Breakthrough Device Designation Request

for

Openwater LVO Stroke Alert

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1 Background

According to the World Health Organization, every year over 15 million people suffer a stroke, 5 million of whom die and another 5 million are left permanently disabled (World, 2002). In the United States alone, there is one new stroke approximately every 30 seconds, 87% of which are acute ischemic strokes (AIS) (Virani et al., 2020). Due to the rapid loss of brain tissue during stroke, emergent diagnosis and treatment is critical for improving stroke outcomes (Silva & Nogueira, 2020).

Large vessel occlusions (LVOs) due to acute blockages of the proximal intracranial anterior and posterior circulation account for up to 46% of 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.

Despite these advances, long term outcomes after endovascular therapy demonstrate that >55% of LVO patients undergoing thrombectomy are left with a poor outcome of death or severely disabled dependent state (McCarthy et al., 2019). However, 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 (Goyal et al., 2016).

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 median loss in net monetary benefit of thrombectomy is calculated to be $1059 per minute, with every 10-minute reduction in average workflow time calculated to result in a $250 million in savings annually across the US healthcare system (Kunz et al., 2020). These findings highlight the critical impact a pre-hospital LVO stroke alert can have on post-hospital arrival workflows, as with advance notification the receiving hospital teams and resources can be mobilized in preparation for the patient ahead of time, in parallel to transport. As such, generating pre-hospital LVO stroke alerts in and of themselves would have significant clinical benefit in reducing post-hospital arrival workflows by 50 minutes on average, which would amount to an estimated $1.25 billion in savings annually across the US healthcare system.

1.1 Challenges in the current standard of care LVO Stroke workflow

Figure 1 shows the typical standard of care workflow in detecting and treating an LVO stroke. Individuals who call 911 upon observing stroke-like symptoms are evaluated at the location by Emergency Medical Services (EMS) and taken by ambulance to the closest hospital or primary stroke center (PSC) to get neuroimaging. The recent success of 5 endovascular randomized control trials (RCTs) has changed best practice guidelines to include endovascular therapy (EVT) for patients with an anterior LVO stroke. However, EVT is only offered at a limited number of advanced endovascular capable centers (ECCs), which makes access to this highly beneficial therapy difficult for patients who are outside the catchment area of an ECC. Given the finding that >55% of patients in EVT RCTs had poor long-term outcomes of severe morbidity or death, whereas >90% of patients had good neurological outcomes with minimal to no deficits if they received EVT within 2.5 hours of onset, there is a critical need to get patients to an ECC as soon as possible. Currently however patients are routed to closest hospital or PSC for initial workup, which often is not capable of providing EVT, resulting in significant delay in care due to interfacility transfer time delays (Southerland et al., 2016).

Southerland et al recently modeled the benefit of EMS transport directly to ECC versus the interfacility transfer delays that result from routing through closest hospital that is a non-endovascular capable center (nECC) and found the median delay of onset to reperfusion as a consequence of stopping at nECC was over 2 hours on average from SWIFT-PRIME (presented at ESOC, Glasgow, 2015). This highlights the clear benefit of direct to ECC routing since the delay for stopping at nECC for the purpose of neuroimaging would almost always result in the patients falling outside the optimal window of within 2.5 hours identified in SWIFT-PRIME. This has resulted in many experts (Southerland et al., 2016) advocating patients not be transferred to primary stroke centers (PSCs) in favor of direct to comprehensive stroke center (CSC) routing arguing “that we bypass the PSC and transport LVO patients directly to the CSC.” If a pre-hospital LVO stroke alert were available, improved EMS routing decisions can be made to consider direct to ECC routing in order to address the median delay to reperfusion of over 2 hours on average that occurs as a consequence of stopping at nECC for triage neuroimaging (Southerland et al., 2016) as well as enabling advance notification of the receiving hospital teams so that resources can be mobilized in preparation for the LVO stroke patient ahead of time.

As such, there is a great unmet need for early detection of anterior LVO from ICA and M1 occlusions in the prehospital setting to improve early notification and direct-to-endovascular capable center routing times in order to improve patient outcomes.

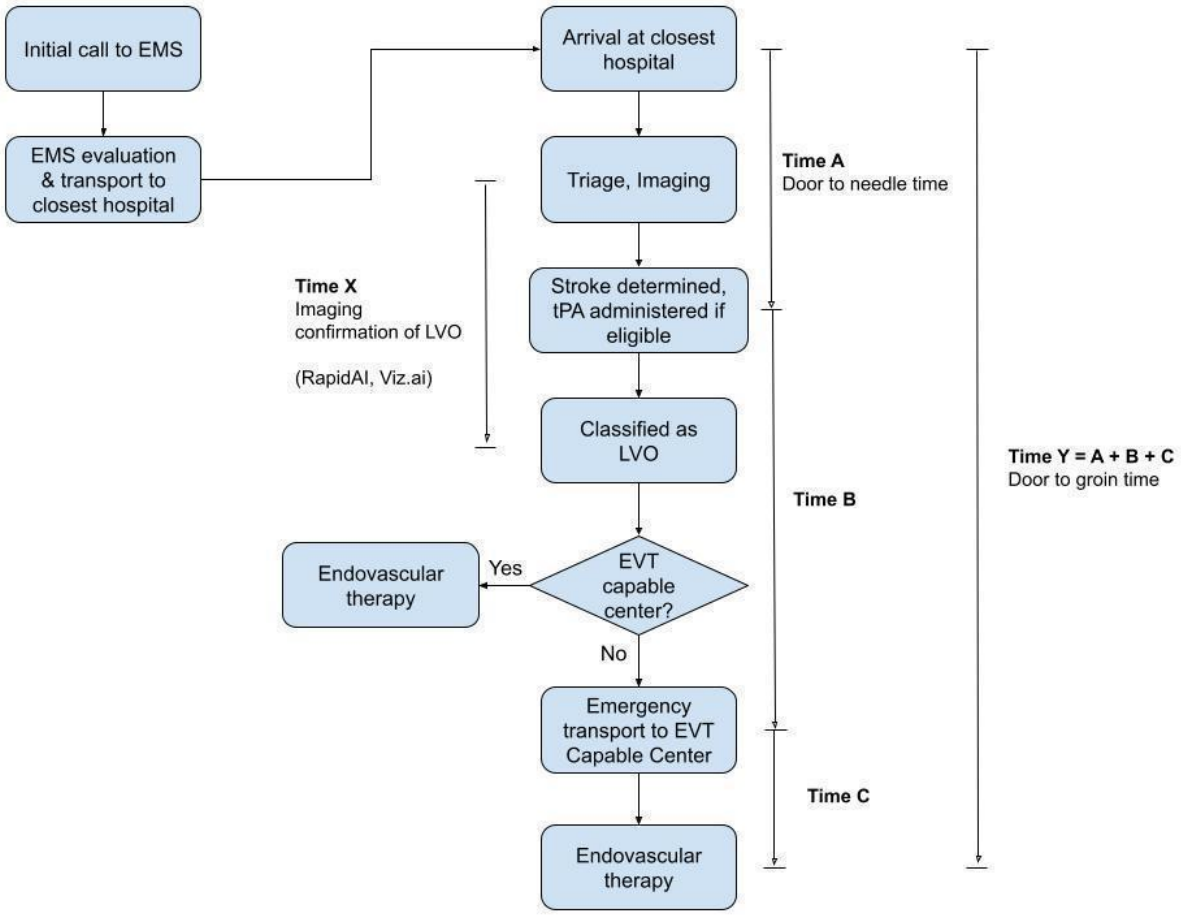

Figure 1: Current clinical workflow for an LVO stroke patient

1.2 Recent improvements in LVO Stroke workflow

Recently, the FDA has cleared Artificial Intelligence (AI)-based algorithms that automatically detect asymmetric blood flow patterns evident within digital representations of image feature sets from CT or MRI that indicate the probability of an underlying LVO (K200941, Rapid LVO, and DEN170073, Viz.AI Contact) for the purpose of generating alerts that can improve the workflows in LVO stroke care. As shown in Figure 1, while these systems can help make the "Time X" faster, they do not provide the benefit of a prehospital detection of LVO stroke leading to advanced notification for faster arrival time workflows and/or the potential for better routing decisions to be made for the patient (i.e., transport to closest hospital, with resulting inter-facility transfer time delays, instead of direct transport to an EVT capable center).

1.3 Proposed Openwater Solution

Openwater is proposing to introduce a noninvasive early notification system to identify and communicate blood flow data on patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery. This portable device is intended to operate in a prehospital emergency setting to generate pre-hospital LVO stroke alerts that can improve current arrival time workflows, enable advanced notification to receiving hospitals, facilitate new EMS routing protocols (Figure 2) that allow for direct transfer of eligible patients to an endovascular capable center to improve the LVO stroke workflow for times to reperfusion, and allow more patients to achieve good neurological outcomes than is currently possible with existing workflows.

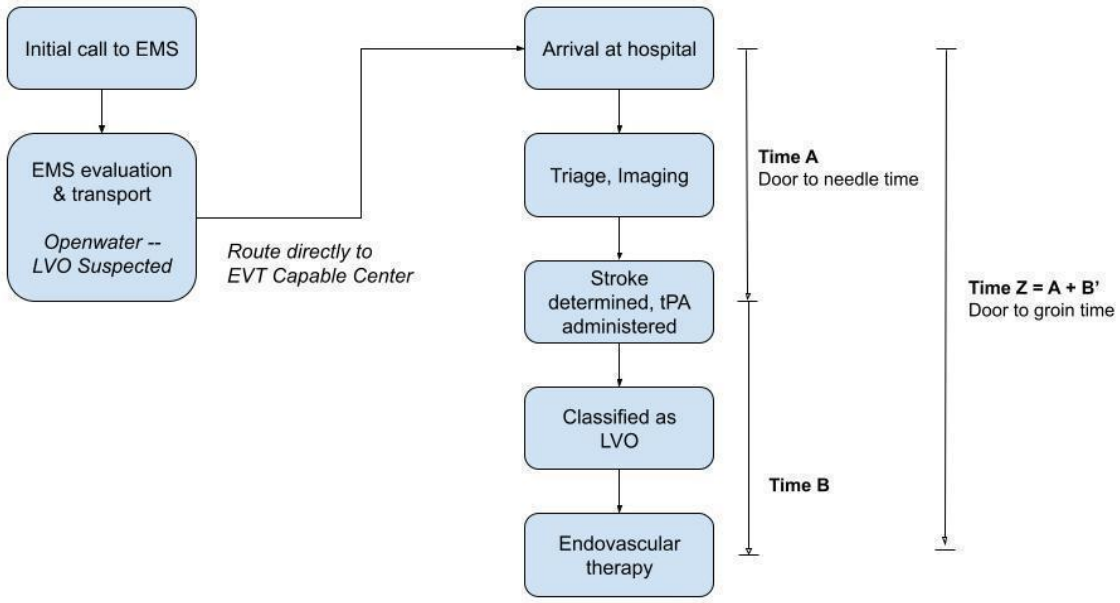

Figure 2: Clinical workflow for an LVO stroke patient undergoing direct-to-ECC routing based on an Openwater LVO Stroke Alert, provided patients meet all other clinical requirements for transport directly to an ECC per standard-of-care EMS workflows and protocols.

Openwater is aware of at least one other technology that is being independently pursued to address the problem of identifying LVO strokes in a prehospital setting, including Forest AlphaStroke, which was recently included in FDA's Breakthrough Device program (Forest Devices, 2021). Openwater's approach has the advantage of directly measuring blood flow to characterize the presence of occlusion, instead of relying on indirect assessments of neuronal activity from surface electrical recording technologies. As such, Openwater believes that the proposed device, Openwater LVO Stroke Alert, similarly satisfies the criteria necessary for Breakthrough Designation, as set forth in 515B(b) of the FD&C Act. Openwater LVO Stroke Alert is being developed to enable Emergency Medical Services (EMS) personnel to perform an assessment on-site to identify and communicate blood flow data on specific patients suspected of LVO stroke for the purpose of early notification and to improve routing decisions for faster time to endovascular therapy and reperfusion.

2 Device Description

Openwater LVO Stroke Alert is indicated for use as an early notification system to identify and communicate blood flow data on 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 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 a non-invasive device intended to monitor blood flow in tissue, including the brain. The Openwater Headset is intended for monitoring of adults.
    - The Openwater Headset is the base platform that is used to acquire the blood flow information.
- Openwater LVO Stroke Alert
    - Openwater LVO Stroke Alert is a software as a medical device (SaMD) that analyzes the blood flow data from Openwater Headset to identify and communicate blood flow data on specific patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery.

These two device components are discussed further in Sections 2.1, and 2.2. Note that the focus of this Breakthrough Designation request and Q-submission is the Openwater LVO Stroke Alert. However, since the proposed device relies on the underlying technology and output of Openwater Headset, this Q-submission also provides details on the headset device and its principles of operation.

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 under development, and proposed design of the console, are displayed in Figure 3. The core technology housed within the prototype version of Openwater Headset is in a wand configuration and is currently being used in clinical studies (Figure 4). The final Openwater Headset would

essentially be a wearable version of multiple wands that automates the process of multiple manual wand placements.

Figure 3: Openwater Headset design including proposed carrying case with the electronics under current development.

Figure 4: Current Openwater Headset technology in a wand configuration as used in the current clinical studies.

In the current prototype wand design (Figure 4) used under IRB-approved clinical feasibility protocols, the patient interface connected via cable from the console consists of a wand containing the core Openwater technology of the optical fiber for both the delivery and collection of light to and from the subject. This wand is placed at specific surface locations on the head manually to evaluate underlying cerebral blood flow.

In contrast to the current wand-based prototype design, the headset will reduce motion artifacts and will be more convenient to position and automate the measurements of multiple locations without the need to manually reposition to interrogate the locations of interest.

The Openwater Headset will provide the following cerebral blood flow information:

- **Blood Flow Index:** an Openwater proprietary format, based in laser speckle contrast analysis, that provides a measure of the flow rate of blood in the underlying tissue below

the sensor, similar to other transcranial optical devices that provide measurements of relative cerebral blood flow index (rCBFi).

- **Blood Volume Index:** an Openwater proprietary format, based on measurements of the concentration of absorbing chromophores within the underlying tissue below the sensor, and similar to other transcranial optical devices that provide measurements of relative total tissue hemoglobin concentration (rTHb).

More details of the Openwater Headset output and preclinical testing information is provided in Section 3.

2.2 Openwater LVO Stroke Alert

Openwater LVO Stroke Alert is a software as a medical device (SaMD) that analyzes the blood flow data from Openwater Headset to identify and communicate that a large vessel occlusion of the internal carotid artery or proximal middle cerebral artery is suspected.

Openwater LVO Stroke Alert analyzes blood flow data generated in the acute setting using Openwater Headset and provides information to the operator that a large vessel occlusion of the internal carotid artery or proximal middle cerebral artery is suspected.

An early notification can then be provided to the relevant clinicians for expedited review to result in more timely treatment decisions, including advanced preparation of staff and resources to improve arrival time workflows, as well as EMS routing decisions on how best to triage and route the patient differently, e.g., to transport directly to a thrombectomy-capable center with early notification to prepare the catheter suite ahead of time for the patient. In this way, the amount of time between onset of an LVO stroke and definitive treatment with endovascular therapy for reperfusion can be minimized, which can in turn maximize the potential for good functional neurological outcomes.

2.3 Device Operation, Use Model, Device Output

Headset-only operation

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
    a. Device executes a test to check for full contact with the patient’s head
4. If the headset is properly placed, initiate scan
    a. 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:

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

Headset + "LVO Stroke Alert" Operation

When the headset is used in conjunction with OpenWater LVO Stroke Alert SaMD:

7. The device 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 is described in the subsequent sections.

2.4 Principles of Operation

The Openwater Headset combines diffuse optics with measurements of laser speckles using short pulses of monochromatic laser light diffused through underlying brain tissue to measure cerebral blood flow.

Noninvasive diffuse optical methods have long been used for continuous, bedside, transcranial monitoring of cerebral blood flow (CBF), and these techniques have been previously validated against Xenon CT and MRI perfusion as measured by Arterial Spin Labeling (ASL) (Yu et al., 2007) (Kim et al., 2010). The use of transcranial optical monitoring has been carried out for several years using a variety of commercial near-infrared devices (Greenberg et al., 2016) including for the evaluation of brain blood flow-related changes during thrombectomy for the endovascular treatment of LVO stroke (Ritzenthaler et al., 2017) (Hametner et al., 2015).

Openwater Headset utilizes several of these techniques used to transmit laser light through the surface of the skin in order to measure tissue properties of the underlying brain and to characterize brain blood flow. Additional Openwater innovations include pulsing of the laser source (as opposed to continuous laser used in Diffuse Correlation Spectroscopy [DCS]) for the purpose of detecting changes in interference of the light waves produced (known as laser speckle) over time and optimizing the source-detector separation for collecting the returning photons from the signal that is most sensitive to brain blood flow changes.

The background and details of utilizing Near Infrared Spectroscopy (NIRS), diffuse optics, and speckle contrast analysis to measure cerebral blood flow are discussed further in the following sections.

2.4.1 Near-infrared window and depth

Biomedical optics is a rapidly expanding field that is providing biologists and clinicians new ways to detect, diagnose, and study disease. While many optical techniques can only be used to gain information near the tissue surface (Vo-Dinh, 2014) – e.g., confocal microscopy is only capable of imaging up to 50 µm below the tissue surface, and even optical coherence tomography only images at depth of up to 2-3 mm in opaque tissues – the spectral region in the near infrared (NIR) range overcomes inherent limitations of other light ranges to enable looking deeper into tissue than possible with visible light, as this range does not suffer from the same high degree of light absorption and scattering by tissue. As shown in Figure 5, the absorption of light by oxy- and deoxy-hemoglobin drops dramatically at around 600 nm. Likewise, the absorption of light by water is very low through wavelengths up to around 900 nm. As a result, there is a window in the NIR from about 650-950 nm where light at safe power limits can penetrate more deeply into tissue by many centimeters, including transcranial through soft tissue and bone (Jagdeo et al., 2012)

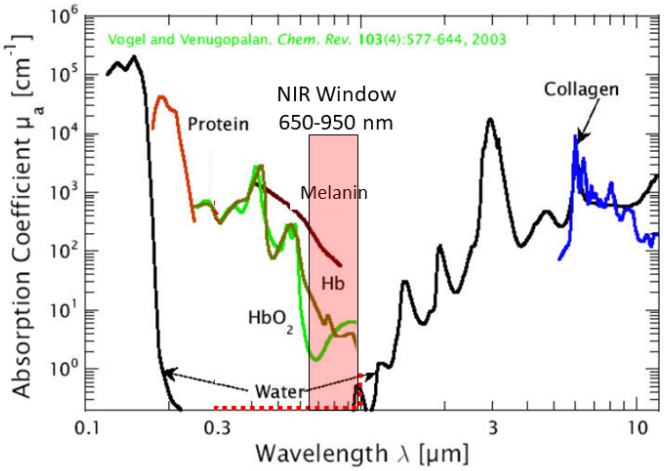

Figure 5: Near-infrared absorption spectrum of light absorbing chromophores in tissue demonstrating the spectral window from 650 - 950 nm where light can penetrate to depths of many centimeters, including transcranial through soft tissue and bone.
Adapted from (Vogel & Venugopalan, 2003)

2.4.2 Diffusion and depth selectivity

As NIR light has been shown to be able to safely penetrate deeply into underlying tissue and provide diagnostic information from as much as 10 cm of depth (Culver, Choe, et al., 2003), a key observation has emerged in the development of diffuse optical methods, which is that the paths of NIR photons in tissue can be described as a random walk with a step length equal to the distance over which their directions become randomized (Yodh & Chance, 1995). As a result, if experiments are performed over distances much greater than the step length, the propagation of the NIR photons can be modeled as a diffusive process. As shown in the Figure 6, when NIR light from an optical fiber is transmitted into tissue, the light intensity decreases with distance from the position of the light source. When a set of detector fibers at different lengths from the

source collect light exiting the tissue at various points, it is possible to use the detected light to gain information about the tissue at the depths through which the majority of returning photons has passed (which follow the probabilistic "bananas" shown) (Eggebrecht et al., 2014; Hoshi et al., 2005; Jelzow et al., 2014; O'Leary et al., 1995) including information on the concentration of absorbing chromophores such as oxy- and deoxy-hemoglobin and the underlying blood flow in the tissue. In particular, this information can be utilized to develop:

(1) **Blood Flow Index:** based in laser speckle contrast analysis, that provides a measure of the flow rate of blood in the underlying tissue below the sensor, and similar to other transcranial optical devices that provide measurements of relative cerebral blood flow index (rCBFi); and

(2) **Blood Volume Index:** based in light intensity analysis, that provides a measure of the concentration of absorbing chromophores within the underlying tissue below the sensor, and similar to other transcranial optical devices that provide measurements of relative total tissue hemoglobin concentration (rTHb).

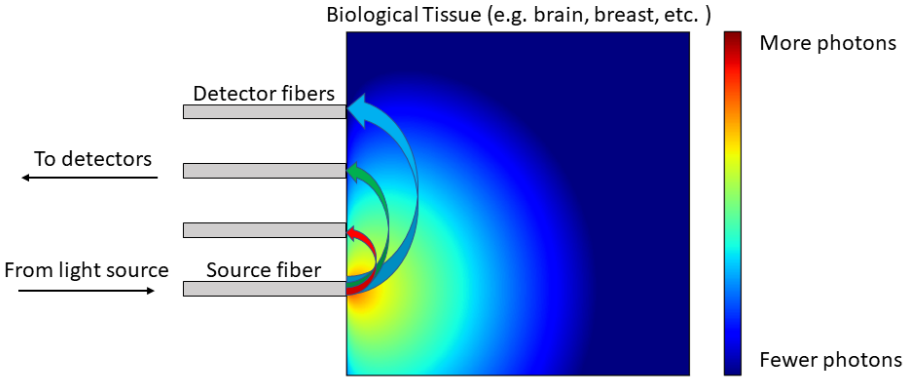

Figure 6: Schematic of the diffusion of light through tissue. The photons penetrate and scatter following patterns described via mathematical models of diffusion. The remitted light collected by optical fibers at the surface is used to determine optical properties of the underlying tissue. The greater the source-detector separations, the greater the depth of penetration of the majority of remitted photons being detected at that position (following the probabilistic "bananas" of the photon paths depicted). As such, source-detector separations can be optimized to collect information from distinct depths of tissue interrogation.

2.4.3 Laser speckle and blood flow

When laser light is reflected from a rough surface and then detected (e.g., by the retina or a camera) the resulting image contains randomly located light and dark spots commonly referred to as "speckle" (Goodman, 2007). The light and dark spots are due to the constructive and destructive interference between light waves that travel different distances. This phenomenon can be readily observed by shining a laser pointer at a wall and observing the reflected light (see Figure 7). This similar phenomenon occurs when NIR laser light passes through highly scattering media such as biological tissue.

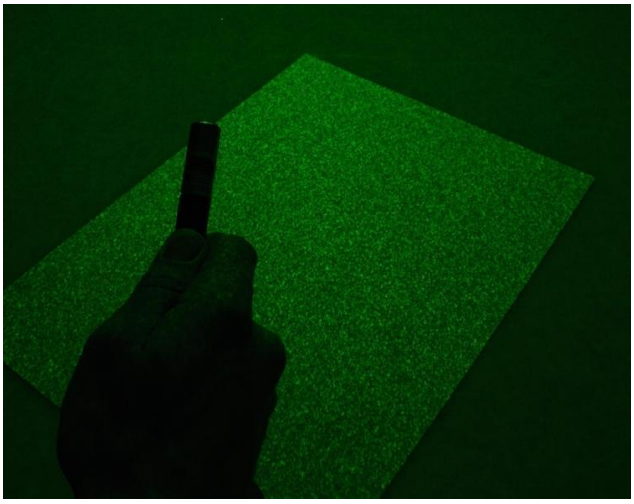

Figure 7: Reflected laser speckles created by lighting the opposite white wall with a 50 mW laser pointer.

If the light scattering particles that compose the scattering media are in motion, the locations of constructive and destructive interference of the light waves (i.e., the speckle) change over time. If light interference changes occur on a time scale equal to or shorter to the exposure time of the light detector, the contrast of the speckle (i.e., the difference between bright and dark spots) decreases. As a result, the contrast of the speckle pattern correlates to the motion of the interfaces scattering the light. More motion, due to either the light scatterers moving faster, or more of the light scatterers moving, decreases speckle contrast (Fercher & Briers, 1981). This phenomenon provides the basis by which the Openwater technology is able to determine blood flow changes in the underlying brain tissue.

2.4.4 Speckle analysis technique for blood flow index

Speckle contrast is a measure of how strongly spots of random interference, called speckle, appear in an optical image (Goodman, 2007). It is defined as the standard deviation of pixel values divided by the mean, and can be calculated according to:

$$Contrast \equiv \frac{\sigma_M}{\underline{M}} = \sqrt{\frac{2\beta}{T}\int_0^T d\tau\,(1 - \frac{\tau}{T})\left|g_1(\tau)\right|^2} \quad (1)\,.$$

Here $\underline{M}$ is the mean of the measured pixel values in the image, σ_M is the standard deviation, T is the exposure time, β is a constant ranging from 0 to 1 which depends on the pixel size, imaging configuration, light polarization, and aberrations in the imaging optics. In ideal circumstances, where the pixel size is much smaller than the speckle size and the light is completely polarized, β =1. Finally, $g_1(\tau)$ is the normalized electric field auto-correlation function defined as:

$$g_1(\tau) \equiv \frac{<E^*(t)E(t+\tau)>}{<E^*(t)E(t)>} \quad (2).$$

The normalized auto-correlation function is equal to 1 at τ=0, and decays as τ increases. It is a measure of how fast the electric field is changing. (i.e., a faster decay means the electric field is changing faster). It is related to the power spectral density S(ω) by a Fourier Transform. For a laser with a very narrow bandwidth, the auto-correlation function decreases more slowly. It is common to say that such a light source has a long coherence time, which is usually defined as:

$$\tau_c = \int_{-\infty}^{\infty} \left| g_1(\tau) \right|^2 d\tau \quad (3).$$

When light interacts with moving scatterers, the light is doppler shifted. For example, when the scatterers oscillate in a uniform manner due to the application of an ultrasonic wave, the light power spectrum obtains side lobes at the ultrasonic frequency. Similarly, if the particles are moving with a variety of velocities (speeds and/or directions), the power spectral density S(ω) of the light will be broadened. In the time domain, this same effect will appear as a faster decay of $g_1(\tau)$. There exists an entire field of study referred to as dynamic light scattering, in which researchers measure either S(ω) or the normalized intensity correlation $g_2(\tau)$, and use these measurements to determine $g_1(\tau)$. Based on a knowledge of $g_1(\tau)$ and a theoretical model, the dynamics of the sample under study can be determined (Berne, 1976).

In order to relate the speckle contrast to blood flow in the brain, Openwater uses the theoretical model for $g_1(\tau)$. Various researchers have derived the form of $g_1(\tau)$ in highly scattering media in different geometries (Boas & Yodh, 1997; Pine et al, 1990). Briefly, light correlation diffuses through the sample in a manner analogous to light intensity, as shown in the solution for a semi-infinite medium and geometry used in Openwater experiments:

$$G_1(\rho, \tau) = \frac{exp[-K(\tau) r_1]}{r_1} - \frac{exp[-K(\tau) r_2]}{r_2} \quad (4)$$

Where,

$$K^2(\tau) = 3\mu_a \mu_s' + \mu_s'^2 k_0^2 \alpha < \Delta r^2(\tau) > \quad (5)$$

Here $G_1(\rho, \tau)$is the unnormalized auto-correlation coefficient such that:

$$g_1(\rho, \tau) = G_1(\rho, \tau) / G_1(\rho, 0), \quad (6)$$

$k_0 = 2\pi n/\lambda$ is the wavenumber, μ_a is the absorption coefficient, $l^* = 1/\mu_s'$ is the reduced scattering length, $r_1 = (\rho^2 + l^{*2})^{1/2}$ is the distance from the light source to the detector where ρ is the distance on the surface, and the source is modelled as a point source located l^* below the

surface of the medium. $r_2 = (\rho^2 + (l^* + 2z_b)^2)^{1/2}$ is the distance between a virtual source and the detector where the extrapolation distance z_b is determined by the index of refraction mismatch at the sample surface, alpha is a unitless factor denoting the fraction of scatterers that are moving, and $< \Delta r^2(\tau) >$ is the mean squared displacement of the scatterers. For scatterers undergoing Brownian motion $< \Delta r^2(\tau) >= 6D_B\tau$ where D_b is the effective Brownian diffusion coefficient (distinct from the thermal Brownian diffusion coefficient). For scatterers which undergo random flow (e.g., red blood cells in capillary networks), $< \Delta r^2(\tau) > = < \Delta V^2 > \tau^2$ where $< \Delta V^2 >$ is the mean square velocity of the scatterers (e.g., red blood cells).

In summary, there is a relationship between the measured speckle contrast and the amount of blood flow in the tissue. The Openwater technique models this relationship using equations 1, 4 and the Brownian motion approximation of scatterer motion. Based on these equations, Openwater calculates a blood flow index based on the speckle contrast measured by surface cameras. The blood flow index is the mean squared displacement of moving light scatterers such as red blood cells per laser pulse width, multiplied by the fraction of light scattering events involving the moving scatterers, and is therefore directly proportional to the amount of blood flow in the interrogated tissue volumes.

2.4.5 Combined method to measure blood flow transcranially

Openwater's technology combines diffuse optics with measurements of laser speckles to obtain measurements of the blood flow in the brain of an individual at the point-of-care. Optical fibers transmit short pulses of monochromatic near-infrared laser light transmitted through the skin surface, and the photons propagate into the underlying brain tissue. Light detectors, which receive the laser light exiting the underlying tissue, are positioned to receive the respective exit signals from different interrogation depths. When photons encounter moving objects such as blood flow, it results in a doppler shift effect that broadens the spectrum and reduces the coherence of the laser light. Less coherence corresponds to increased blood flow, and more coherence corresponds to decreased blood flow. The light exiting the skin is captured by one or more detectors containing an image sensor. The contrast (standard deviation over the mean) of the resulting image is a measure of the coherence of the detected laser light. This image processing technique is a way of expressing the coherence as a measurement of laser speckle contrast. The contrast of the measured speckles is related to the number of moving red blood cells and their speed. A blood flow index is then calculated using an algorithm based on a mathematical model of the relationship between scatterer motion and laser speckles to provide a measure of the flow rate of blood in the underlying tissue below the sensor, in a manner similar to other transcranial optical devices that provide measurements of relative cerebral blood flow index (rCBFi). Assessment of cerebral blood flow via Diffuse Correlation Spectroscopy (DCS) is weighted toward comparatively long photon paths returning from deeper tissues compared to standard NIRS techniques (Selb et al., 2014) and thus leads to more sensitive optical monitoring of cerebral blood flow (Forti et al., 2019; Figure 8).

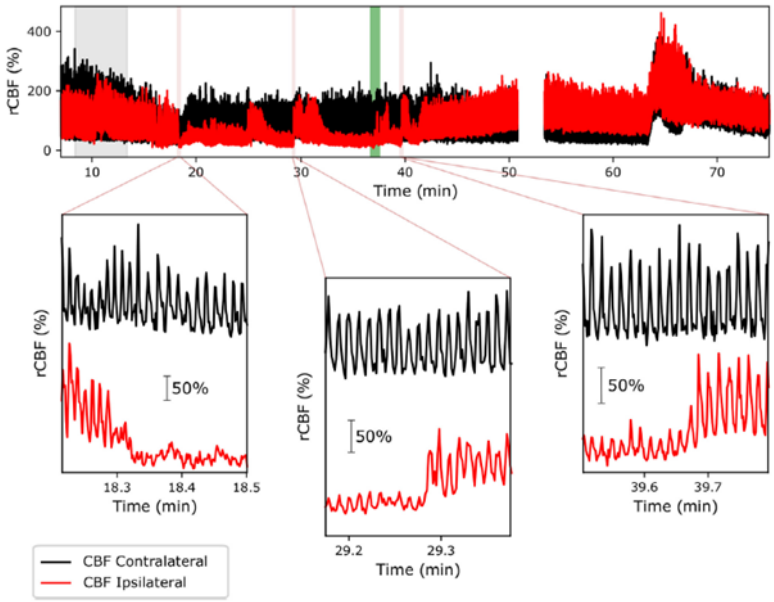

Figure 8: Example transcranial optical measurement of ipsilateral (red) and contralateral (black) Cerebral Blood Flow (CBF) changes during endovascular revascularization procedure for large vessel occlusion stroke from ICA occlusion, using a similar 785nm laser technology in an academic proof-of-principle study (adapted from R.M. Forti et al 2019). The top panel shows optical measurements of CBF waveforms with changes throughout the procedure over time. The green bar indicates the time of recanalization, and the grey-shaded region indicates the baseline period. Each of the 3 bottom panels exhibit scaled zoomed-in versions of ipsilateral and contralateral CBF to show the difference in blood flow waveforms across the different hemispheres and time.

2.4.6 LVO Stroke Detection

The cerebral blood flow data obtained from the Openwater headset in patients suspected of having a stroke is analyzed by the proprietary Openwater algorithm to compare differences between symmetrically located measurements from the left and right hemisphere of the brain. For example, measurements made on the forehead and temple scalp on the left hemisphere corresponding to regions of underlying blood flow relating to the left internal carotid artery (ICA) and left middle cerebral artery (MCA), are compared to measurements made on the forehead and temple scalp on the right hemisphere, corresponding to regions of underlying blood flow relating to the right ICA and MCA. The extent of the differences between the symmetrically located vascular distributions in the left and right hemisphere of the brain indicate probability of an underlying blood vessel occlusion. In situations where the left to right hemisphere measurement differences is greater than a threshold difference, the algorithm computes the probability of a large vessel occlusion (LVO) of an underlying blood vessel segment and returns an LVO Stroke Alert if the pattern is consistent with classification for suspected anterior circulation LVO.

3 Current Performance Data

The following sections describe the preliminary data collected by Openwater with the prototype version of Openwater Headset and the initial data in support of the development of Openwater LVO Stroke Alert. As described in section 2.4, the prototype measures both the speckle contrast and the intensity of light remitted from tissue and detected by an imaging sensor. From the measurements of speckle contrast, a blood flow index (BFI) is calculated. From the measurements of light intensity, a blood volume index (BVI) is calculated. In the results below, the raw data (speckle contrast and light intensity) and/or calculated outputs (BFI and BVI) are shown depending on the context. When the goal is to show a difference between the left and right hemispheres of the brain, the left-right difference for one or more of the above parameters is shown.

3.1 Preclinical Phantom Data

Preclinical phantom data was utilized to initially validate the wand prototype version of Openwater Headset against known simulated blood flow rates and confirm the sensitivity of laser speckle analysis. Figure 9 shows an example experimental model that demonstrates resolution of simulated blood flow at a depth of 30 mm below the surface of a tissue-simulating phantom. Laser pulses are directed into the phantom by an optical fiber, and remitted light is detected by optical fibers located at distances of 15 mm and 35 mm away. Light detected 35 mm from the source has on average traveled deeper into the phantom than the light collected 15 mm away. A fatty emulsion with optical properties similar to human blood is pumped through a 6 mm diameter tube whose top surface is 30 mm below the surface of the phantom (Figure 9A). As the speed at which the emulsion flow is increased, the speckle contrast decreases for the 35 mm detector, whereas the speckle contrast for the 15 mm detector remains unchanged (Figure 9B). Figure 9C shows an example of real time monitoring in which the flow in the tube is turned from an off state to an on state, and then is shut back off again. The speckle contrast of the 35 mm detector, but not the 15 mm detector, tracks the changes accordingly confirming the goal depth selectively. Using the flow verification testing with this blood-mimicking fluid within a calibrated flow phantom model with optical properties approximating human tissue, Openwater technology confirmed sensitivity for signal changes caused by the syringe pump driven fluid flow at resolution of velocity changes well within the range relevant to small blood vessels in clinical applications (e.g., down to 1-2 mm/s resolution). Two distinct flow phantom setups were developed that allowed flow to be measured at varying depths with different tissue properties, number of blood vessels, and blood vessel sizes. Testing was also performed on solid and liquid phantom with no flow with a variety of tissue properties. Data capture and analysis was performed across approximately 50 phantom studies that were used to optimize system performance.

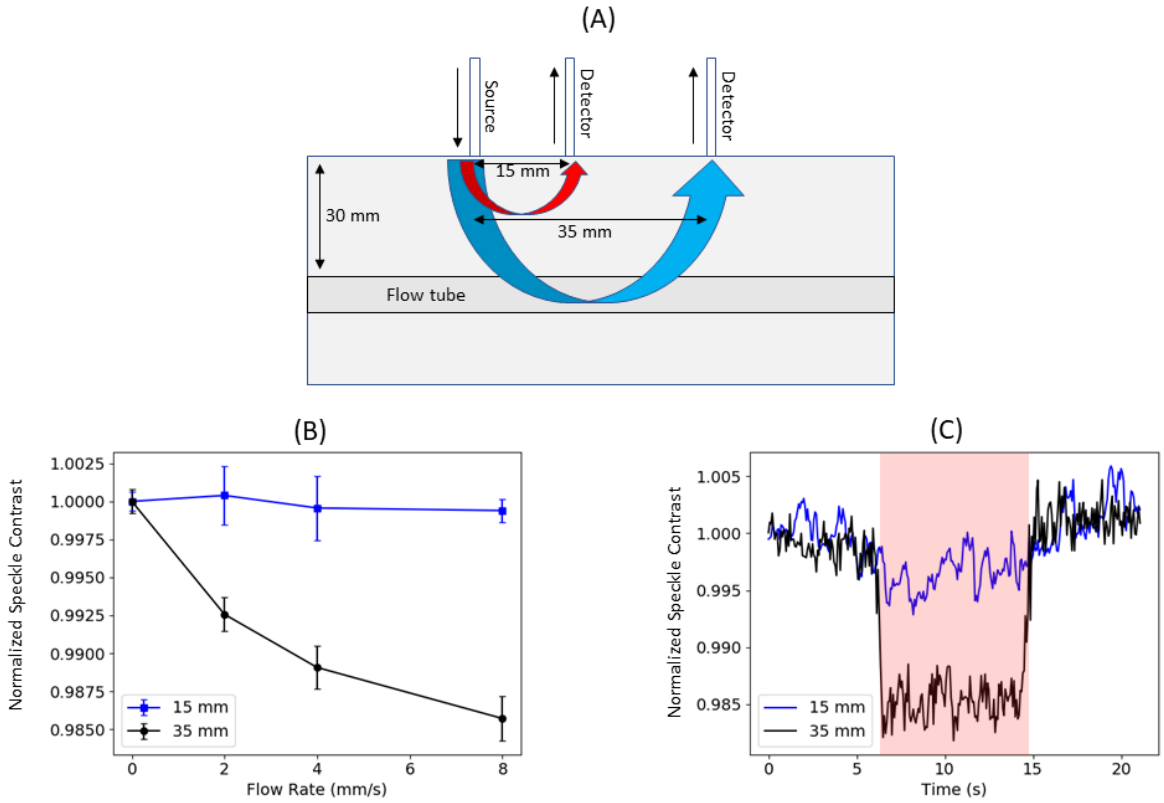

Figure 9: Example preclinical phantom data utilizing the Openwater prototype in tissue and blood-mimicking phantoms with variable flow rates, including simulated large vessel occlusion (A) a schematic of a tissue-simulating phantom used in experiments, in this case having a tube located 30 mm below the surface, with distinct source-detector separations at the surface (B) speckle contrast measurements logged for various flow rates inside the tube demonstrating the sensitivity of source-detector separations for different depths of the underlying tissue, and (C) a time trace of the speckle contrast as the flow speed in the tube was varied from 0 mm/s, to 8 mm/s, and then back to 0 mm/s (i.e. simulated occlusion). Note that the speckle contrast changes for the detector located at 35 mm away from the laser source position, but not for the detector located at 15 mm which is only sensitive to superficial flow. Lower values indicate faster blood flow.

3.2 Preclinical Animal Model Data

3.2.1 Inhaled gas challenges for augmented cerebral blood flow

Preclinical small animal in vivo experiments were conducted to test noninvasive transcranial measurements and sensitivity to blood flow changes caused by the inhalation of varying gas mixtures. Anesthetized rats (0.5 L/min air flow with 2% isoflurane) were given hypercapnic and hypoxic gas challenges. The hypercapnic challenge consisted of increasing the CO2 in the gas mixture from 0% to 5% for 30 seconds, and the hypoxic challenge consisted of reducing the O2 in the inhaled mixture from 20% to 10% for a period of 30 seconds (Figure 10). Figure 10B and 10C display results for optical absorption coefficient and blood flow index (BFI) respectively during a hypercapnic challenge. Dilation of blood vessels due to the inhalation of excess levels

of CO2 results in increases in both blood volume and blood flow. Figure 10D and Figure 10E display the results of a hypoxic challenge. As the rat is deprived of oxygen, a decrease in hemoglobin oxygenation leads to a decrease in the optical attenuation coefficient (μ_{eff}) at 850 nm (the wavelength of light that was used for this experiment), with no change in BFI as blood flow remained constant. Note: the current Openwater Headset system uses a wavelength attenuated to a similar extent by oxygenated and deoxygenated hemoglobin (the "isospectic point") and is thus optimized to be primarily sensitive to changes in blood volume instead of the hemoglobin oxygen saturation, to allow for blood volume index (BVI) to perform more accurately without attenuation by hemoglobin oxygenation changes, as in the optical absorption coefficient below. In all the graphs the blue lines represent the raw time curves which are then smoothed to produce the orange curves. The oscillations in the raw blood flow curves are due to the pulse of the rat, highlighting the sensitivity of the noninvasive transcranial optical flow measurements. Measurements were made on 3 separate days, including data capture and analysis across a total of N=19 gas challenges with varying cerebral blood flow physiology.

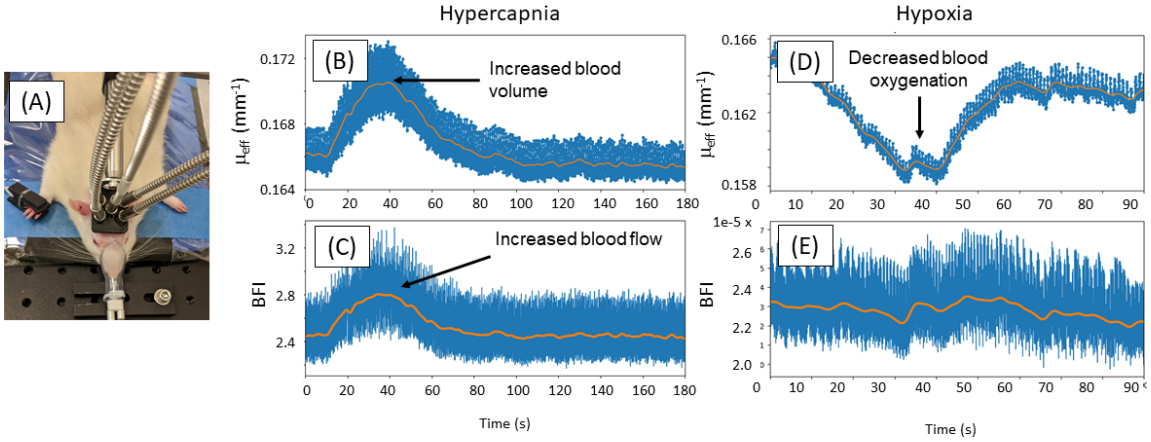

Figure 10: Preclinical data from a rat undergoing hypercapnic and hypoxic inhaled gas challenges for augmented cerebral blood flow during transcranial optical cerebral blood flow measurements using Openwater technology. (A) photograph of the rat with the noninvasive fiber optic probe placed on the surface of the head. During hypercapnia the Openwater device was sensitive to detecting increases in both (B) the optical attenuation coefficient μ_{eff}, and (C) blood flow index (BFI). During hypoxia the Openwater device was sensitive to detecting (D) a decrease in optical attenuation coefficient μ_{eff}, and (E) a constant BFI, reflecting no change in the rate of blood flow.

3.2.2 Temporary MCA occlusions

Preclinical rat small animal model of temporary occlusion of the middle cerebral artery (MCA) was next utilized to demonstrate feasibility in detecting LVO stroke. For each rat, a small hole was bored in the rear portion of the right side of the skull exposing the MCA. Once the MCA was exposed, blood flow was noninvasively monitored with the Openwater technology by transmitting the laser light via the optical fiber from the surface of the head and detecting the remitted light with three detectors located at the right rear, middle, and left front of the head. After two minutes of data collection, a microvascular clip was applied to occlude the MCA. The clip remained in place for 1 minute before being removed, then the rat was monitored for an

additional 2 minutes (Figure 11). The noninvasive Openwater system was sensitive to the experimental LVO occlusion, as application of the clip resulted in an immediate increase in speckle contrast (indicating occlusion of blood flow), which returns to normal range of blood flow measurement as soon as the clip was removed (indicating revascularization). Furthermore, the increase in speckle contrast was greatest for the detector on the right side of the head, which probed the right hemisphere of the brain over the vascular distribution of the occluded MCA. In contrast, the detectors toward the center and front left of the head did not demonstrate the same change induced by the right MCA-occluding clip, consistent with preserved blood flow in those underlying vascular territories. The study was repeated in duplicate across N=2 rats assessed with and without temporary MCA occlusion, including data capture and analysis across a total of N=4 temporary occlusions.

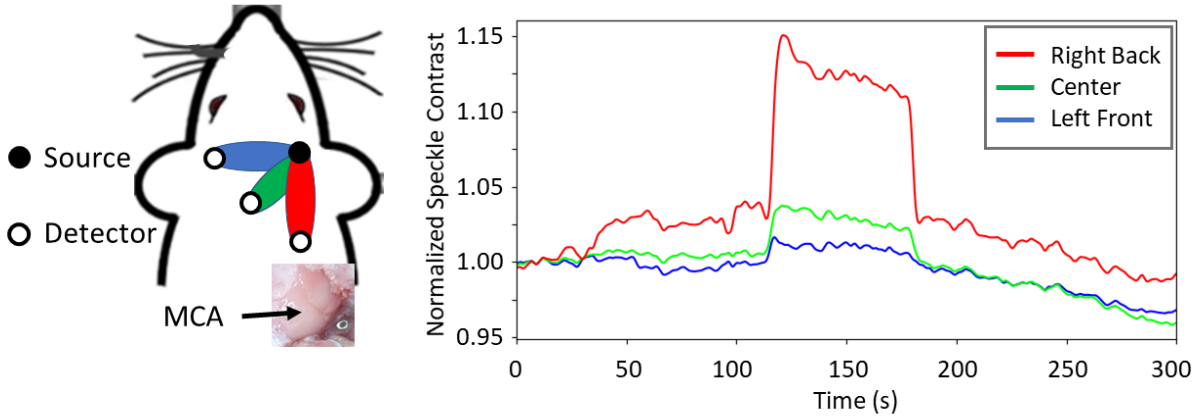

Figure 11: Results of temporary middle cerebral artery (MCA) large vessel occlusion (LVO) animal model. The Openwater technology noninvasively measures underlying brain blood flow at three locations, directly above the vascular territory of the MCA (red line) versus over other vascular territories more toward the center (green line) and farther toward the right MCA (blue line). When the ipsilateral MCA is temporarily occluded with a microsurgical clip to simulate LVO, the speckle contrast rises specifically under the area of the ipsilateral MCA surface detector. When the clip is removed and flow is restored, the contrast returns to baseline.

3.2.3 Permanent MCA occlusions

A preclinical rat small animal model of permanent occlusion of the middle cerebral artery (MCA) was next utilized to further demonstrate feasibility in detecting LVO stroke via left versus right hemisphere blood flow differences. Rats received a permanent occlusion of their right MCA following previously established methods (Davis et al., 2013). Measurements were taken on the left and right sides of the head both before and after surgery. A total of six rats were measured, out of which 10 baseline pairs of left/right measurements (two rats were measured multiple times) and 5 post "stroke" (right MCA occlusion) pairs of left/right measurements were made (one rat died during surgery), for a total of N=15 total measurements. On average, left to right hemisphere differences were 7x larger after occlusion (Figure 12). In addition, the smallest post occlusion difference (0.06) in any of the rats was twice as large as the largest baseline difference (0.03) among all the rats, demonstrating that a measurement threshold based on

mismatch between symmetrically located vascular territories could easily be established to demonstrate presence of LVO stroke.

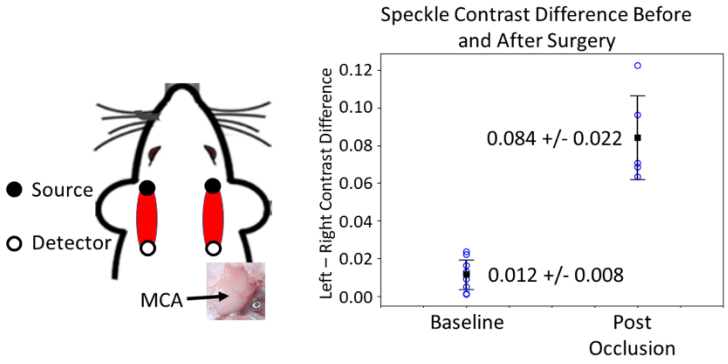

Figure 12: Results of permanent middle cerebral artery (MCA) large vessel occlusion (LVO) stroke study. The left and right sides of 6 rats were measured both before and after permanent MCA occlusion. Differences in speckle contrast between the left and right hemispheres were on average 7x greater after occlusion than before, demonstrating that noninvasive measurement with Openwater technology could easily demonstrate presence of LVO occlusion via mismatch between surface measurements of flow between symmetrically located vascular distributions.

3.3 Clinical data in human subjects

3.3.1 Human forearm measurements with simulated large vessel occlusions

The wand-based prototype of the core Openwater technology was used to monitor blood flow in the forearm of healthy human volunteers. In the experiment shown in Figure 13, measurement was made over 90 seconds, and following a 30 second baseline, a blood pressure cuff was inflated on the upper portion of the arm with pressure maintained for 30 seconds, following which the cuff was deflated with monitoring continued for another 30 seconds. As shown in Figure 13, the effect of the cardiac pulse on blood flow in the underlying tissue is clearly visible with Openwater technology using noninvasive laser speckle contrast during the initial and final 30 seconds, highlighting the sensitivity of speckle contrast to blood flow changes throughout the cardiac cycle in the underlying tissue. As the cuff is inflated to simulate a large vessel occlusion of the brachial artery, and for the duration of the occlusion, the pulse is no longer visible, and the speckle contrast accurately detects loss of underlying tissue blood flow. Once the cuff is deflated again, the speckle contrast quickly detects restoration of blood flow to the underlying human tissue being interrogated noninvasively with the Openwater system.

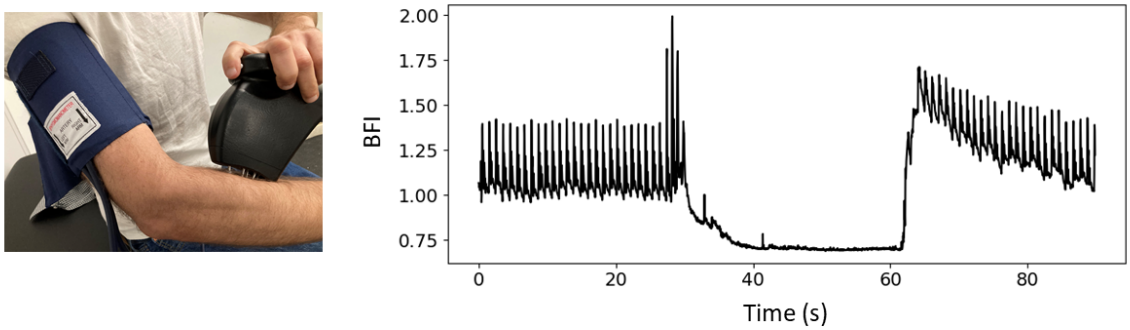

Figure 13: Use of noninvasive Openwater blood flow index (BFI) in the forearm of a healthy human subject during temporary large vessel occlusion of the brachial artery. The effect of the cardiac cycle is easily observed within the speckle contrast, highlighting the sensitivity to underlying tissue perfusion changes over time. At approximately 30 seconds a blood pressure cuff is inflated for 30 seconds. During the occlusion, evidence of tissue perfusion disappears, and the mean blood flow value is reduced beyond threshold, accurately detecting the simulated large vessel occlusion in human tissue. Once the cuff is deflated, the noninvasive speckle contrast registers restoration of blood flow.

3.3.2 Human head surface measurements with simulated large vessel occlusions

Figure 14 shows blood flow waveforms over time from noninvasive measurements made on the surface of the head of a healthy human volunteer. The speckle contrast measurements illustrate waveforms of the change in blood flow in the underlying tissue during the cardiac cycle. Morphological features in this data such as the waveform average, amplitude, and modulation depth (i.e., amplitude/average) may indicate salient differences in blood flow that themselves could be used to detect features of health and disease that will be the subject of future research and provide features for machine learning algorithms.

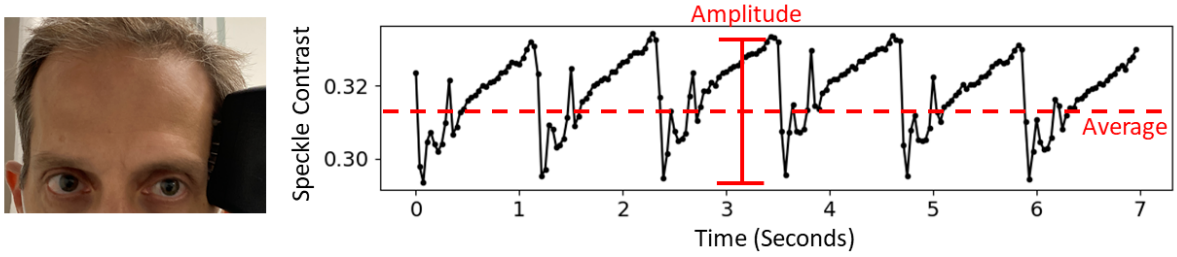

Figure 14: Typical speckle contrast waveform detected using Openwater technology for noninvasive surface measurements on the head of a healthy human volunteer.

Figure 15 demonstrates the use of two source-detector distances with simultaneous acquisition by the Openwater system, with the smallest source-detector distance (top row at 7.6mm) representing shallow photon interrogation of blood flow near the surface of the skin, and the larger source-detector distance (bottom row at 42.8mm) representing deeper photon interrogation of blood flow from the underlying brain. Simulated large vessel occlusion of the extracranial carotid artery circulation was performed by inflation of a circumferential pneumatic headband pressure cuff temporarily occluding head surface blood flow, resulting in loss of speckle contrast

signal in the shallow source-detectors. The blood flow waveforms detected from the source-detector pair with larger separation continue to demonstrate blood flow data while the head cuff is inflated, confirming they contain blood flow data of deeper photon paths in the intracranial space.

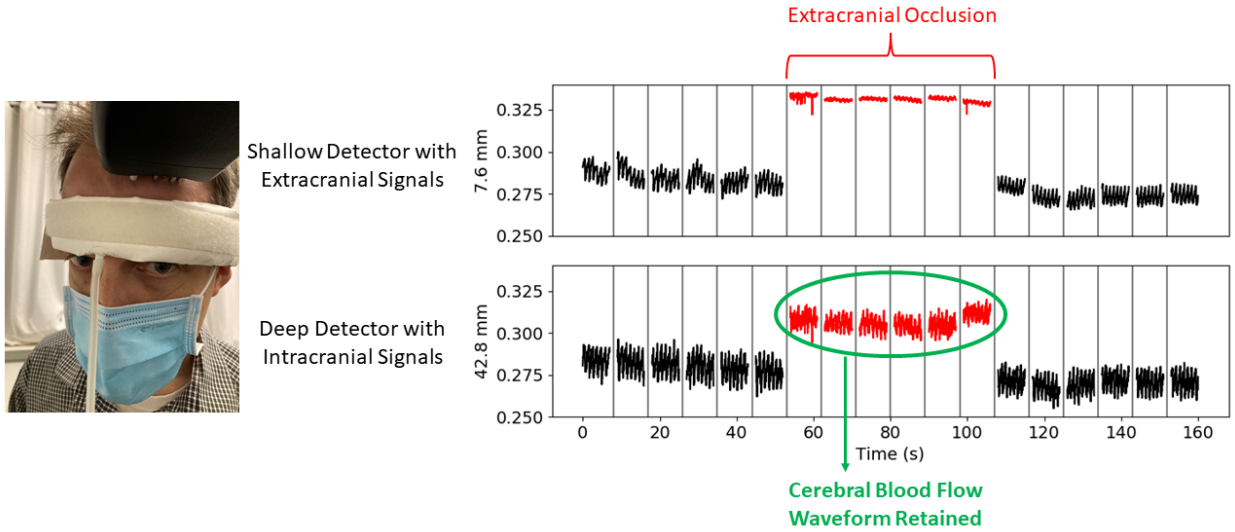

Figure 15: Speckle contrast waveforms from a healthy human forehead during large vessel occlusion of the surface extracranial carotid circulation. Shown is data from two simultaneous detectors at two distances (7.6 and 42.8 mm) from a laser source position. Six acquisitions of seven seconds each are acquired before and after a pneumatic headband cuff is inflated to simulate large vessel occlusion of the extracranial carotid artery, occluding surface blood flow to the scalp. During the occlusion (red) the amplitude of the waveform in shallow cameras change past a threshold that allows noninvasive detection of the presence of occlusion of this vascular territory. The deeper cameras continue to demonstrate blood flow waveform data even during the complete surface occlusion, confirming they contain blood flow data of deeper photon paths from the intracranial space.

3.3.3 Human Healthy Controls and Stroke Data

A total of N=64 healthy subjects enrolled under an IRB-approved protocol at Hartford Healthcare (Hartford, Connecticut) were analyzed with the Openwater system. The initial N=34 subjects were enrolled with the initial wand prototype ("Generation 1A"), which was improved in a second iteration ("Generation 1B") to adjust the wand to be more ergonomic, to reduce the associated hardware cart size, and to adjust the laser for more light. In addition, the Generation 1A laser was continuous using a shutter to make the output light pulsed, whereas the Generation 1B laser itself operates in pulsed mode, which will be part of the core Openwater technology moving forward. The next N=30 human subjects were enrolled to represent normal healthy control range measurements (shaded in grey in the images throughout this section). Inclusion criteria for the study included adults aged between 18 and 89 years of any gender. Subjects with scalp conditions, previously known history of stroke or intracranial injury, and pregnant women were excluded from the study. The healthy subjects enrolled via convenience sample to the health center included 22 females and 8 males, 24 aged under 60 years and 6 aged 60 years or above (mean age of the study was 44). Ethnicities include 27 European American, 1 African American, 1 Asian, and 1 Hispanic subject.

Under a separate IRB-approved protocol in the Comprehensive Stroke Center (CSC) neurointensive care unit (neuroICU) at Hartford Healthcare, patients with acute ischemic stroke were enrolled in an initial feasibility study using the Openwater system. For each patient, up to 15 measurement locations on each side of the head for a total of up to 30 measurement locations could be performed. In addition, up to 3 repeats scans could be performed at each position. Measurement positions consisted of locations on the forehead and temple that involved vertical (V) and horizontal (H) orientations of the wand against the surface of the head, as well as diagonally (D) oriented positions approximately along the sylvian fissure.

A medium vessel occlusion (MeVO) patient with an acute ischemic stroke from complete occlusion of the middle cerebral artery (MCA) at the second segment (M2) inferior temporal branch was enrolled for analysis with the Openwater system with results shown in Figure 16.

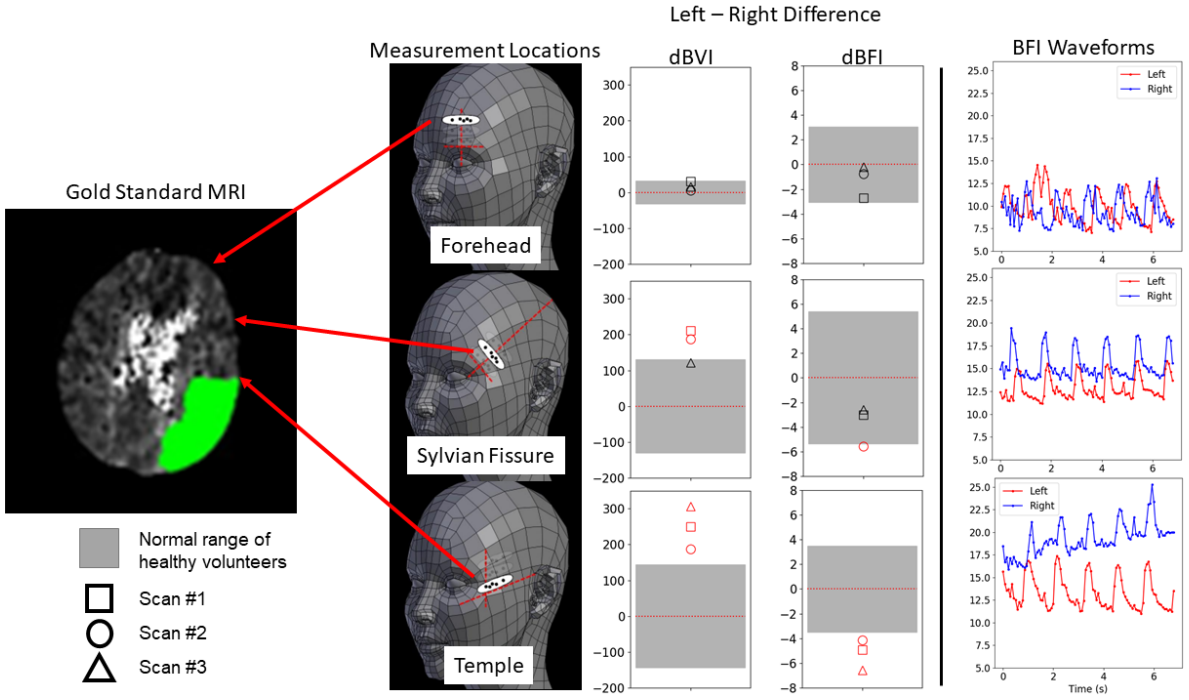

Figure 16: Assessment of Unilateral M2 Inferior Occlusion with Openwater Technology. Results from the measurement of a patient with an occlusion of a medium vessel occlusion (MeVO) of the inferior M2 branch of the middle cerebral artery. Three complete scans were performed during a single session. Shown are differential blood volume index (dBVI), differential blood flow index (dBFI), and representative underlying source blood flow index (BFI) waveforms from trial #3 used to generate the dBFI; all demonstrating the differences between the left and right hemispheres at the 3 locations pictured. As the noninvasive optical interrogation location approached the underlying affected vascular distribution, the measurements deviate from the control range from the healthy population shaded in grey to trigger suspicion for intracranial vessel occlusion when probing an affected underlying territory.

Figure 16 above shows the resulting data from three scans conducted at three positions, namely the forehead, the sylvian fissure, and the temple. The figure shows the differences between the left and right hemispheres as the differential blood volume index (dBVI), the differential blood flow index (dBFI), and representative underlying source blood flow index (BFI) waveforms used to generate the dBFI. The Openwater system detected normal appearing dBFI and dBVI when measuring over unaffected vascular territories on the forehead, however blood flow abnormality relative to healthy controls was seen as the probe was moved toward measuring directly over the affected vascular distribution. These findings confirm that surface optical interrogation found no evidence of complete ICA or M1 occlusion in this patient but did detect evidence of inferior temporal abnormality in blood flow consistent with the underlying M2 inferior MCA occlusion in this patient.

A second patient with a distinct form of acute ischemic stroke from diffuse bilateral globally reduced cerebral blood flow was enrolled at the Hartford neuroICU with results shown below in Figure 17. Here a total of 30 individual surface measurements are displayed using the Openwater system to highlight that this patient demonstrated diffusely low cerebral blood flow at every measurement position tested. These findings were consistent with the patient's MRI perfusion imaging ("Tmax" [time to maximum contrast] showing significantly delayed blood flow on both sides of the brain as shown in blue in Figure 17A). The Openwater system measured average speckle contrast (Figure 17B) and speckle contrast waveform modulation depth (Figure 17C) outside the range of healthy volunteers at all measured locations. However, of note, the superficial measurements using the 15 mm source to detector separation (representing extracranial blood flow) were within normal values, and only the 35 mm source to detector separation measurements which probe deeper into the brain were outside the normal range. These findings further highlight the sensitivity of the source-detector separations for cerebral blood flow abnormalities.

These findings highlight the sensitivity of the system to detect intracranial cerebral blood flow abnormalities in acute ischemic stroke, including due to intracranial vessel occlusions in human, with the pattern of blood flow changes observed correlating to the underlying vascular distribution(s) affected, thereby providing additional diagnostic information of the type of vessel occlusion and stroke subtype.

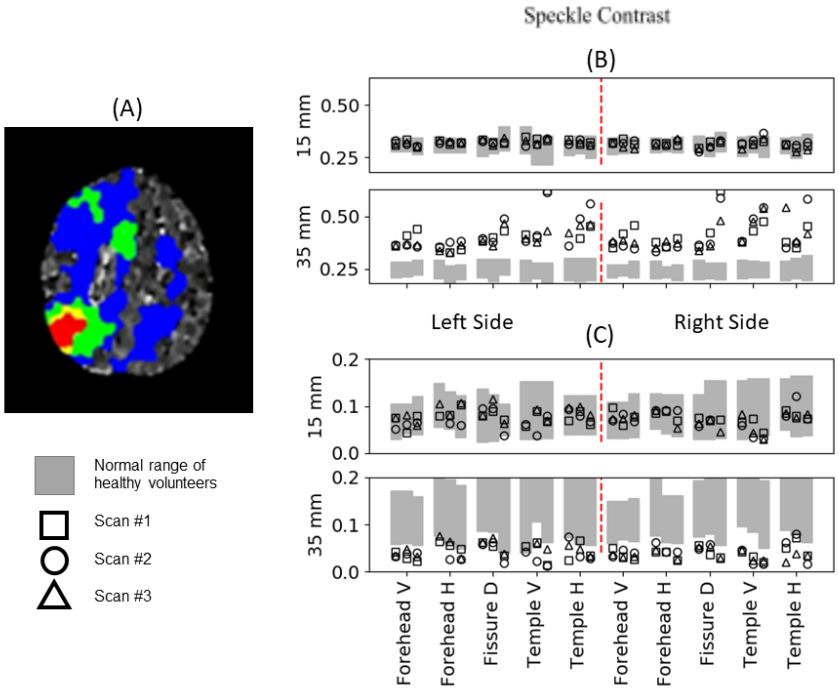

Figure 17: Assessment of Bilateral Global Diffuse Cerebral Ischemia with Openwater Technology. Results from a patient with diffusely low cerebral blood flow (A) MRI perfusion imaging with bilaterally elevated Tmax (time to maximum contrast arrival in blue). (B) A total of 30 measurement positions performed on the surface of the forehead and temple bilaterally confirmed diffusely abnormal average speckle contrast consistent with bilateral intracranial cerebral blood flow abnormality and (C) smaller than normal modulation depth of the speckle contrast waveform suggests reduced pulsatile blood flow. Of note, the superficial measurements from the 15 mm detector (reflecting extracranial scalp blood supply) are within the normal range, highlighting the results from the deeper probing 35mm detector were accurate for intracranial cerebral blood flow.

3.4 Summary of Preclinical and Clinical Findings

To summarize the data presented over the previous sections:

- **Preclinical Evidence**
    - Openwater has demonstrated in multiple preclinical phantom models across N=50 studies performed that different surface source-detector separations have depth sensitivity to detect blood flow changes at specific depths of interrogation in underlying tissue, and these data were utilized to develop and validate the Blood Flow Index (BFI) and optimal source detector separations.
    - Openwater has demonstrated in animal models measured that this technology can be applied for noninvasive, transcranial measurements sensitive to detect physiological changes in cerebral blood flow during the cardiac cycle and with inhaled gas challenges with hypercapnia, hypoxia, and changes in inhaled anesthetic across N=19 studies performed.
    - Openwater has demonstrated in animal models of Large Vessel Occlusion (LVO) across N=10 rats including multiple studies measuring temporary and permanent MCA occlusion stroke models, that noninvasive transcranial BFI can detect LVO measuring over the affected vascular territory.
- **Early Human Feasibility Evidence**
    - Openwater has demonstrated the ability to measure BFI in the arm of healthy human subjects across N=5 volunteer subjects and multiple studies measured, with sensitivity to small changes in flow throughout the cardiac cycle, as well as assessment with and without temporary vessel occlusion of the brachial artery to clearly differentiate signal change in the presence of occlusion.
    - Openwater has demonstrated the ability to measure BFI on the surface of the head in a total of over N=60 healthy human subjects, including in a subset with and without temporary vessel occlusion of the extracranial carotid circulation, with shallow detectors able to detect the surface occlusion, while deep detectors continued to measure flow from the intracranial space, confirming depth of interrogations for cerebral blood flow.
    - Openwater has demonstrated early human feasibility to noninvasively detect cerebral blood flow changes in acute ischemic stroke, including in differentiating intracranial vessel occlusion patterns from other forms of ischemic stroke. In a patient with an occlusion of the middle cerebral artery (MCA), abnormality was specifically identified when probing directly over the affected vascular territory consistent with the gold-standard MR perfusion imaging. In another patient with acute ischemic stroke from global diffuse reduction in cerebral blood flow, abnormality was identified when probing at all surface positions across vascular territories, consistent with the gold-standard MR perfusion imaging. Importantly

shallow detectors accurately reported normal surface blood flow through the extracranial carotid circulation, while deep detectors measured the flow abnormalities from the intracranial space, again confirming depth of interrogation needed for an accurate relative regional cerebral blood flow index.

Given these findings, Openwater requests FDA Breakthrough Designation in support of the continued clinical development efforts of this technology given the significant unmet medical need for a point-of-care pre-hospital LVO stroke detection device. The designation would give Openwater the needed opportunity to work closely with the FDA in developing and executing clinical studies to demonstrate the efficacy of Openwater LVO Stroke Alert.

4 Proposed Indications for Use/Intended Use

Openwater proposes an Indications for Use statement as follows:

- Openwater Headset
    - Intended use: The Openwater Headset is intended to monitor blood flow in tissue.
    - Indications for use:
      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.

- Openwater LVO Stroke Alert:
    - Intended use: Openwater LVO Stroke Alert is intended to identify and communicate blood flow data on specific patients suspected of large vessel occlusion (LVO) of the internal carotid artery or proximal middle cerebral artery.
    - Indications for Use:
      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..

5 Regulatory History

There have been no previous submissions or discussions with FDA for this device.

6 Regulatory Pathway and Predicate Analysis

The focus of the breakthrough device designation is the Openwater LVO Stroke Alert software as a medical device. Since this device requires the specific laser speckle measurement data relating to cerebral blood flow and volume generated by the Openwater Headset, the regulatory pathway analysis explores both device elements needed to deliver the final proposed solution.

6.1 Openwater Headset Regulatory Pathway

The device's indications are to monitor blood flow and blood volume characteristics in tissue by laser speckle contrast and optical absorption. Based on a detailed review of potential product codes, Openwater believes that the product code DPW, "Flowmeter, Blood, Cardiovascular", under the following regulation would be appropriate for the headset device:

> *Sec. 870.2100 Cardiovascular blood flowmeter.*
> *(a) Identification. A cardiovascular blood flowmeter is a device that is connected to a flow transducer that energizes the transducer and processes and displays the blood flow signal.*
> *(b) Classification. Class II (performance standards).*

Openwater conducted an extensive search for potential predicates and proposes the following:

- Proposed predicate: K150268, CerOx Model 3215FOP. CerOx, short for Cerebral Oximetry, has an equivalent intended use for transcranial optical monitoring of cerebral oximetry and blood flow in tissue, including the brain, and intended to monitor oxygen saturation and blood flow in tissue.
    - Of note, additional references related to the predicate include: K093923 and K100875, CerOx Model 3210 and 3210F, which uses equivalent transcranial optical laser technology intended to monitor regional hemoglobin oxygen saturation of blood in the brain of an adult and intended to monitor oxygen saturation and blood flow in tissue including blood in the brain, respectively.
- In addition, Openwater proposes to include one or more reference predicates that utilize similar technology to evaluate cerebral blood characteristics, specifically:
    - K200203, Infrascanner Model 2500, which uses equivalent transcranial optical laser technology to detect measurement features related to intracerebral hemorrhage
    - K182868, INVOS PM7100 Patient Monitor, INVOS Adult RSO2 Sensor, which uses equivalent transcranial optical laser technology related to brain oximetry for the purpose of cerebral oximetry
    - K190270, FORE-SIGHT, which uses equivalent transcranial optical laser technology related to brain oximetry for the purpose of cerebral oximetry

6.1.1 Equivalence of Intended Use and Indications for Use

The proposed predicate, K150268, CerOx Model 3215FOP, has the following indications for use:

> *The non-invasive CerOx 3215FOP monitor is intended for use as an adjunct monitor of microcirculation blood flow in tissue. The CerOx 3215FOP monitor is intended for monitoring of newborn - adult.*
> *The prospective clinical value of data from the CerOx 3215FOP monitor has not been demonstrated in disease states. The CerOx 3215FOP monitor should not be used as the sole basis for diagnosis or therapy.*

Both Openwater Headset and CerOx Model 3215FOP have the same intended use of monitoring blood flow in tissue, including the brain. Both are applied on the surface of the head to provide a proprietary measure of blood flow.

6.1.2 Equivalence of Patient Population

Both the subject and primary predicate devices are intended for adults; the predicate is additionally intended for use with newborns to adolescents. Both devices are for prescription use populations.

6.1.3 Equivalence of Safety and Technological Characteristics

Both devices utilize near infrared light and speckle that is captured using a photodetector to measure blood flow in the brain. The predicate additionally utilizes 1MHz ultrasound transmitted into tissue. The predicate utilizes ultrasound pressure to modulate optical path lengths that causes speckles to fluctuate in time at the ultrasound frequency and the intensity of remitted light is detected with a photodetector. The predicate then utilizes the reduction in amplitude of the measured oscillation, which is attributed to a loss of light coherence (and thus speckle contrast) due to motion of scatterers (red blood cells) inside the sample to estimate blood flow in a proprietary format. In the subject device, pulses of coherent NIR light are transmitted into tissue. Motion of red blood cells inside the tissue sample decreases speckle contrast measured on an image sensor. Multiple source detector separations are used to generate shallow and deeper measurement volumes and the proprietary Blood flow index (BFI) is calculated based on the contrast (difference between high and low) of the measured camera image.

The use of multiple source detectors that are separated to achieve and control the depth of measurement is similarly utilized by the reference predicates, K200203, Infrascanner Model 2500, which uses equivalent transcranial optical laser technology to detect measurement features related to intracerebral hemorrhage and K182868, INVOS PM7100 Patient Monitor, INVOS Adult RSO2 Sensor, which uses equivalent transcranial optical laser technology related to brain oximetry for the purpose of cerebral oximetry.

The Openwater device proposes to address any technological differences between the subject device and its predicates through performance testing and demonstrate that the differences should not raise different questions of safety or effectiveness and support the determination of substantial equivalence.

6.1.4 Conclusions

Based on the above analysis, Openwater believes that Openwater Headset is a Class II device that is consistent with product code DPW under regulation 21 CFR 870.2100 and that the devices noted in Section 6.1 would serve as appropriate predicates to establish substantial equivalence.

Table 1: Openwater Headset Substantial Equivalence Summary to Proposed Predicate

Feature	**Openwater Headset**	**K150268, CerOx Model 3215FOP (Proposed predicate)**	**Analysis of differences**
Intended Use	Intended to monitor blood flow in tissue	Intended to monitor blood flow in tissue	Same
Indications for use	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 non-invasive CerOx 3215FOP monitor is intended for use as an adjunct monitor of microcirculation blood flow in tissue. The CerOx 3215FOP monitor is intended for monitoring of newborn - adult. The prospective clinical value of data from the CerOx 3215FOP monitor has not been demonstrated in disease states. The CerOx 3215FOP monitor should not be used as the sole basis for diagnosis or therapy.	Similar. The proposed K150268 predicate is intended for a broader patient population.
Type of use	Prescription use only	Prescription use only	Same
Patient population	Adults	Newborn to adult	Both devices are indicated for adults. Predicate may be additionally used in a pediatric population.

Table 1: Openwater Headset Substantial Equivalence Summary to Proposed Predicate

Feature	**Openwater Headset**	**K150268, CerOx Model 3215FOP (Proposed predicate)**	**Analysis of differences**
Anatomical sites	Head	Head, arms, other tissue	Head is the same. Predicate includes additional anatomical sites
Mechanism of Action / Technology	Pulses of coherent NIR light to capture speckle using a photodetector. Use of multiple source detectors that are separated to achieve and control the depth of measurement	NIR light modulated through ultrasound pressure to capture speckle using a photodetector	Both devices use NIR light but use different mechanisms to generate and measure speckle contrast. Like the reference K200203, Infrascanner Model 2500, the proposed device uses multiple source detectors to detect blood at different depths.

6.2 Openwater LVO Stroke Alert Regulatory Pathway

The intended use of Openwater LVO Stroke Alert is to generate a pre-hospital early notification (LVO Stroke Alert) to identify and communicate blood flow characteristics concerning large vessel occlusion (LVO) of the internal carotid artery or proximal middle cerebral artery in patients suspected of stroke. Openwater conducted a search of previously cleared or approved devices and found that currently, there are no devices that are marketed with this intended use. Openwater found the product code, QAS, Radiological Computer-Assisted Alert and Notification Software, with devices such as DEN170073, ContaCT, K211788, HALO, and K200941, Rapid LVO 1.0, that are used in a similar manner, i.e., identify a large vessel occlusion (LVO), especially in the anterior circulation (K211788). These algorithms are based on automated software interpreting blood flow data as represented within digital feature sets of radiological contrast measurements of asymmetric blood flow generated by noninvasive CT scan. Openwater algorithms are analogous, based on automated software interpreting blood flow data as represented within digital feature sets of optical speckle measurements of asymmetric blood flow generated by the Openwater headset.

Given that there are no other appropriate product codes and that similar devices with similar outcomes are regulated as Class II devices, Openwater believes that Openwater LVO Stroke Alert can be classified as a novel Class II device that with general and special controls can

provide reasonable assurance of safety and effectiveness for the intended use. As such, Openwater requests that FDA review the premarket notification for this device as a de novo request.

7 Breakthrough Designation Criteria

The two criteria, as noted in sections 515B(b) of the FD&C Act (21 USC 360e-3(b)) were evaluated to provide justification that the Openwater LVO Stroke Alert qualifies for the FDA Breakthrough Device program. A summary and a detailed justification for each criterion is described below.

Criterion	**Satisfies criterion?**	**Justification summary**
1. Device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions.	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.
2. Device meets one of the components of the criterion, listed below:		
A. Device represents breakthrough technology;	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.
B. No approved or cleared alternatives exist;	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).

Criterion	Satisfies criterion?	Justification summary
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, 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	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 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.
D. Device availability is in the best interest of patients.	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.

7.1 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.

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 >2hours 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.

7.2 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. 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 (Czap 2020). While these efforts showed improvements in workflow demonstrating the benefits of identifying LVO in a pre-hospital setting (ibid), this option is cumbersome and expensive, requires substantial dedicated manpower, and limited by the availability of such mobile stoke units (Calderon 2018), and thus have not yet become the standard of care. 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).

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)).

8 Proposed Testing

The Openwater LVO Stroke Alert system consists of two separate devices working together to achieve the intended function. The focus of this Breakthrough Designation request and Q-submission is the Openwater LVO Stroke Alert. However, since the proposed device relies on the underlying technology and output of Openwater Headset, this Q-submission provides details on the headset device performance testing to clarify the regulatory strategy and performance testing for each individually.

8.1 Proposed Testing for Openwater Headset

As discussed in Section 6.1, Openwater conducted an extensive search for potential predicates for the underlying headset device and proposes to predicate to K150268, CerOx Model 3215FOP, which has an equivalent intended use for transcranial optical monitoring of cerebral oximetry and blood flow in tissue, including the brain. As both the Openwater Headset and CerOx Model 3215FOP have the same intended use of monitoring blood flow in tissue, including the brain, we propose testing to demonstrate that Openwater Headset is substantially equivalent to CerOx.

Openwater developed the testing plan based on the proposed predicate K150268, CerOx Model 3215FOP and prior testing conducted by Openwater with the Openwater Headset prototype, as discussed in Section 3 and summarized in Section 3.4. The following sections summarize the proposed testing.

8.1.1 Biocompatibility

A biocompatibility risk assessment of all patient-contacting surfaces per ISO 10993-1 will be conducted and appropriate testing to address the risk will be conducted. Given that the device makes brief contact with intact skin, the testing would involve an assessment of cytotoxicity, sensitization, and irritation.

8.1.2 EMC and Safety

The electrical safety and electromagnetic compatibility testing per IEC 60601-1 and 60601-1-2 will be conducted. Additionally, since the proposed Openwater Headset device is equipped with an embedded Class 3B laser that is equivalent to the Ornim C-Flow system, which is a Class 1 laser product equipped with an embedded Class 3B laser, testing to comply with IEC 60825 and IEC 60601-2-22 will also be conducted to demonstrate the safety of the laser.

8.1.3 Software

Product software will be assessed per FDA Guidance, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”, dated May 2005, and cybersecurity assessments based on FDA Guidance FDA Guidance, “Guidance for the Content of Premarket Submissions for Management of Cybersecurity in Medical Devices”, dated October 2018 and FDA Guidance, “Postmarket Management of Cybersecurity in Medical Devices”, dated October 2018. Documentation as required by the guidance will be developed and software verification and validation will be conducted to demonstrate that the Openwater Headset software satisfies its software requirements.

8.1.4 Bench Performance testing

To demonstrate the accuracy of the device flow and volume indices, Openwater proposes to evaluate the device on a phantom, similar to CerOx's phantom-based testing performed in the proposed predicate K100875 (Racheli et al., 2012). This testing is similar to the evaluation discussed in Section 3.1 where the device will be challenged with specific known volume and speed of the blood-mimicking fluid in the calibrated phantom model.

To demonstrate that the device's ability to detect changes in human blood flow, Openwater proposes to evaluate the device on the arm before and after simulated vessel occlusion by blood pressure cuff, as well as on the surface of the head before and after simulated vessel occlusion of the extracranial carotid circulation by pneumatic headband cuff. This is similar to the experiments discussed in Section 3.3.1 and 3.3.2 but performed on the proposed Openwater Headset instead of the wand-based prototype.

8.1.5 Human Factors

Openwater proposes to conduct human factors evaluation per FDA Guidance, "Applying Human Factors and Usability Engineering to Medical Devices", dated, February 2016 as part of its evaluation of Openwater Headset.

8.1.6 Conclusions

On the basis of the above testing plan, Openwater believes a determination of substantial equivalence to the proposed predicate K150268, CerOx Model 3215FOP could be made and that any differences between Openwater Headset and the proposed predicate K150268 should not raise different questions of safety or effectiveness.

8.2 Proposed Testing for Openwater LVO Stroke Alert

The following sections describe the test plan intended to demonstrate the safety and efficacy of Openwater LVO Stroke Alert.

8.2.1 Software

Product software will be assessed per FDA Guidance, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices", dated May 2005, and cybersecurity assessments based on FDA Guidance FDA Guidance, "Guidance for the Content of Premarket Submissions for Management of Cybersecurity in Medical Devices", dated October 2018 and FDA Guidance, "Postmarket Management of Cybersecurity in Medical Devices", dated October 2018. Documentation as required by the guidance will be developed and software verification and validation will be conducted to demonstrate that the Openwater LVO Stroke Alert software satisfies its software requirements.

8.2.2 Clinical Performance 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.

9 Data Development Plan

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

Stage	**Study location**	**Sample size**	**Details**	**Status**
Feasibility	Hartford Healthcare Healthy Volunteer Study	N=64	Openwater prototype wand, core technology feasibility testing	Ongoing
Feasibility	Hartford Healthcare neuroICU Stroke Study	N=3 completed.*	Openwater prototype wand, core technology feasibility testing	Ongoing
Development	To be determined (TBD).	N=30 (planned)	Utilize the headset prototype and finalize Openwater LVO Stroke Alert model	Planned
Validation	TBD Comprehensive Stroke Center	N=TBD Equal number of anterior LVO stroke, and in-hospital control stroke code mimics	Openwater Headset + LVO Stroke Alert algorithm, sensitivity, and specificity efficacy testing	Proposed

* Of the three subjects recorded in the feasibility study, two are discussed in Section 3.3.3, “Human Healthy Controls and Stroke Data”. The data from one subject was not used as it had poor signal quality due to technical issues.

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 8.2.

Title	Optically-Detected Cerebral Blood Flow Features at the Point-of-Care for Automated LVO Stroke Alert
Purpose	Evaluation of Openwater LVO Stroke Alert to support a de novo submission.

Study Design	Prospective cohort control design
Study Population	Acute stroke patients, equal population of confirmed anterior LVO stroke patients versus non-LVO stroke code mimics
Inclusion Criteria	● 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
Exclusion Criteria	● 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)
Safety Endpoints	Safety, adverse events
Effectiveness Endpoints	Sensitivity and specificity for classification relative to gold-standard, LVO stroke neuroimaging
Follow-up Schedule	No follow-up schedule required

10 Specific Questions for Initial Discussion

If the FDA designates Openwater LVO Stroke Alert as a breakthrough device, Openwater requests that the initial discussion includes the following topics:

1) Does FDA agree the proposed regulatory pathway is appropriate for the underlying Openwater Headset device as a 510k submission using the identified predicate?

2) Does FDA agree the proposed regulatory pathway is appropriate for the Openwater LVO Stroke Alert as a de novo submission for a new Software as a Medical Device (SaMD)?

3) Does FDA have any feedback on the proposed indications for use for the underlying Openwater Headset device or the Openwater LVO Stroke Alert SaMD?

4) For the Openwater Headset device, does the FDA have any comments on the proposed testing described in Section 8 that would be used to establish substantial equivalence to the proposed predicate in a future 510k submission?

5) For the Openwater LVO Stroke Alert, does the FDA have any comments on the proposed clinical testing, as described in Section 8.2.2 and summarized in Section 9, to evaluate the efficacy of the algorithm to support a future de novo submission of Openwater LVO Stroke Alert?

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