow time calculated to result in a \$250 million in savings annually across the US healthcare system. Clinical trials have demonstrated that the time from arrival to arterial access to begin endovascular treatment can be improved by 50 minutes on average when there is a pre-hospital notification that the patient is being transferred from another hospital. These findings highlight the critical need to route patients directly to endovascular therapy as quickly as possible, with significant clinical and economic value in workflow improvements and early notifications. A device that is capable of accurately detecting LVO blood flow abnormalities at the point-of-care would be considered a breakthrough technology.

Criterion 2.B. No approved or cleared alternatives exist.

Guidance: FDA considers whether there is a drug, biological product, or device that has received FDA marketing authorization after premarket review for the same indications being considered (i.e., whether there is an alternative product that FDA has approved, cleared, or licensed, or for which FDA has granted a De Novo request).

There are currently no devices available on the market that can quickly and accurately identify LVO stroke in the pre-hospital setting, and there is a critical need to improve the point-of-care pre-hospital diagnosis and early notification of LVO stroke. While there are no alternatives that are part of the pre-hospital standard of care, the following methods are utilized to address this problem, albeit with limited success:

- Prehospital stroke scores: There are stroke visual assessments that are used to score and classify whether a patient potentially has a stroke, but these have limited efficacy in determining an anterior LVO. While safe to administer, these stroke scales have shown poor sensitivity in actual practice, as low as 38% in some studies (Nguyen et al., 2021) and additionally suffer from particularly poor specificity as low as 20% in some studies (English et al., 2018). They further suffer from their highly variable nature, with poor objectivity across different EMS users. Even when the stroke score is indicative of an ischemic stroke, the score has poor differentiation between an anterior LVO stroke that is refractory to tissue plasminogen activator (tPA) and requires urgent transport to an EVT-capable stroke center, and a non LVO stroke that requires urgent infusion of tPA and thus direct transport to the closest stroke center. As such, the Openwater LVO Stroke Alert would offer significantly improved speed and efficacy in identifying an anterior LVO as compared to prehospital stroke scores (see Section 3) for current clinical performance of this device).
- Mobile Stroke Units (MSU): In hospital settings, a Computed Tomography (CT) scan would be the gold standard to determine the presence of an anterior LVO and as noted in Q211873 submission, efforts have been made to develop “mobile stroke units” that outfit ambulances with CT imaging devices to detect the presence of LVO and the need for emergent transport for endovascular therapy (Czap 2020). While MSUs have been available for over a decade to utilize pre-hospital CT scans, there are only a total of 20 MSU programs currently available in the US, which represents <0.01-0.02% coverage of all US ambulances responding to prehospital stroke assessments, with several studies outlining the prohibitive cost to scaling this solution to a larger number of patients especially in rural areas and globally (Calderon 2018). Even in the exceedingly rare situation where an MSU is available to make a pre-hospital CT scan feasible, 911 alerts to EMS only transmit to MSUs if there is a known likelihood of stroke at the time of dispatch, and in most cases, this is not known until further clinical workup ensues and transport time then becomes key thereby making additional MSU evaluation difficult in most cases. In addition, when MSUs are dispatched, they are always dispatched in addition to the standard ambulance transport because more than 80% of the 911 alerts that do include MSUs do not eventually result in an MSU transport and instead require routine EMS transport (Parker SA 2020).

Furthermore, and perhaps most importantly, a key distinction is that MSUs are being used to evaluate patients who may potentially be eligible to receive intravenous tPA,

whereas the unmet clinical need is for a prehospital diagnostic device with high specificity and sensitivity for LVO, which is refractory to tPA. Thus, the intended usage of the proposed Openwater device is to facilitate clinical interpretations that can expedite the transport of these LVO patients to endovascular-capable centers, which is distinct and not competitive with the goals of MSUs.

Comparatively, the proposed Openwater device would be safer to administer given the use of a Class I laser compared to the radiative effects of a CT scan. The device would also be faster to use with a scan completed in about 5 minutes compared to a MSU workup that takes as much as 37 ± 10 minutes [Parker SA 2020]. The proposed Openwater device is significantly more portable and cost-effective compared to MSUs, thus enabling wider deployment and accessibility. The preliminary evidence of performance (discussed below) indicate that the Openwater LVO Stroke Alert would compare favorably with standard of care CT and MR analyses.

The Openwater solution is easier to use and can assess the presence of an anterior LVO quickly (in less than 5 minutes) thereby enabling improved workflows to manage LVO strokes [Calderon et al., 2018; Czap et al., 2020]. Preliminary evidence of Openwater LVO Stroke Alert supports the reasonable expectation of the potential for technical and clinical success (see Section 3). Note that Openwater LVO Stroke Alert is not intended to replace standard of care for in-hospital evaluation of strokes but to support and speed up existing workflows.

Criterion 2.C. Device offers significant advantages over existing approved or cleared alternatives

Guidance: In determining whether a device meets the criterion of offering “significant advantages over existing approved or cleared alternatives,” FDA considers the potential, compared to existing approved or cleared alternatives, “to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients’ ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies.”

The standard of care requires routing to a closest hospital to get a CT scan often at a hospital not capable of providing endovascular therapy, which can result in >2hrs of transfer time delays. Recently, the FDA has approved Artificial Intelligence (AI)-based algorithms that automatically detect imaging features on CT and MRI that indicate the probability of an underlying LVO (K200941 Rapid LVO, DEN170073 Viz.AI Contact) for the purpose of generating alerts that can improve the workflows in LVO stroke care. While CT and MR imaging technologies have been able to support the use of AI-enabled LVO stroke detection algorithms (Viz.AI Contact, Rapid LVO), these diagnostics require transport to a specialized imaging suite, use of intravenous contrast agents, and do not provide the prehospital diagnosis needed for early notification and improved routing decisions that expedite time to endovascular therapy.

The closest existing alternatives is the development of mobile stroke units, that outfit ambulances with Computed Tomography (CT) imaging devices to detect the presence of LVO. As discussed in Criterion 2.C above, these units are limited in availability due to the expense and the expertise needed to operate them.

The Openwater solution provides significant advantages over these existing options in that it can be quickly and easily operated by EMS personnel in a pre-hospital acute setting. The device enables notification of transport for the receiving hospital to be able to prepare in advance for a potential LVO stroke patient in transport as well as improved EMS transport protocols to endovascular therapy capable stroke centers.

Criterion 2.D. Device availability is in the best interest of patients.

Guidance: In determining whether the device meets the criterion “availability [of the device] is in the best interest of patients,” FDA considers whether the proposed device and indications for use provide another type of specific public health benefit.

Availability of the device is in the best interest of patients, as a prehospital notification can save 50 minutes on average in workflow times per SWIFT PRIME. More importantly going to the closest hospital to get neuroimaging can create >2hr delay in getting rerouted to endovascular therapy due to interfacility transfer time delays. Time to endovascular therapy is the most important determinant of outcome and why >55% of LVO stroke patients undergoing thrombectomy are left with a poor outcome of death or severely-disabled dependent state – whereas if thrombectomy can be performed within 2.5 hours of LVO stroke onset, there is a >90% chance of a good neurological outcome, with minimal or no deficit.

The median loss in net monetary benefit of thrombectomy is calculated to be \$1059 per minute, with every 10 min reduction in average workflow time calculated to result in a \$250 million in savings annually across the US health care system. Clinical trials have demonstrated that the time from arrival to arterial access to begin endovascular treatment can be improved by 50 minutes on average when there is a pre-hospital notification that the patient is being transferred from another hospital. These findings highlight the critical need to route patients directly to endovascular therapy as quickly as possible, with significant clinical and economic value in workflow improvements and early notifications. A device that is capable of accurately detecting LVO blood flow abnormalities at the point-of-care would be considered a breakthrough technology.

In summary, based on the analysis above, Openwater believes that this technology satisfies both criterion 1 and criterion 2 (conditions A, B, C, and D) of the Breakthrough Device criteria as defined in sections 515B(b) of the FD&C Act (21 USC 360e-3(b)).

7 Proposed Clinical Testing

Openwater LVO Stroke Alert is still in development and the specific methods to clinically validate the device will require refinement as additional data is gathered. However, a preliminary proposed plan is discussed in this section.

The Openwater LVO Stroke Alert algorithm will be validated following similar procedures as other recent FDA-approved LVO AI software (DEN170073 Viz.AI ContaCT) cleared for detecting LVO stroke using blood flow feature data.

Briefly, in DEN170073 Viz.AI ContaCT, a retrospective analysis was performed on a set of blood flow image feature data containing digital representations of CT imaging data and contrast patterns of blood flow, with approximately equal numbers of positive and negative cases (feature sets with LVO and without LVO, respectively, as categorized by an expert neuro-radiologist). All feature data had been obtained from patients who were older than 22 years of age when presenting to the healthcare facility, with CTA performed during a stroke protocol assessment. The underlying feature data produced by each study was uploaded into the ContaCT algorithm, and then processed and analyzed. When the ContaCT AI algorithm identified a suspected LVO stroke from the feature data on the basis of asymmetric blood flow evident within the underlying digital representations of the CT imaging data and contrast patterns of blood flow, it generated a notification alert. A log of notifications was maintained and compared with respect to the Ground Truth neuro-radiologist diagnosis for each case. Each case was classified based on the following table:

		Device Output (Recommends Urgent Review)	
		Yes	No
Ground Truth (Emergent Review Recommended)	Yes	True Positive (TP)	False Negative (FN)
	No	False Positive (FP)	True Negative (TN)

For the Viz.AI ContaCT DEN170073, the validation was performed with a primary analysis of Sensitivity and Specificity. The sensitivity and specificity of the software device performance was calculated using two-sided 95% Clopper-Pearson confidence intervals. Sensitivity was calculated as follows: TP / (TP+FN) while Specificity was calculated as follows: TN / (TN+FP).

Openwater will follow the similar procedures to validate the LVO Stroke Alert software, following the above process for validating automated LVO detection in underlying blood flow feature datasets for the FDA. Briefly, a sample cohort will be prospectively enrolled at a Comprehensive Stroke Center that matches the cohort design used in DEN170073, i.e., including equal numbers of acute anterior LVO stroke patients (ICA or proximal M1 occlusion) eligible for emergent thrombectomy workflows, and other acute in-hospital stroke code patients with negative neuroimaging for LVO, as confirmed by gold-standard neuroradiology reading of CT angiogram and/or catheter-based angiogram. This will be done prospectively so that in addition to the gold standard imaging data, the Openwater Headset data will be acquired on all patients during the acute evaluation of these patients undergoing stroke code workup and/or endovascular therapy. Openwater LVO Stroke Alert will analyze the data collected from Openwater Headset and an analysis of its performance to detect the presence and absence of an anterior LVO will be evaluated.

8 Data Development Plan

The following is a summary list of ongoing and proposed clinical studies.

Stage	Study location	Sample size	Device	Details	Status
Feasibility	Hartford Healthcare	N=34 healthy volunteers	Gen 1A - Wand prototype	Openwater prototype wand, core technology feasibility testing. Baseline of healthy subjects.	Complete
Feasibility	Hartford Healthcare neuroICU Stroke Study	N=4 LVO N=3 non-LVO stroke N=30 healthy volunteers	Gen 1B - Wand prototype	Openwater prototype wand, core technology feasibility testing	Complete
Feasibility	UPenn	N=25 healthy volunteers	Gen 2 – Headset	TCD/Optical comparison to characterize correlation between speckle and TCD CBFv	Complete
Feasibility	UPenn, Brown	N=68 LVO N=90 non-LVO stroke code	Gen 2 – Headset	Study to detect LVO	Complete
Validation	TBD Comprehensive Stroke Center	N=TBD Equal number of anterior LVO stroke, and in-hospital control stroke code mimics	Openwater Headset + Openwater LVO Stroke Alert	Openwater Headset + LVO Stroke Alert algorithm, sensitivity, and specificity efficacy testing	Proposed

The following table provides a summary of the proposed study to validate the OpenWater LVO Stroke Alert. The structure and methods of this study are discussed in detail in Section 7.

<i>Title</i>	Optically-Detected Cerebral Blood Flow Features at the Point-of-Care for Automated LVO Stroke Alert
<i>Purpose</i>	Evaluation of Openwater LVO Stroke Alert to support a de novo submission.
<i>Study Design</i>	Prospective cohort control design
<i>Study Population</i>	Acute stroke patients, equal population of confirmed anterior LVO stroke patients versus non-LVO stroke code mimics

<i>Inclusion Criteria</i>	<ul style="list-style-type: none">• Patients meeting all of the following criteria will be included:• All genders• Adults (aged greater than and including 18)• Patient being evaluated as part of acute ischemic stroke workup, eligible for referral for endovascular therapy if confirmed LVO of the ICA or M1 on CT angiography and/or catheter-based angiogram
<i>Exclusion Criteria</i>	<ul style="list-style-type: none">• Non-adults (aged < 18 years)• Aged >99 years• Pregnant women• Patients outside the acute setting with stroke onset > 24 hours prior, or unknown stroke onset• Absence of confirmatory imaging (as per inclusion criteria definition)
<i>Safety Endpoints</i>	Safety, adverse events
<i>Effectiveness Endpoints</i>	Sensitivity and specificity for classification relative to gold-standard, LVO stroke neuroimaging
<i>Follow-up Schedule</i>	No follow-up schedule required

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10 List of Attachments

A1 Headset Placement Guide

Provides instructions on how to appropriately place the headset on a subject, as used in current clinical studies.

A2 Comparative Analysis of TCD to Speckle Contrast

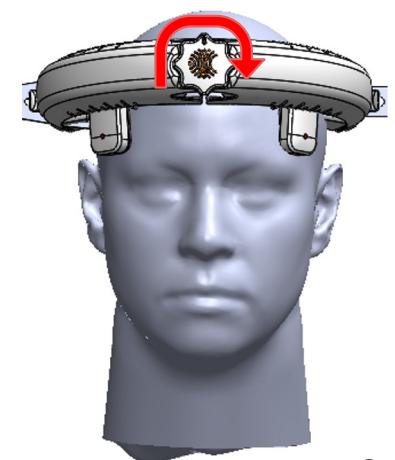
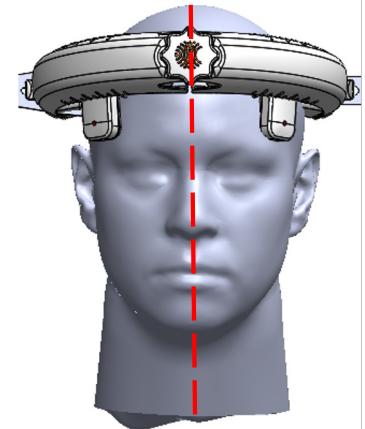
Provides the results of the study comparing CBFv waveforms obtained using a transcranial ultrasound doppler to concurrently recorded Openwater Headset speckle contrast waveforms.

Headset-Placement Guide

Openwater

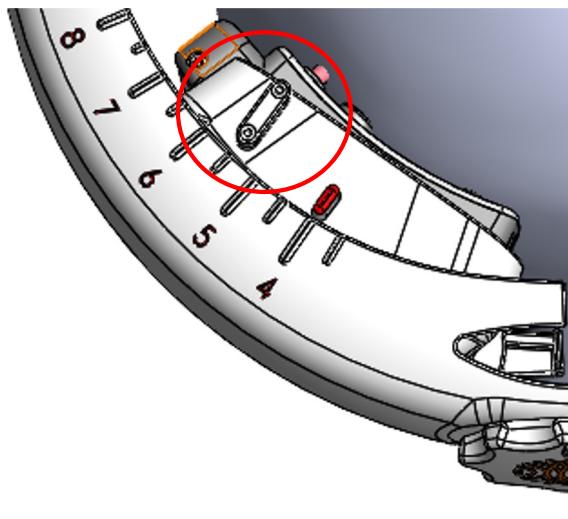
How to place and fit the headset

1. Pull hair back from forehead with provided hair band,
2. Wipe with antiseptic cloth
3. Set dial to position 4 on headset
4. Slide headset on patient head loosely, with the dial centered medially
5. Headset should be perpendicular to forehead surface (it is ok to have a tilt in visor relative to eyebrow plane)
 - a. Ensure all optodes touch skin not hair
6. Holding visor Tighten head strap left and right to get a firm, secure fit without being too tight (stable even with slight head movement)
7. Pull back headset and place it back gently so force is evenly distributed between the two sides
8. Fine tune dial between positions 3.5 and 6
9. Headset must be below hairline by .5 to 1 mm and can touch the outer eyebrows
 - a. Some people have a bigger “landing area” than others
10. Recheck medial symmetry and sensor contact to skin
11. Reseat headset by pulling back visor and lightly replace, this assures the symmetric loading on both sensors
12. Initiate headset “contact” check on the screen
 - a. Reseat headset and dial adjustment if poor their is poor sensors contact (red, not green)

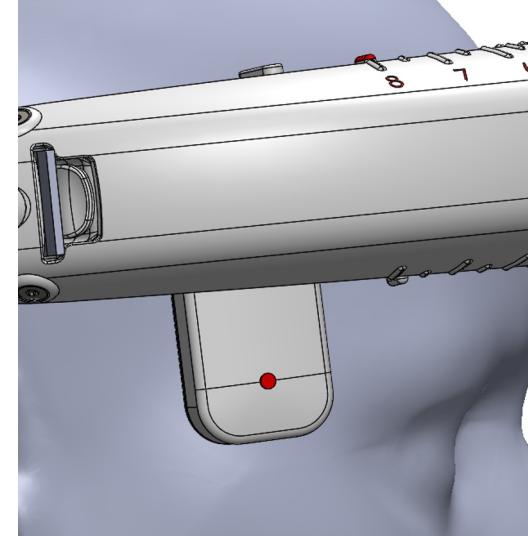


Proper placement - indicators

- Headset should be placed so that optodes are not in the hairline:
- Visible indicators
 - Cable clamp is directly above laser (left)
 - Red dot is the locations of the vertical camera (right)



Confidential



Idealized optode points

- Laser source position
- Camera sensor position



Optode imprint from subject



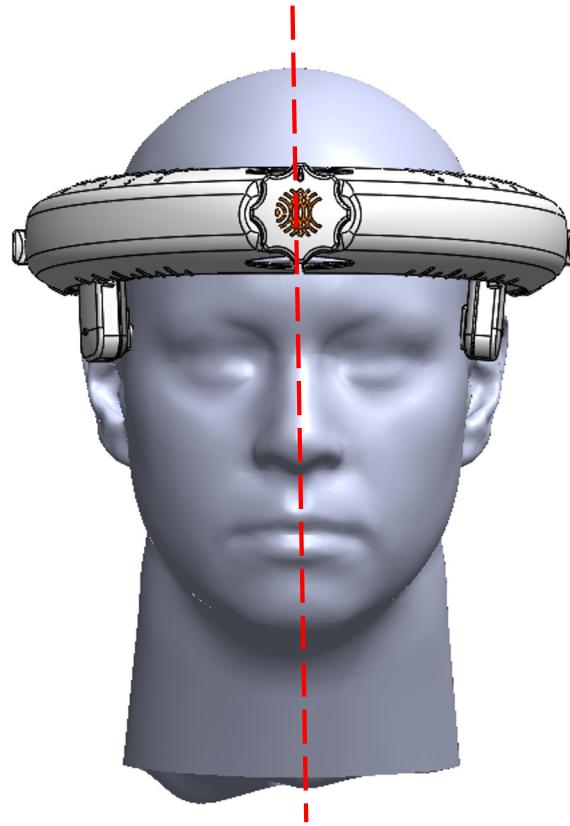
Confidential

Prep forehead

- If patient has long hair assure that hair is pulled back with hair band supplied
- Make sure forehead is clear of hair, wipe with antiseptic cloth

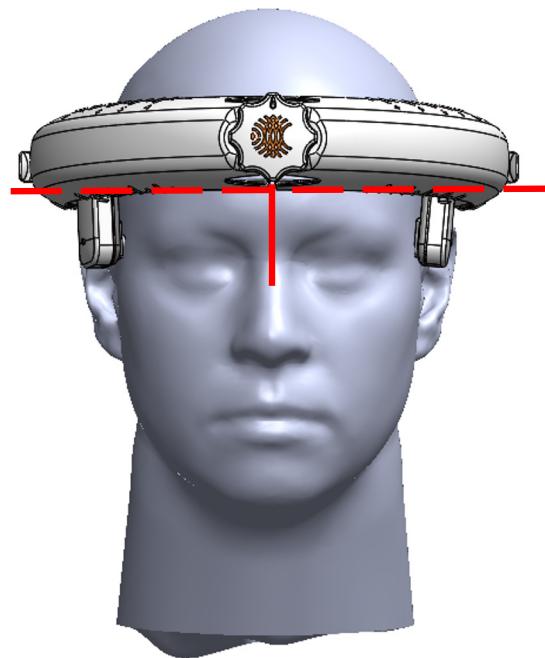
Slide on headset

- Slide headset on patient head loosely
- Center dial on patient nasal plane
- Very important to keep centered



Proper placement

- Headset should sit high on the forehead with sensors dial set as wide as possible without indicators (see next slide) being in the hairline
- It is critical that the headset sits perpendicular to midline and not at an angle

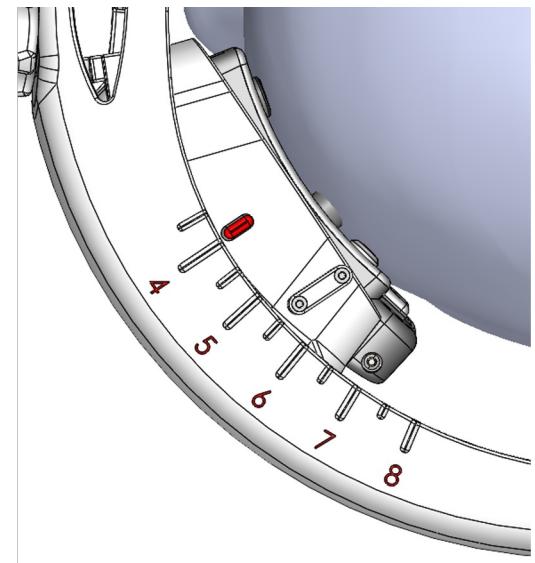
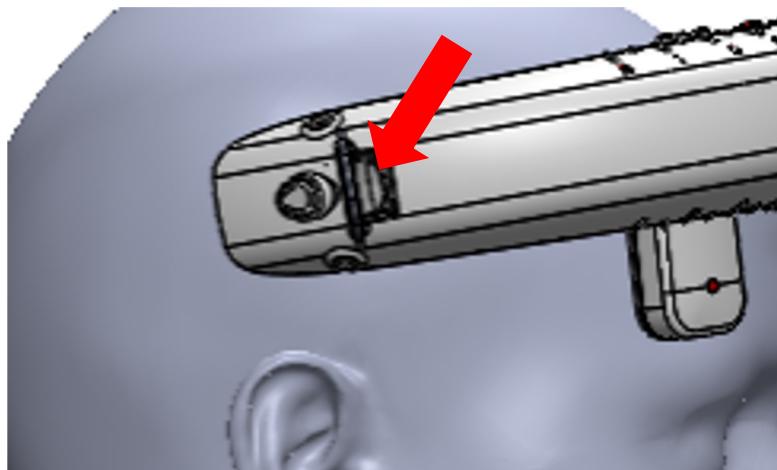


Run headset test button

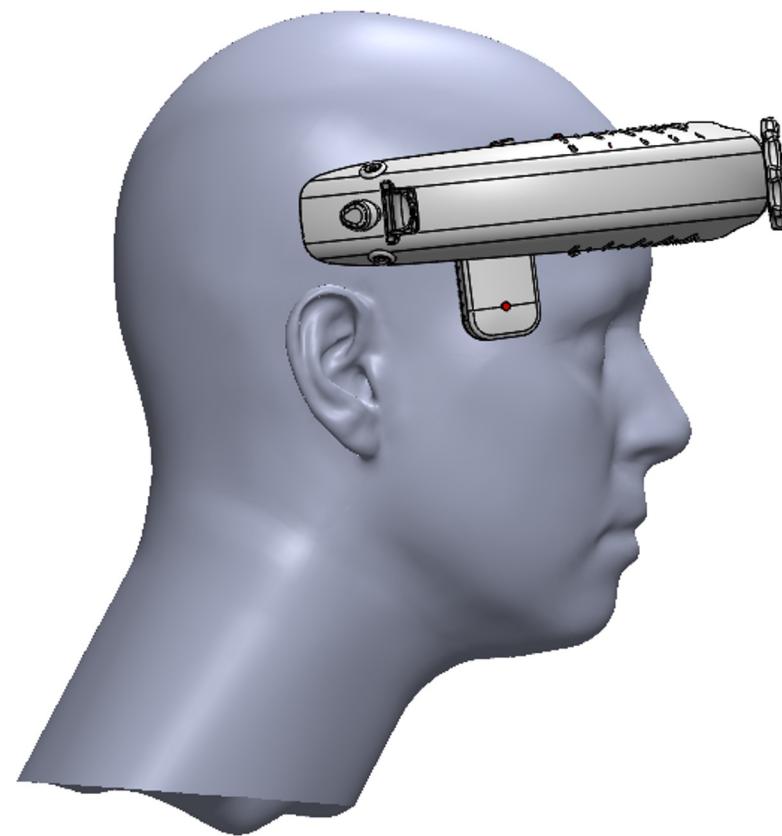
Realign or fine tune adjustment if all sensors are not lit green

Removal

1. Before removing headset, record position number that red tick mark aligns to on headset to nearest $\frac{1}{4}$
2. To remove head strap, release the latch tab by pushing towards dial on headset, both sides and slide off



Side view



Landing area on forehead

Tape is the hairline or “keep out” area



Confidential

Non-invasive cerebral hemodynamic monitoring during hypercapnia: validating a novel optical blood flow monitor

INTRODUCTION

A key element of cerebrovascular health is the ability to supply sufficient blood flow to meet the tissue's metabolic demand. Cerebrovascular reactivity (CVR) approximates this capacity by quantifying the increase in cerebral blood flow (CBF) in response to a vasoactive stimulus. Across a range of cerebrovascular and cardiovascular disease states, CVR impairment reflects an increased risk of stroke. Exposure to chronic CVR impairment also increases the risk of brain atrophy and cognitive decline in patients. Beyond its clinical utility, CVR testing provides a large change in CBF, which in turn presents an opportunity to validate novel instruments aimed at quantifying CBF.

A wide range of imaging modalities can be used to quantify CBF during CVR testing. Advanced imaging modalities such as O¹⁵-positron emission tomography, single-photon emission tomography, and advanced MRI techniques provide reliable CBF quantification. However, advanced imaging is logistically impractical and unavailable at many centers. In contrast, transcranial Doppler ultrasonography (TCD) is widely available, inexpensive, non-invasive, and can be easily deployed at the bedside. TCD has thus emerged as the most commonly used tool for CVR testing. TCD provides a measure of cerebral blood flow velocity (CBFv), rather than CBF, but this limitation is mitigated by the fact that changes in velocity are proportional to changes in flow, assuming the arterial diameter remains unchanged. TCD has been validated against a range of other CBF imaging modalities in CVR testing, justifying its routine use in both clinical practice and clinical research. However, TCD imaging requires a qualified technologist and an adequate temporal acoustic window, which may be absent in nearly 20% of the population and may disproportionately affect females. Thus, there is a need for alternative non-invasive tools to measure CBF at the bedside. Biomedical

optimal imaging techniques are particularly appealing. Cerebral oximetry based near-infrared spectroscopy (NIRS) is widely available and has been used as a surrogate of CBF, but changes in the NIRS signal may not mirror changes in CBF if there are fluctuations in arterial oxygen saturation or cerebral metabolism, which may be a particularly relevant limitation in cerebrovascular disease states. The NIRS signal is also contaminated by scalp blood flow and may therefore describe a combination of systemic and cerebral hemodynamics.

In this study, we aim to evaluate the Openwater headset - a novel, low-cost, wearable optical system that leverages measurements of laser speckle contrast to continuously monitor microvascular CBF. Here, we use CVR testing in healthy volunteers to provoke a large shift in CBF, which provides a means for validating the Openwater headset by comparison with TCD.

METHODS

Participants

Healthy individuals between the ages of 18 and 45 were eligible to participate. Subjects were excluded if they had a history of hypertension, type-2 diabetes, hyperlipidemia, heart failure, stroke, cerebrovascular abnormality, intracranial mass lesion, or skull defect with could interfere with TCD monitoring at the temporal region. The study protocol was approved by the University of Pennsylvania Institutional Review Board, and all study procedures were conducted in accordance with the ethical standard of the Helsinki Declaration. All study participants provided written informed consent prior to any study procedures. The study conforms to STROBE guidelines for observational studies.

Transcranial Doppler Ultrasonography

CBFv was assessed using a Multigon Industries® TCD system (Elmsford, NY). The left middle cerebral artery (MCA) was insonated via the trans-temporal window at a depth of 40-65 mm. The vessel was confirmed by its characteristic depth range, Doppler signal, direction, and velocity. To ensure signal stability for the duration of the monitoring period, a 2MHz TCD probe was secured directly to the Openwater® headset using a custom clamp designed to facilitate continuous vessel insonation, while minimizing motion induced artifacts or signal loss. MCA waveform and beat-to-beat mean CBFv were recorded at 125 Hz and synchronized with optical data.

Optical Blood Flow Instrumentation

The hemodynamic measurement device (Openwater, CA) consists of a wearable headset and a console. The headset contains two modules that are positioned at symmetric locations on either side of the head on the surface directly overlying the vascular territories of the anterior circulation of the brain. Each module contains a built-in optical fiber for the delivery of low power laser light to the subject, as well as CMOS (complementary metal oxide semiconductor) image sensors utilized for the measurement of light from the subject. The console contains the laser, electronics, touchscreen, and computer.

The source fiber in each module emits pulses of highly coherent near-infrared laser light near the isospecfic point for hemoglobin (785 nm, 400 uJ, 250 us) at a rate of 40 Hz. After passing through the subject's tissue, the light pulses are collected by an aperture in the module at a distance of 35 mm from the source position. By pulsing the laser light, we are able to sample the dynamics of the sample on the same time scale as the decay of the temporal auto-correlation function, while at the same time collecting sufficient light to enable a long source detector separation. Using a long source detector

separation increases the sensitivity of the measurement to deeper tissue [Fabbri et al. 2004]. Making the laser pulse width closer to the autocorrelation decay time increases the amount of change in speckle contrast with respect to small changes in flow, resulting in a more sensitive measurement [Yuan et al. 2005]. Note, this time scale is much shorter for multiply scattered light which samples below the tissue surface than it is for single scattered light which is reflected from the tissue surface light as is done with laser speckle imaging [Pine et al. 1990, Boas et al. 1997].

Cerebrovascular Reactivity Protocol

All studies were conducted in a single examination room within the Neuro-diagnostic suite at the Hospital of the University of Pennsylvania. The room was quiet and temperature controlled (23°C) throughout the duration of monitoring. Subjects were positioned in a hospital stretcher with the head-of-bed elevated to 45°. The Openwater headset was placed on the participant's head to ensure the optical probes were along the upper border of the forehead. The headset size was adjusted using a built-in dial to ensure the optical probes were on the lateral margin of the forehead (while avoiding hair). The TCD probe was then secured to the Openwater headset via an adjustable clamp in order to insonate the left MCA. TCD and optical data were synchronized at the beginning of each subject's monitoring session.

After 1-minute of baseline data, a 30-second breath hold was completed. The breath-hold was initiated at the end of expiration to avoid pre-oxygenation and elicit a more reliable hypercapnic response. After 2 minutes of rest, another 30-second breath-hold was completed. The first breath-hold was used for analysis, but if the subject was unable to perform the breath-hold or if there was signal loss with either imaging modality, the second breath-hold could be used.

Optical and TCD Waveform Analysis

We used three metrics to compare the measured optical speckle contrast and TCD blood velocity waveforms: average value, pulsatile index, and waveform morphology. In order to make these comparisons, data processing was done as follows.

For each image acquired on the CMOS sensor, we calculated the mean intensity I and variance σ^2 of the digital values of the pixels on the sensor. A small offset corresponding to the mean intensity value of the sensor when the laser was off was subtracted from the mean. Likewise, offsets corresponding to shot noise and read noise were subtracted from the variance. We then calculated the speckle contrast C for each image as $C = \sqrt{\sigma^2}/I$. We then subtracted an offset from the contrast corresponding to the contrast measured when a temporally incoherent light source was used.

The resulting speckle contrast and mean intensity values which were acquired at 40 Hz were then upsampled to 125 Hz in order to enable comparison with the 125 Hz TCD data. An algorithm identified the starting time just prior to systole of each individual pulse in both the optical and TCD waveforms. For each pulse, we then calculated 3 metrics resulting in a time-series for each of these metrics for both the optical and TCD data. These metrics were the mean value, the pulsatility index (i.e., $PI = (maximum - minimum)/mean$), and the duration. Maximizing the normalized cross-correlation between the speckle contrast and TCD pulse duration time-series was then used to align the optical and TCD time-series such that the optical and TCD data for each pulse could be compared.

For each time-series, a baseline value was calculated as the average across 30 seconds prior to initiation of the breath-hold. The relative change from baseline for each time-series was then calculated as:

$$rContrast(t) = 1 - \frac{C(t) - C_{baseline}}{C_{baseline}}$$

$$rCBFv(t) = 1 + \frac{CBFv(t) - CBFv_{baseline}}{CBFv_{baseline}}$$

$$rPI_{Contrast}(t) = 1 - \frac{PI_{Contrast}(t) - PI_{Contrast_Baseline}}{PI_{Contrast_Baseline}}$$

$$rPI_{CBFv}(t) = 1 + \frac{PI_{CBFv}(t) - PI_{CBFv_Baseline}}{PI_{CBFv_Baseline}}$$

Note the change in sign of the optical (i.e., speckle contrast) vs. the doppler ultrasound formulas is due to the fact that speckle contrast decreases when blood flow increases.

The resulting optical and TCD time-series were compared in two ways. First, we calculated the correlation between the optical and TCD time-series on a point-by-point basis. Second, we calculated the correlation between optical and TCD for the maximal change between start and the end of the breath hold. The starting value was calculated as the average value of data 5 seconds before and after the start of the breath hold. The ending value was calculated as the maximum (for mean values) or minimum (for PI) value within 5 seconds before and after the end of the breath hold.

We also compared the morphology between the speckle contrast and TCD waveforms. After waveforms for both modalities were divided into individual pulses and aligned in time, each pulse was then normalized such that its first and last point were zero and its highest value was one. Approximately 30 seconds of pulses just prior to the hold and 10 seconds just after the hold were averaged together in order to provide pulses used for final analysis (Fig. 3 B-I). In a few subjects, motion artifacts after the end of the

breath hold made TCD waveforms too noisy for this analysis. For these cases, 10 seconds of data was selected from up to 15 seconds before the end of the breath hold in order to provide an averaged waveform. From these averaged pulses, three peaks were dissected (Fig. 3 B): (1) Peak 1 represents ejection of blood from the left ventricle, (2) peak 2 represents the pulse wave reflected by the closing aortic valve, and (3) peak 3 represents the diastolic flow. The ratio of peak 2 to peak 1, which is a measure of cerebrovascular stiffness, was calculated for baseline and hypercapnia. The change in P2/P1 between baseline and the end of the breath hold was then compared between optical and TCD as shown in Fig. 4.

RESULTS

Of the 25 subjects who completed the monitoring protocol, three were excluded due to poor TCD data quality and 22 were included in the final analysis. Of the 22 included subjects, 21 successfully completed the first breath-hold for the analysis. After a brief rest, the other subject completed an adequate repeat breath-hold which was included in the analysis. The study protocol was well tolerated without any adverse events. The average age was 33.3 years (standard deviation of 8.3 years), 68% were female and 32% were male, the average Fitzpatrick scale of the subjects was 1.8.

Correlations were strong for all three metrics. As shown in Figure 1, for the full time-series analysis comparing percent changes in average values of rContrast and rCBFv, the Pearson correlation was 0.79 for the aggregate of all subjects' data, the average and standard deviation of the subjects' individual correlation values was 0.82 ± 0.18 , and the average difference between rContrast relative to rCBFv was +5.8 %. Maximal effect analysis comparing percent changes in average values of rContrast and rCBFv resulted in a higher Pearson correlation of 0.88, and an average difference between rContrast relative to rCBFv of +5.0 %.

As shown in Figure 2, for the full time-series analysis comparing percent changes in the pulsatility index of rContrast and rCBFv, the Pearson correlation was 0.54 for the aggregate of all subjects' data, the average and standard deviation of the subjects' individual correlation values was 0.48 ± 0.23 , and the average difference between rContrast relative to rCBFv was only -0.6 %. Maximal effect analysis comparing percent changes in the pulsatility index of rContrast and rCBFv resulted in a higher Pearson correlation of 0.82, and an average difference between rContrast relative to rCBFv of only +0.8 %.

Figure 3 illustrates the visual agreement between rContrast and rCBFv waveform morphology. On the left (Figure 3b, c, f, g), average waveforms from an individual with a large morphology response to the breath hold are shown. At baseline, both rContrast and rCBFv have three distinct peaks, and the first two peaks are of similar height. Post breath hold, both modalities show a similar change with a dominant second peak. On the right (Figure 3d, e, h, i), average waveforms from an individual with a small morphology response to the breath hold are shown. For this subject, the first peak is substantially larger at baseline and the second peak increases modestly post breath hold for both rContrast and rCBFv. The quantitative analysis of waveform morphology in Figure 4 shows that the ratio between the first two peaks of the waveform (i.e., P2/P1) increases during the breath hold. This morphological change was seen in both modalities for 21 of the 22 subjects. For the P2/P1 ratio, the Pearson correlation between rContrast and rCBFv was 0.85 for the aggregate of all subjects' data, and the average difference between rContrast relative to rCBFv was only +0.07.

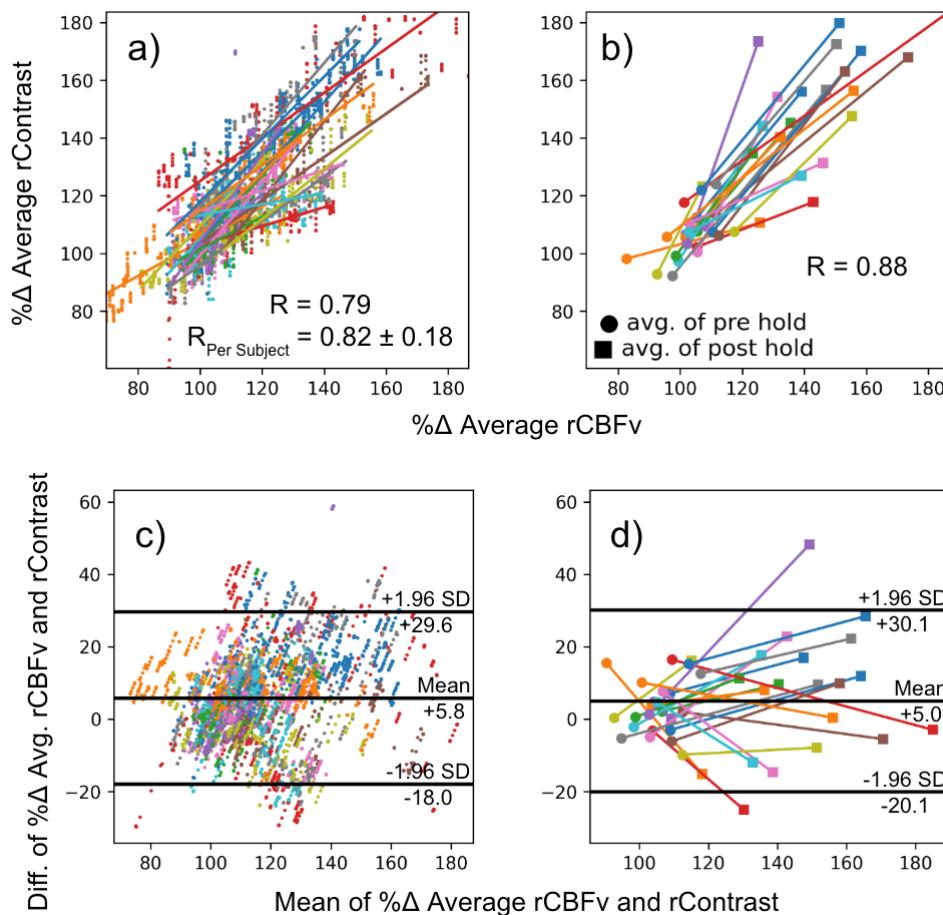


Figure 1. Changes in average rContrast and average rCBFv throughout breath hold are well correlated as demonstrated by (a) full time-series analysis comparing percent changes for each pulse, (b) maximal effect analysis comparing percent changes from before and after the breath hold, and (c-d) Bland-Altman plots corresponding to plots (a-b). For the full time-series analysis in (a), Pearson correlations are shown for both the aggregate of all subjects and the average \pm standard deviation of the individual subjects. Individual linear regressions are plotted for each subject.

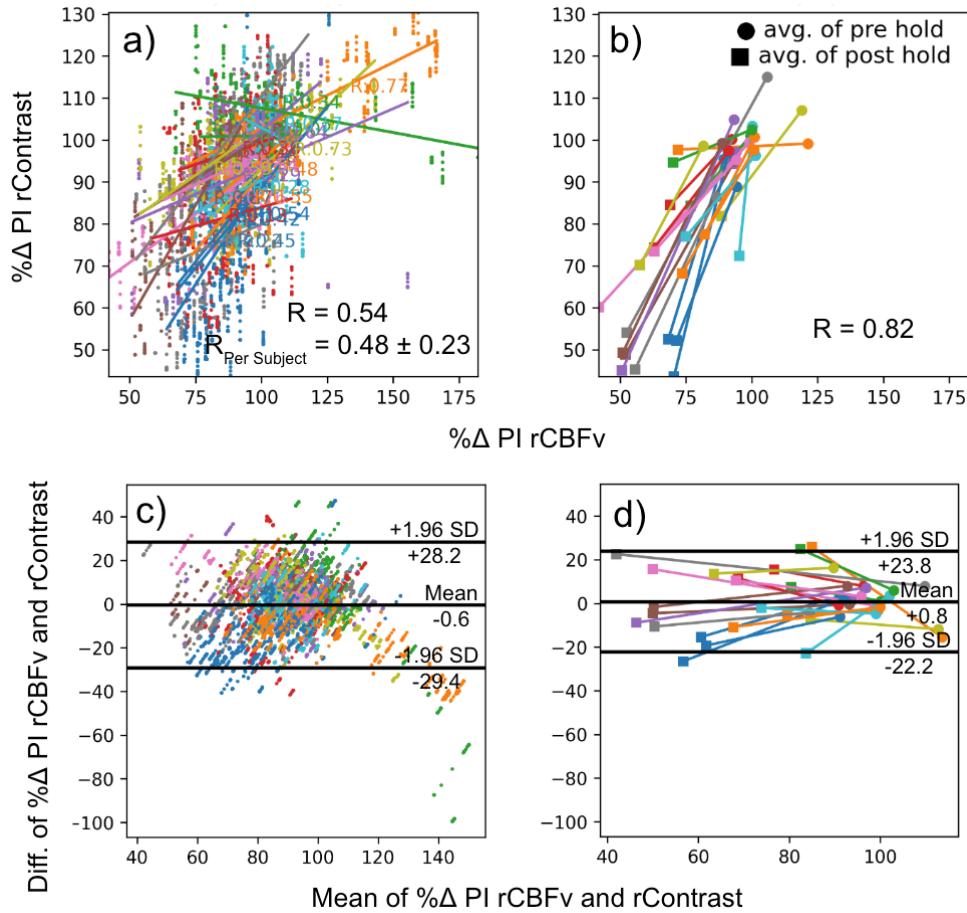


Figure 2. Changes in relative pulsatility index for Contrast and CBFv throughout breath hold are well correlated as demonstrated by (a) full time-series analysis comparing percent changes for each pulse, (b) maximal effect analysis comparing percent changes from before and after the breath hold, and (c-d) Bland-Altman plots corresponding to plots (a-b). For the full time-series analysis in (a), Pearson correlations are shown for both the aggregate of all subjects and the average \pm standard deviation of the individual subjects. Individual linear regressions are plotted for each subject.

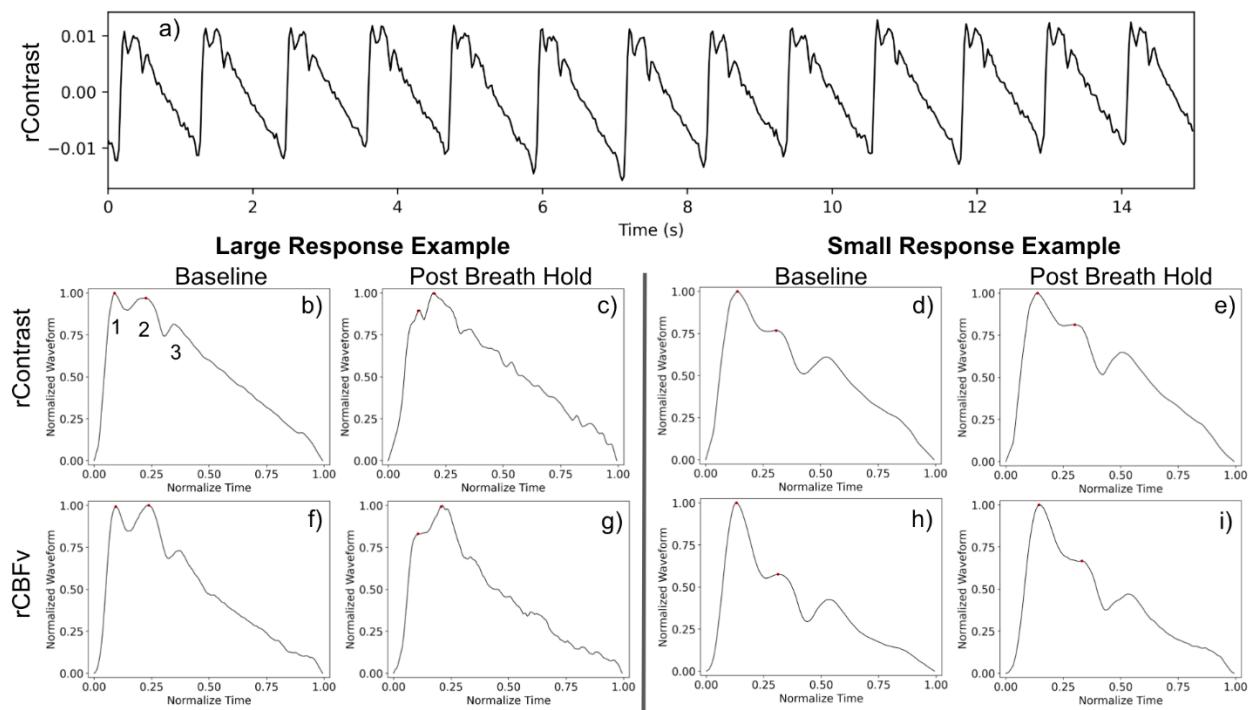


Figure 3. Morphology changes between before and after the breath hold are similar for both rContrast and rCBFv. (a) Example of a rContrast time trace. This time trace was used to generate the average waveform in (b) in which the three peaks used for the analysis are shown. Average waveforms from an individual with a large morphology response are shown for (b) rContrast at baseline, (c) rContrast post breath hold, (f) rCBFv at baseline, and (g) rCBFv post breath hold. Both rContrast and rCBFv have three distinct peaks at baseline, and change to having a dominant second peak post breath hold. Average waveforms from an individual with a small morphology response are shown for (d) rContrast at baseline, (e) rContrast post breath hold, (h) rCBFv at baseline, and (i) rCBFv post breath hold. For this subject, the first peak is substantially larger at baseline and the second peak increases modestly post breath hold for both rContrast and rCBFv.

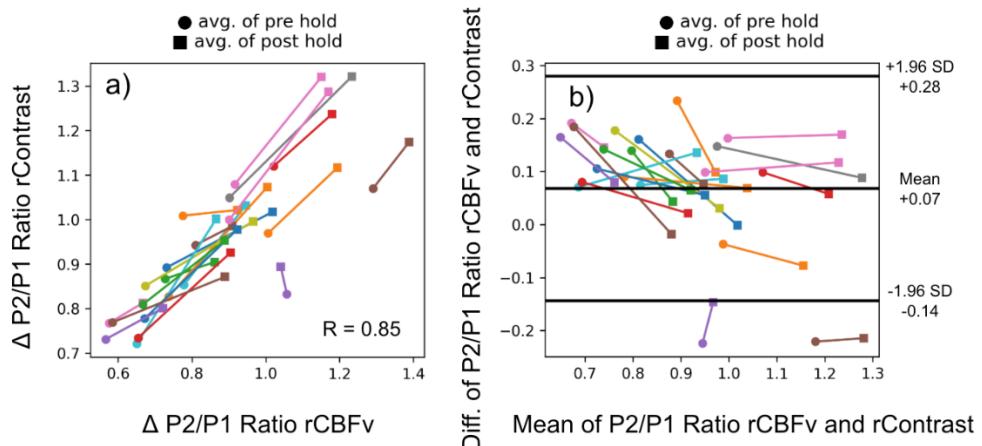


Figure 4. Changes in the waveform P2/P1 ratio correlate well between rContrast and rCBFv as demonstrated by (a) percent change and (b) Bland-Altman plots of the maximal effect between P2/P1 ratios at baseline and post breath hold.

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Acknowledgement Letter

08/15/2023

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Dear Prabhu Raghavan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your submission. This submission has been assigned the unique document control number below. All future correspondence regarding this submission should be identified prominently with the number assigned and should be submitted to the Document Control Center at the address listed below. Failure to do so may result in processing delays. If you believe the information identified below is incorrect, please contact the Office of Product Evaluation and Quality (OPEQ) submission support at (301) 796-5640 or OPEQSubmissionSupport@fda.hhs.gov.

Submission Number: Q211873/S001

Received: 08/15/2023

Applicant: Openwater

Device: Openwater LVO Stroke Alert

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