Presubmission Meeting Request

for

Openwater Headset

December 02, 2021

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1 Executive Summary

The Openwater Headset is a non-invasive device intended to monitor blood flow in the brain, specifically in the anterior portion. The Openwater Headset is intended for monitoring of adults. Openwater Headset is a platform that acquires this blood flow information by utilizing an Openwater proprietary technology that combines laser speckle imaging and diffuse correlation spectroscopy. 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 Headset consists of 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 and a console with electronics to drive the headset and process the signal. The Openwater Headset provides two cerebral blood flow information, namely,

- **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).

Openwater has conducted feasibility validation on animal and human studies, as well as developed a phantom model for verification of the two measurements.

Openwater has previously discussed this device with the FDA in the context of a request for a breakthrough device designation for the Openwater LVO Stroke Alert device that utilizes the Openwater Headset data. There have been no other discussions specifically on the Openwater Headset with the FDA.

Based on a regulatory pathway analysis, Openwater believes that the Openwater Headset device would be classified as a Class II device under product code DPW, “Flowmeter, Blood, Cardiovascular”, regulation 21 CFR Sec. 870.2100, “Cardiovascular blood flowmeter”. For a premarket notification for the Openwater Headset, Openwater proposes to utilize K150268, CerOx Model 3215FOP as a predicate, and K200203, Infrascanner Model 2500, as a reference predicate for the technology. To support the premarket notification, Openwater proposes testing to demonstrate that Openwater Headset is substantially equivalent to K150268, including demonstration of the consistency of the blood flow and volume measurements using a calibrated phantom, and to demonstrate the repeatability and reproduceability of the device measurements.

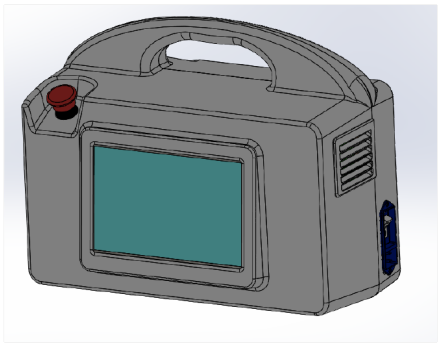
Openwater is seeking FDA feedback on the regulatory classification, potential predicates, and the performance testing methodology in this presubmission request.

2 Device Description

The Openwater Headset is a non-invasive device intended to monitor blood flow in the brain, specifically in the anterior portion. The Openwater Headset is intended for monitoring of adults. Openwater Headset is a platform that acquires this blood flow information by utilizing an Openwater proprietary technology that combines laser speckle imaging and diffuse correlation spectroscopy (see Section 2.2 for details).

Openwater Headset consists of the following:

- Wearable headset: 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 (Figure 1(b)). The fibers and image sensors are assembled into a module that is positioned at symmetric locations on either side of the head on the surface directly overlying the vascular territories of the anterior circulation of the brain. Specifically, the locations include one module over the temple and one over the forehead on either side of the head. Each module includes two sensors, namely a shallow sensor and a deep sensor, that is based on the separation of the sensor from the source laser. (See Section 2.2 for details)
- Console: 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 (Figure 1(a)).



(a)

(b)

Figure 1: Openwater Headset design including proposed (a) Console with a (b) Wearable Headset that is under development

The Openwater Headset is under development, and proposed design of the console, are shown in Figure 1. 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 2). The final Openwater Headset would essentially be a wearable version of multiple wands that simplifies the process of multiple manual wand placements.

Figure 2: Left: Current Openwater Headset technology in a wand configuration as used in the current clinical studies. Right: The wearable headset will include several of these wands that will be optimized to fit in a headset configuration

In the current prototype wand design (Figure 2) 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. Note that the headset modules are adjustable to ensure appropriate positioning.

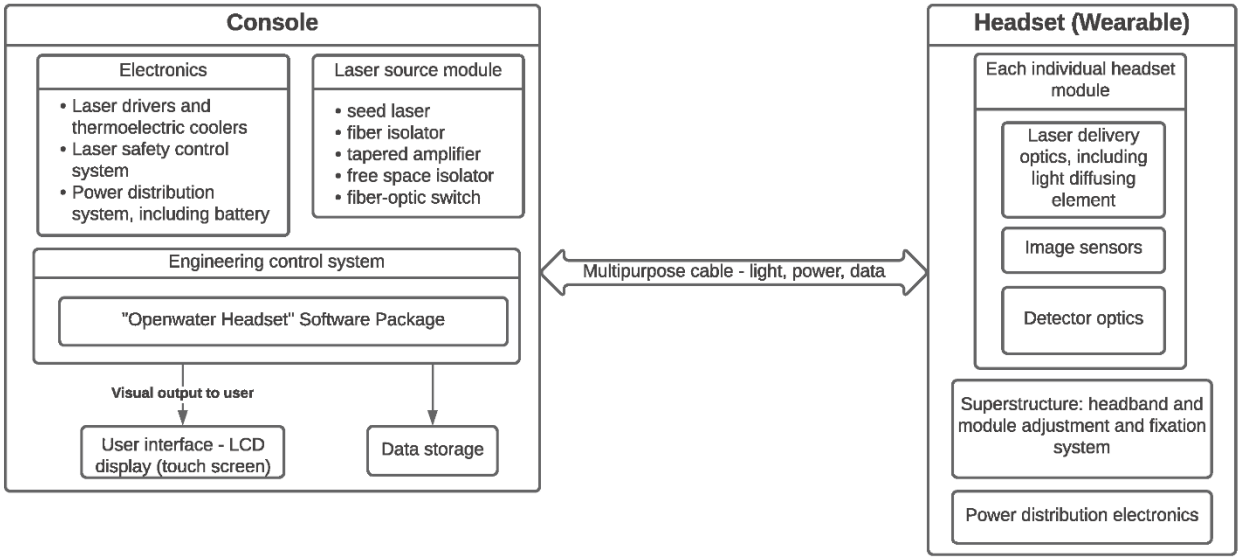


Figure 3: Block diagram showing Openwater Headset components, including the Console, the wearable headset and the multipurpose cable connecting the two.

A block diagram of the various elements of Openwater Headset is shown in Figure 3. The wearable headset communicates with the console using a physical multipurpose cable that includes optical fibers to transmit the list, wires to transmit power, and data. The components do not use or require any wireless or cellular paths of transmission for the data and all of the data is transmitted through physically wired means.

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). Note that the device does not provide hemoglobin oxygenation levels, i.e., the device may not be used for oximetry.

Figure 4 shows an example of the proposed output of Openwater Headset. Note that the BFI and BVI information shown in the example below were measured by placing the Openwater wand prototype at the forehead and the temple location of a healthy control. With the Openwater Headset wearable form factor, such repeated placement would not be necessary.

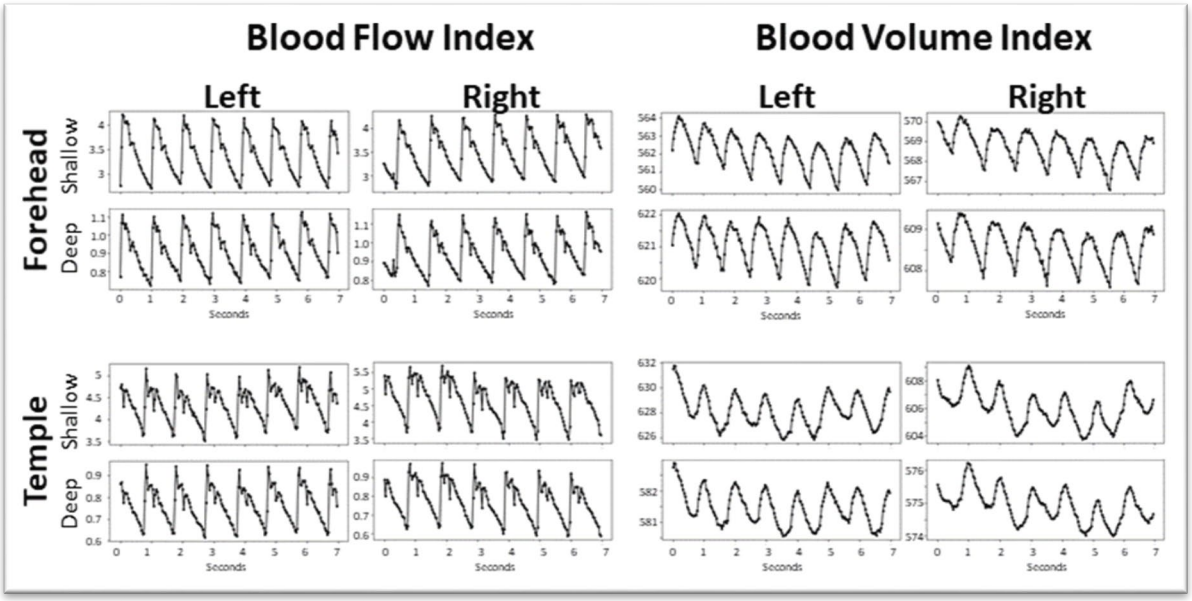


Figure 4:Example of the proposed Openwater Headset, recorded on a normal control subject

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

2.1 Device Operation and Use

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, which takes about 30 seconds.
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. **BFI**: a proprietary **Blood Flow Index**, measure of the flow rate of blood in the underlying tissue below the sensor, which is similar to measures from other devices like rCBFi or relative cerebral blood flow index.
        ii. **BVI**: a proprietary **Blood Volume Index** based on measurements of the concentration of absorbing chromophores within the underlying tissue below the sensor, which is similar to relative total tissue hemoglobin concentration (rTHb).

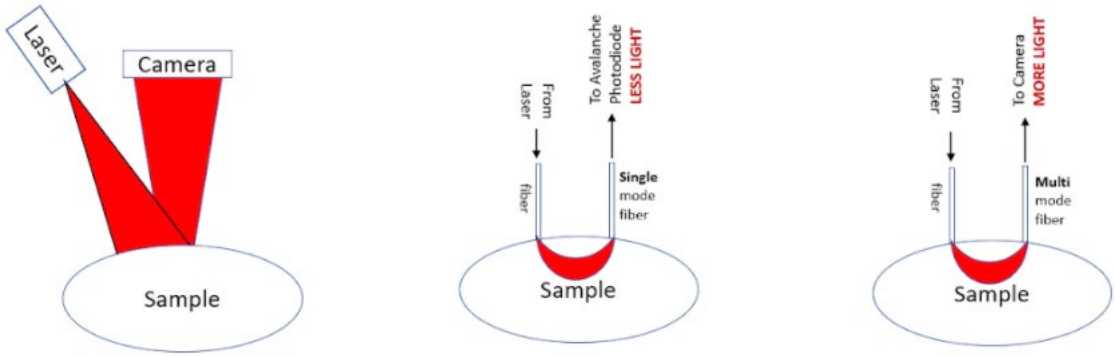
        Note: The headset includes 4 modules, where each module has one source laser and two sensors, a shallow and a deep that is defined by its separation from the source. The output thus provides two BFI and BVI measurements, one for each sensor, per module. With 4 modules, two at each temple and two at the left and right forehead, and with two sensors each, a total of 8 measurements are provided (see Figure 4 for details)
    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

The scientific explanation for these outputs is described in the subsequent sections.

2.2 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).



(a) Laser Speckle Imaging	*(b) Diffuse correlation spectroscopy*	*(c) Openwater's approach*
Coherence is measured by looking at many speckles on camera. This detects primarily light reflected near the surface	Coherence is measured by looking at a single speckle over time on the detector – an avalanche photodiode. Light is collected with a single-mode fiber with a diameter of a few microns	Coherence is measured by interference on a camera through an aperture of several millimeters and is able to gather >1000 times more light than approach (b). With more light, more depth can be achieved.

Figure 5: Openwater Headset's technology compared to traditional laser based approaches.

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-sensor separation for collecting the returning photons from the signal that is most sensitive to brain blood flow changes. Compared to traditional laser speckle imaging and diffuse correlation spectroscopy, Openwater's approach achieves significantly improved light collection and scanning depth (Figure 5).

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.

2.2.1 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 6, 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)

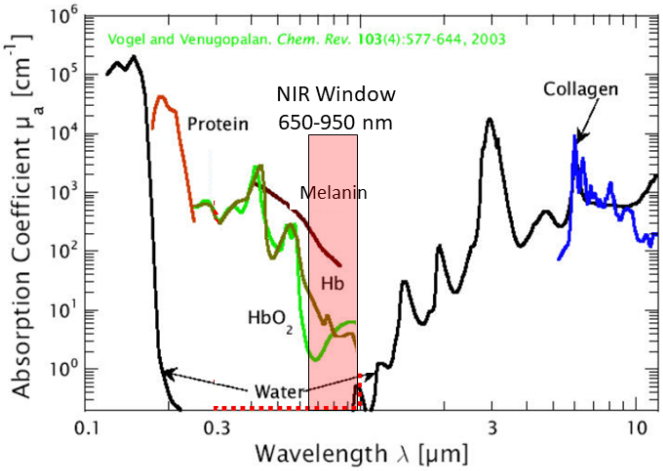


Figure 6: Near-infrared absorption spectrum of light absorbing chromophores in tissue demonstrating the spectral window from 650 - 950 nm where light can penetrate to depths of many centimeters, including transcranial through soft tissue and bone.
Adapted from (Vogel & Venugopalan, 2003)

2.2.2 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 7, 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).

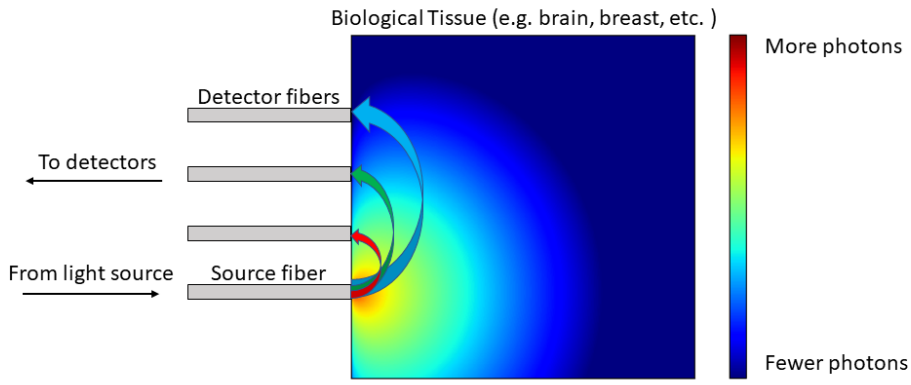


Figure 7: Schematic of the diffusion of light through tissue. The photons penetrate and scatter following patterns described via mathematical models of diffusion. The remitted light collected by optical fibers at the surface is used to determine optical properties of the underlying tissue. The greater the source-detector/sensor 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.

2.2.3 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 8). This similar phenomenon occurs when NIR laser light passes through highly scattering media such as biological tissue.

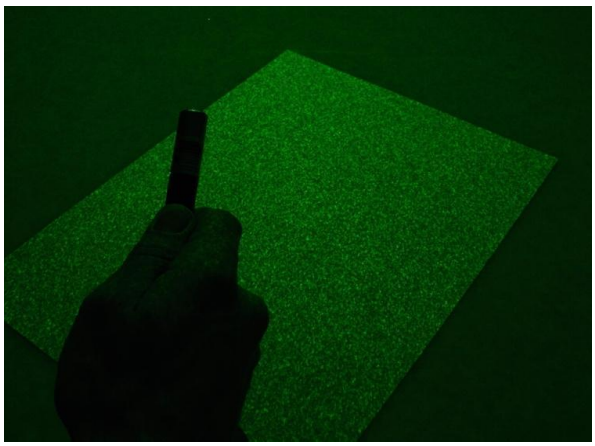


Figure 8: Reflected laser speckles created by lighting the opposite white wall with a 50 mW laser pointer.

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.

2.2.4 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:

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

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:

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

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 used in Openwater experiments:

$$G_1(\rho,\tau) = \frac{exp[-K(\tau)\rho]}{\rho^2} \quad (4)$$

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:

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

$k_0 = \; 2\pi n/\lambda$ is the wavenumber, $\mu_a$is the absorption coefficient, μ_s' is the reduced scattering coefficient, ρ is the distance on the surface between the source and the detector, α 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), the mean squared displacement can be modeled as $< \Delta r^2(\tau) > = < \Delta V^2 \; > \tau^2$ 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 effective Brownian diffusion D_b times the fraction of scatterers that are moving α (i.e. BFI = α D_b), and is therefore directly proportional to the amount of blood flow in the interrogated tissue volumes.

2.2.5 Intensity analysis technique for blood volume index

In order to compute the blood volume index, we again use equations 4 and 5, but we set the 2nd term in equation 5 to zero such that $K^2 = \; 3\mu_a\mu_s'$. Equation 4 now represents the intensity of light exiting the tissue due to the injection of light at a distance ρ away. Since this distance is known, we are able to solve for *K* using the intensity of the light measured at the detectors. At this point we assume an approximate value of the reduce scattering coefficient μ_s' taken from the literature (Racheli et al., 2012, Matcher, SJ, 1997, Jacques SL, 2013), allowing us to solve for the absorption coefficient μ_a. The absorption coefficient is equal to the sum of the concentrations of

absorbing chromophores times their extinction coefficients ε. At our 785 nm laser wavelength the principle absorbing chromophores in tissue are oxyhemoglobin and deoxyhemoglobin, and their extinction coefficient are almost the same (Prahl, S., 1999). (Even an enormous 10% change in tissue oxygen saturation only yields a ~3% change in absorption at 785 nm). Putting it all together the total hemoglobin concentration (cHbT) is proportional to absorption coefficient according to

$$\mu_a = \varepsilon_{HbO2} cHbO2 + \varepsilon_{Hb} cHb = \varepsilon_{HbT} cHbT. \quad (7)$$

2.2.6 Combined method to measure blood flow and blood volume transcranially

Openwater's technology combines diffuse optics with measurements of laser speckles to obtain measurements of the blood flow and volume 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 and can be used to calculate a blood flow index.

Figure 9 shows blood flow and blood volume waveforms over time from noninvasive measurements made on the surface of the head of a healthy human volunteer with the temple with a single sensor. The measurements illustrate waveforms of the change in blood flow and volume 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.

A blood flow index provides 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 10).

Likewise, the intensity of the detected light is related to the absorption of light by hemoglobin. Since our laser emits light near the isosbestic point where both oxyhemoglobin and deoxyhemoglobin absorb the same amount of light, we are able to use the intensity of detected light to calculate a blood volume index proportional to the total hemoglobin concentration

similar to standard NIRS devices (e.g., K200203, Infrascanner Model 2500 that is proposed as a reference predicate in Section 6.1.2).

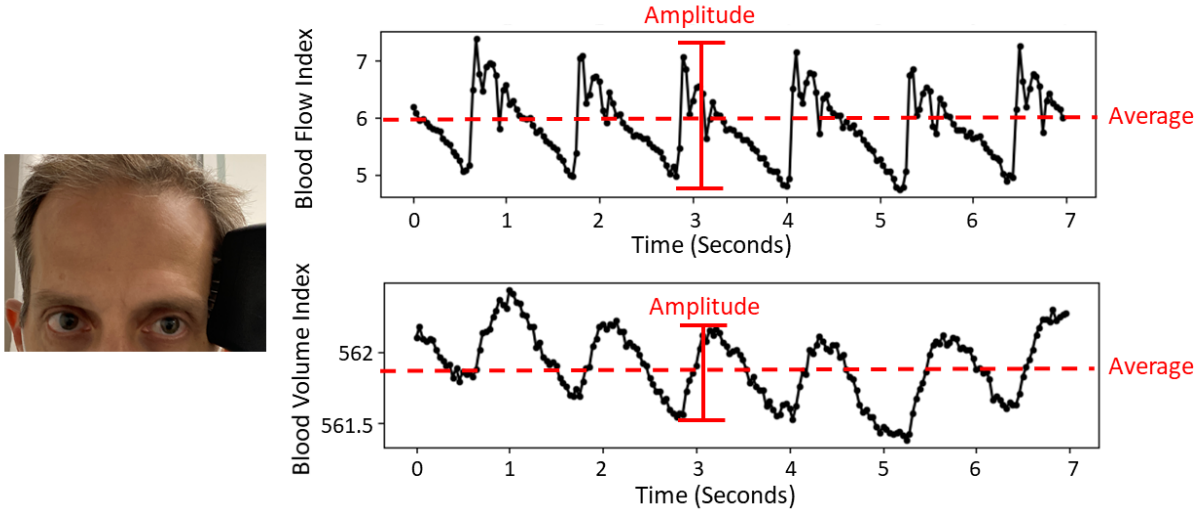


Figure 9: Typical blood flow index and blood volume index waveforms detected from a single sensor using Openwater technology for noninvasive surface measurements on the head of a healthy human volunteer.

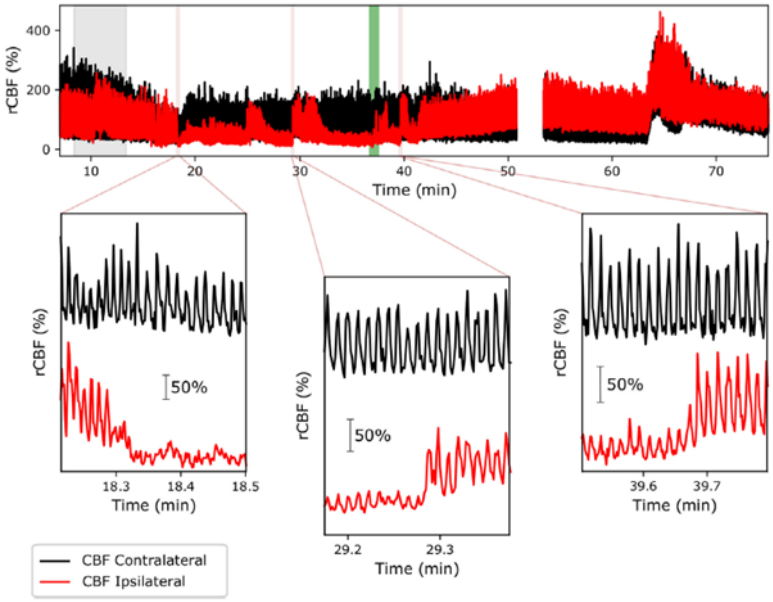


Figure 10: Example transcranial optical measurement of ipsilateral (red) and contralateral (black) Cerebral Blood Flow (CBF) changes during endovascular revascularization procedure for large vessel occlusion stroke from ICA occlusion, using a similar 785nm laser technology in an academic proof-of-principle 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.

2.3 Sources of variability

As part of product development, Openwater analyzed several factors that may affect device performance. Note that the current prototype device used in clinical studies is in the "wand" form factor and has to be manually applied at specific locations by the operator. Users in the clinical studies are instructed to use existing anatomical physical markers (midline, mid pupillary line, the eye sockets, ears, etc.) for proper placement of the wand device for each of the measurements. This is itself a source of variability that is mitigated by the development of a headset with a wearable form factor. Such a device would utilize fixed lasers and sensors and would speed up device placement for a scan.

Table 1: Sources of variability and their mitigations

Source of variability	**Discussion/Mitigations**
Placement as affected by head size, forehead size, facial symmetry	The proposed design of the wearable component of Openwater Headset includes wand elements that can be individually adjusted to ensure optimal placement for each patient (see Figure 1 for proposed design of the wearable). Once each module is in the optimal location, each one can be individually secured in place. Each of the modules will have visual cues to aid in the adjustment to the optimal anatomical location for each patient relative to their unique anatomy (such as the midpupillary line).
Forehead curvature	The Headset modules have a self-conforming mechanism to conform to the patient's unique surface curvature.
Movement	Once the Headset is placed on the head, it will be secured to the head with a fixation strap. Along with being locked once they are in the optimal position, the individual modules will be biased with spring force to make contact with the head. These design elements ensure that the laser and sensors make good contact with the head and any minor movement by the patient does not affect the measurements.
Body position and Level of consciousness	The device requires no active patient interaction and thus the patient's level of consciousness does not affect the measurements. The wearable headset is placed on the front of the head and is secured using straps. Thus, the patient body position causes no interference in how the headset can be installed or used. As such, neither the body position nor the level of consciousness should not be a determining factor in the use of the device.
Skin tone	Skin tone should have minimal effect on Openwater Headset's measurements for various reasons: • The first step in calculating the blood flow index by Openwater Headset is to calculate the speckle contrast. The speckle contrast is calculated by dividing the standard deviation of pixel values on the image sensor by the mean value of the pixels. If the amount of light hitting the sensor changes by some fraction (e.g. due to increased absorption of the light by the skin), both the standard deviation and the mean have the same relative change, and their quotient (i.e. the contrast), does not change.

Table 1: Sources of variability and their mitigations

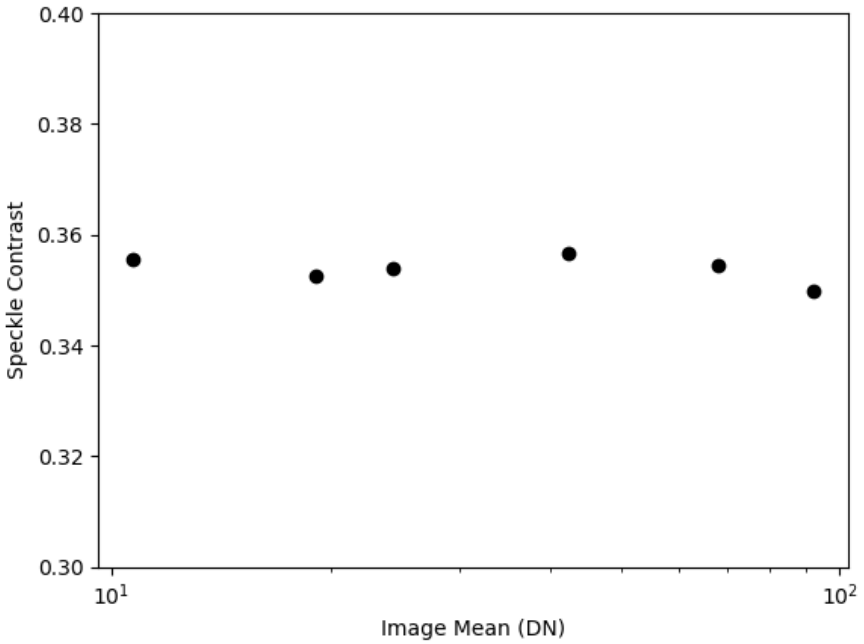
Source of variability	Discussion/Mitigations
	In an experiment to simulate the effect of a thin absorbing layer, Openwater performed the following experiment: a variable neutral density filter was used to reduce the amount of detected light over a 10x range when measuring a tissue simulating phantom. As can be seen in the figure below, standard deviation of the speckle contrast values is less than 0.6% of the mean over the entire range of intensities. This experiment will be repeated as part of the device verification activities.  • Pulse oximetry, which uses relative absorption of light at 660 and 940 nm to determine oxygen saturation, is sensitive to skin tone because the absorption of light by melanin differs between those wavelengths. Unlike pulse oximetry, Openwater Headset operates at a single wavelength (785 nm) where the absorption of light by melanin is quite small (Jacques 1991) (see chart below showing the extinction coefficient of eumelanin and pheomelanin at various wavelengths (Jacques n.d.)). When the absorption due to skin tone at this wavelength was calculated by Openwater, the differences between various skin tones was minimal.

Table 1: Sources of variability and their mitigations

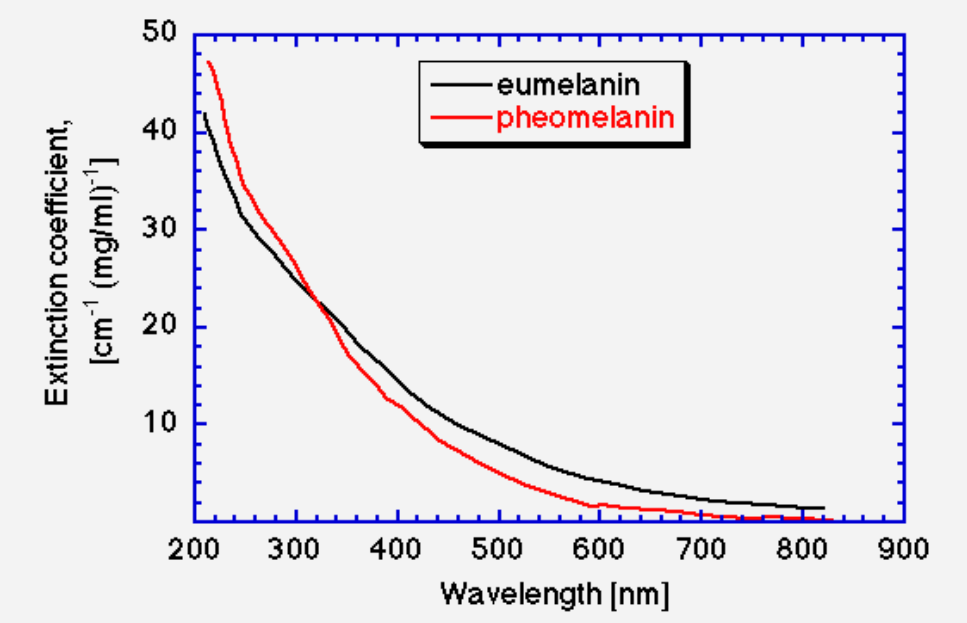
Source of variability	**Discussion/Mitigations**
	
Hair	Hair may be a source of interference. By design, hair length should not affect readings as the device is intended to be utilized in front of the hairline on the forehead and temple overlying the frontal lobe and temporal lobe. The Headset will additionally include physical features to mitigate the risk of stray hair coming into contact and affecting the measurement. Device labeling will instruct the operator to pull the patient's hair under the headband portion of the headset such that the operator can sweep and hold the hair under the headband and away from the forehead. The positioning of each of the modules is visible to and adjustable by the operator to avoid placement on hair. The modules can be temporarily lifted from the skin without altering the position to aid the operator in removing stray hair. Finally, in the case that hair is still obscuring either the laser light or the image's sensors, the Headset software will verify for each scan that the sensors detected a sufficient amount of light. In the case that insufficient light is detected, it will instruct the operator to make the necessary adjustments and repeat the scan.
Environmental	The Headset is designed to withstand the range of temperature and humidity conditions in the intended use operating environment and these specifications will be verified and validated as part of the normal product development and design control process.

Table 1: Sources of variability and their mitigations

Source of variability	**Discussion/Mitigations**
	Ambient light could be a source of interference, but the design of the laser probes and the sensors are spring loaded to ensure they make good contact with the head surface. Additionally, the Openwater Headset includes an 800 nm hard coated broadband band-pass interference filter in the light detection optics that blocks all light in the visible spectrum. Band-pass filters transmit only the target range of wavelengths in the spectrum to pass through, while blocking all light with wavelengths above or below the band. The band-pass filter in the Openwater Headset has a bandwidth of 50 nm and OD (optical density) average greater than 4.0 outside the band-pass range.
Sweat	As shown in Figure 6, the absorption of light by water is very low through wavelengths up to around 900 nm. This is a key reason for the spectral window from 650 - 950 nm where near-infrared light can penetrate to depths of many centimeters, including transcranially through bone and soft tissue (with high water content). As such, any sweat should not be a source of interference for the device measurements.

3 Preliminary Performance Data

The following sections describe the preliminary performance data collected by Openwater with the wand prototype version of Openwater Headset. As described in section 2.2, 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.

3.1 Initial Validation of Openwater Technology

To validate that the Openwater Headset's underlying technology works as intended, Openwater collected animal and human clinical data. The validation focused demonstrating that the technology is sensitive to changes in blood flow. Verification of the BFI and BVI indices was performed separately in a phantom model (see Section 3.2).

3.1.1 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 11). Figure 11B 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 11D and Figure 11E 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.

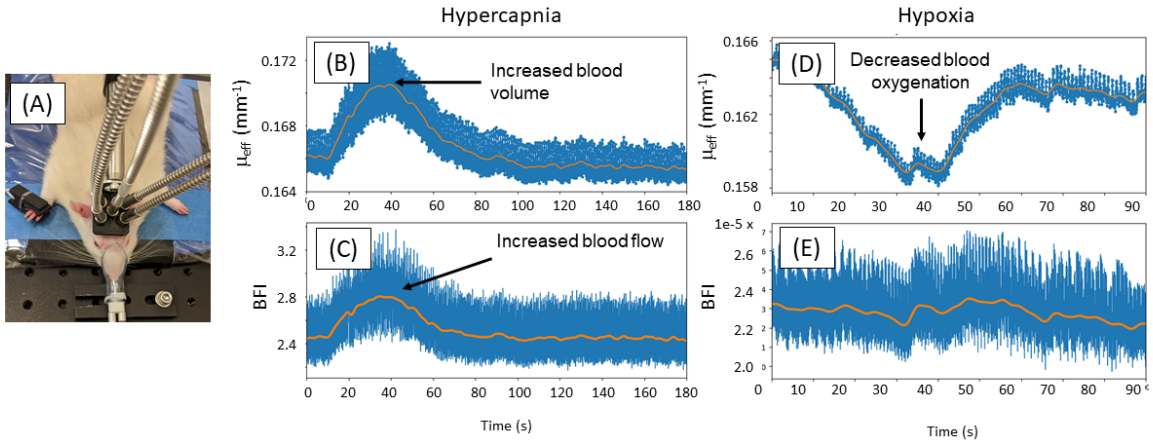


Figure 11: Preclinical data from a rat undergoing hypercapnic and hypoxic inhaled gas challenges for augmented cerebral blood flow during transcranial optical cerebral blood flow measurements using Openwater technology. (A) photograph of the rat with the noninvasive fiber optic probe placed on the surface 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.

3.1.2 Temporary vessel occlusions

Preclinical rat small animal model of temporary occlusion of the middle cerebral artery (MCA) was next utilized to demonstrate feasibility in detecting blood flow and volume changes due to an arterial occlusion. 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 12). The noninvasive Openwater system was sensitive to the experimental arterial 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.

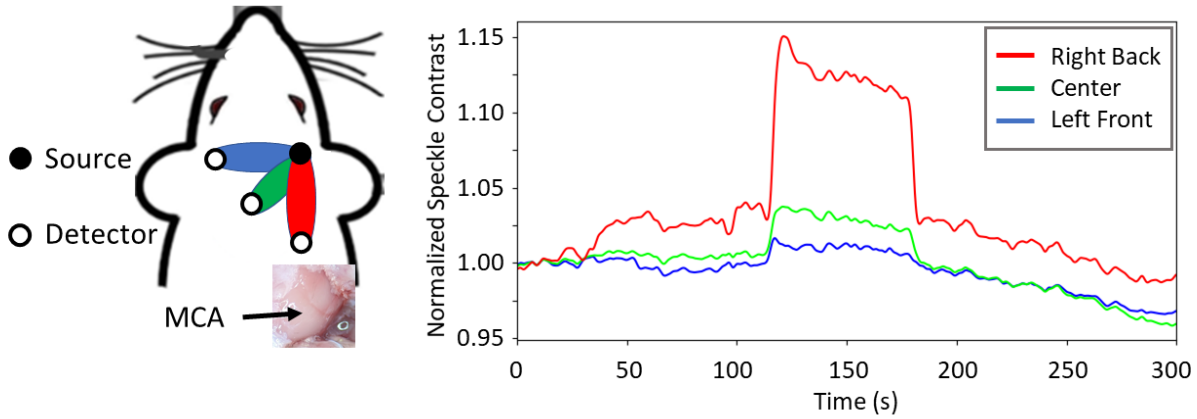


Figure 12: Results of temporary middle cerebral artery (MCA) occlusion animal model. The Openwater technology noninvasively measures underlying brain blood flow at three locations, directly above the vascular territory of the MCA (red line) versus over other vascular territories more toward the center (green line) and farther toward the right MCA (blue line). When the ipsilateral MCA is temporarily occluded with a microsurgical clip, 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.

3.1.3 Human Cerebral Blood Flow Validation Data

The following validation demonstrates that the technology can differentiate between surface flow and transcranial flow by observing the flow/volume differences between the shallow and deep sensors. Two different validation tests are discussed, one in which the surface flow is occluded temporarily using a circumferential pneumatic headband pressure cuff (Section 3.1.3.1). In the second discussion, the flow differences due to an ischemic stroke is measured (Section 3.1.3.2).

3.1.3.1 Human head surface measurements of blood flow and volume

Figure 13 demonstrates the use of two source-sensor distances with near simultaneous acquisition by the Openwater wand prototype, with the smallest source-sensor distance (top row at 7.6mm) representing shallow photon interrogation of blood flow near the surface of the skin, and the larger source-sensor 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-sensors. The blood flow waveforms detected from the source-sensor 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.

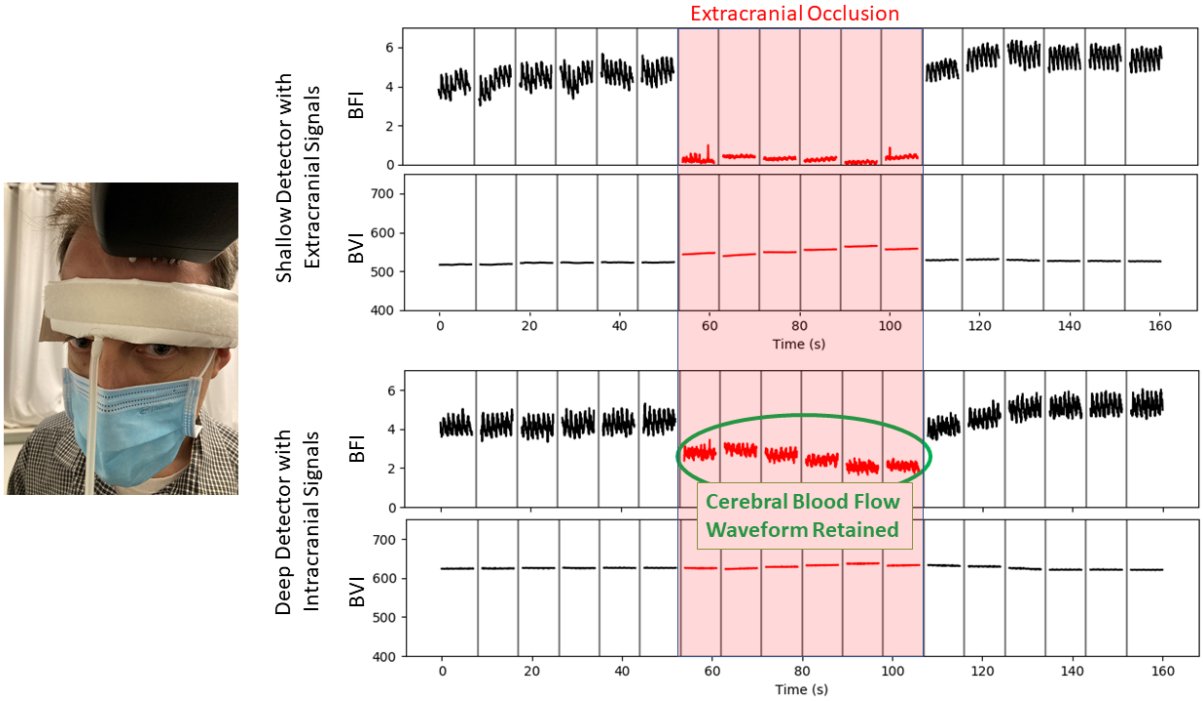


Figure 13: BFI and BVI waveforms from a healthy human forehead during large vessel occlusion of the surface extracranial carotid circulation. Shown is data from two simultaneous sensors at two distances (7.6 and 42.8 mm) from a laser source position. Six acquisitions of seven seconds each are acquired 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 BFI 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.

3.1.3.2 Human Cerebral Blood Flow Validation Data

Under an 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.

The Openwater system's blood flow and volume measurements were consistent with the imaging data. For example, 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 14.

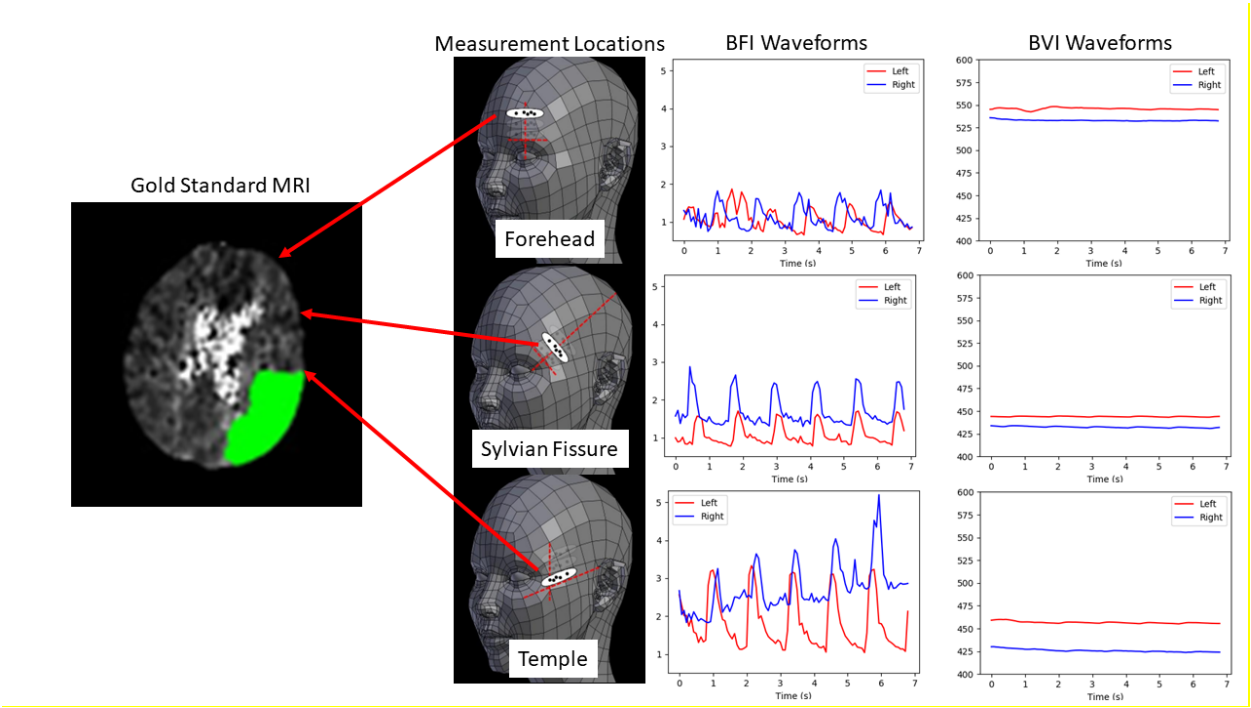


Figure 14: Assessment of Unilateral M2 Inferior Occlusion with Openwater Technology. Results from the measurement of a patient with an occlusion of a medium vessel occlusion (MeVO) of the inferior M2 branch of the middle cerebral artery. Three complete scans were performed during a single session. Shown are representative underlying source blood flow index (BFI) and blood volume (BVI) waveforms from trial #3 all demonstrating the differences between the left and right hemispheres at the 3 locations pictured.

Figure 14 above shows the BFI and BVI waveforms from a scan conducted on the left and right sides at three positions, namely the forehead, the sylvian fissure, and the temple. Each position includes the BFI And BVI from the deep sensor at each position. The BFI and BVI show minimal differences between the left and right measurements when measured over unaffected vascular territories on the forehead. However, the measurements appear to diverge in the deep sensor when the probe was moved toward measuring directly over the affected vascular distribution. These findings are consistent with patient's inferior temporal abnormality due to an underlying M2 inferior MCA occlusion validating the capabilities of the deep sensor of the device.

3.2 Phantom Data

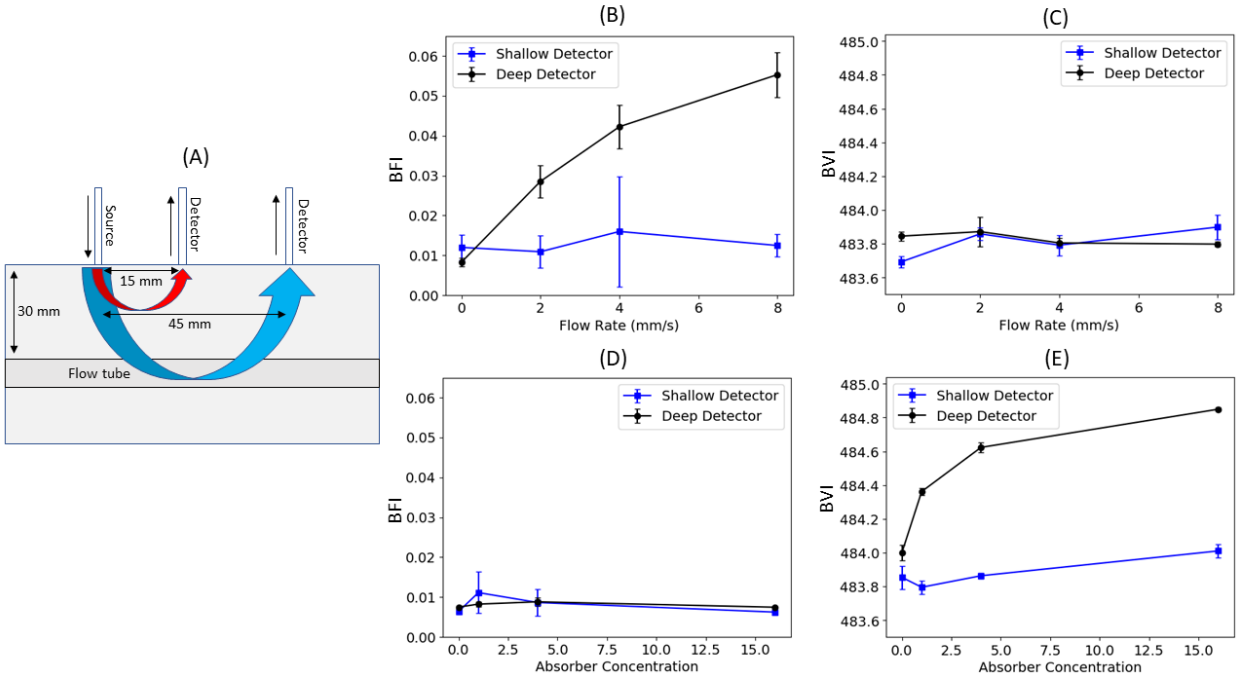


Figure 15: Example preclinical phantom data utilizing the Openwater prototype in tissue and blood-mimicking phantoms with variable flow rates and absorption, including simulated large vessel occlusion (B and C) and simulated bleed (D-E). (A) a schematic of a tissue-simulating phantom used in experiments, in this case having a tube located 30 mm below the surface, with distinct source-sensor separations at the surface (B) BFI measurements logged for various flow rates inside the tube demonstrating the sensitivity of source-sensor separations for different depths of the underlying tissue, (C) BVI measurement demonstrating that blood flow does not affect the BVI, (D) BFI measurements logged for various concentrations of an absorber (ink) inside the tube demonstrating that absorption does not affect BFI, and (E) BVI measured for the various concentrations demonstrating higher sensitivity to the deeply located tube by the larger source sensor separation.

Phantom data was utilized to verify the wand prototype version of Openwater Headset against known simulated blood flow rates and light absorption of blood in order to confirm the sensitivity of the optical measurement. Figure 15 shows an example experimental model that demonstrates resolution of simulated blood flow and volume 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 (i.e., detectors with sensors) located at distances of 15 mm and 45 mm away. Light detected 45 mm from the source has on average traveled deeper into the phantom than the light collected 15 mm away. A fatty emulsion with blood-mimicking optical properties is pumped with a syringe pump through a 6 mm diameter tube whose top surface is 30 mm below the surface of the phantom (Figure 15A). As the speed at which the emulsion flow is increased, the blood flow index increases for the 45 mm sensor, whereas the blood flow index for the 15 mm sensor remains unchanged (Figure 15B). The blood volume index, which is not affected by the speed of flow, also remains unchanged (Figure 15C). Likewise, in order to demonstrate sensitivity to blood volume, absorbing India ink is titrated into the emulsion in the flow tube, increasing its optical absorption over a range of ~0 to 16x the absorption of normal brain tissue. As the ink concentration is increased, the blood volume index

increases for the 45 mm sensor, whereas the blood volume index for the 15 mm sensor remains unchanged (Figure 15E). The blood flow index, which is not affected by optical absorption, also remains unchanged (Figure 15D). Using the flow and absorption 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), confirmed sensitivity for signal changes of absorption values corresponding to blood volumes ranging from no blood to bleeds, and demonstrated the ability to distinguish between blood flow and blood volume changes.

4 Proposed Indications for Use/Intended Use

Openwater proposes an Indications for Use statement as follows:

- Intended use:
  The Openwater Headset is intended to non-invasively 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.

5 Regulatory History

The Openwater Headset was discussed in Q211873, which was a request for a breakthrough device designation for the Openwater LVO Stroke Alert device that utilizes the Openwater Headset data. There have been no other discussions specifically on the Openwater Headset with the FDA.

6 Regulatory Pathway and Predicate Analysis

6.1.1 Proposed product code

The Openwater Headset'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).*

Several devices with similar intended use have utilized product codes MUD, "Oximeter, Tissue Saturation", DPT, "Probe, Blood-Flow, Extravascular", as well as QEM, "Cerebral Oximeter". However, since the subject device does not provide any oximetry or SpO2 measurements, and with an intended use of measuring blood flow, Openwater proposes to utilize only the DPW product code.

6.1.2 Proposed predicates

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 optical monitoring of blood flow in tissue, including transcranially in the brain.
    - Of note, the K150268 device was preceded by devices that include K093923 and K100875, CerOx Model 3210 and 3210F, respectively. These devices use equivalent transcranial optical laser technology to monitor blood flow in tissue including blood in the brain, respectively but additionally also monitor regional hemoglobin oxygen saturation of blood in the brain of an adult.
- 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, and achieves interrogation depths similar to the subject device.
    - K190270, FORE-SIGHT, which uses equivalent transcranial optical laser technology related to brain oximetry for the purpose of cerebral oximetry. This device also provides total hemoglobin concentration in blood as well as relative changes in this concentration. The subject device provides a similar measurement that is termed as Blood Volume Index (BVI).
    - 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

6.1.3 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.

6.1.4 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.

6.1.5 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 sensor 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 and the proprietary Blood Volume Index (BVI) is calculated based on the intensity of the measured camera image. Specifically, the Openwater Headset device utilizes two sensors, one to gather surface flow information, while the second to gather deeper flow information, while the predicate device utilizes only one sensor to measure surface flow. In other words, like the predicate, the Openwater headset uses similar technology to measure blood flow but unlike the predicate that uses only one sensor, the subject device uses two sensors to interrogate different depths. The subject device's shallow sensor is similar to the predicate device's sensor with similar

interrogation depth of about 10-15mm while the deeper sensor in the subject device achieves a depth of about 30 mm.

The use of multiple sensors that are separated to achieve and control the depth of measurement by the subject device is similarly utilized by the reference predicate, K200203, Infrascanner Model 2500, which uses equivalent transcranial optical laser technology to detect measurement features related to intracerebral hemorrhage and achieves interrogation depths similar to the subject device. Additional reference predicates include 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. In this performance testing, Openwater proposes to demonstrate the accuracy, repeatability, and reproduceability of measuring the blood flow and volume from the two sensors. This proposed test method is discussed in Section 7.1.

6.1.6 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 6.1.2 would serve as appropriate predicates to establish substantial equivalence.

Table 2: 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	Similar. The proposed K150268 predicate is intended for a broader patient population.

Table 2: Openwater Headset Substantial Equivalence Summary to Proposed Predicate

Feature	**Openwater Headset**	**K150268, CerOx Model 3215FOP (Proposed predicate)**	**Analysis of differences**
		sole basis for diagnosis or therapy.	
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.
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 sensors 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 and measure speckle contrast. The subject device uses two sensors to interrogate deeper tissue instead of one in the predicate – the technology and principles are similar, i.e., the depth is achieved through source sensor separation. This is like the reference K200203, Infrascanner Model 2500, which also uses multiple sensors to detect blood at different depths.

7 Proposed Testing

As discussed in Section 6.1.2, 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 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, and both devices proprietary indices to monitor blood flow, Openwater proposes testing to demonstrate that Openwater Headset is substantially equivalent to CerOx. Note that both devices should not be used as the sole basis for diagnosis or therapy as the prospective clinical value of data from both devices have not been demonstrated in disease states.

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 (Section 3). The following sections summarize the proposed testing.

7.1 Bench Performance testing

To demonstrate the consistency 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 (Racheli et al., 2012). This testing is similar to the evaluation discussed in Section 3.2 where the device will be challenged with specific known volume and speed of the blood-mimicking fluid in the calibrated phantom model.

In the proposed testing, Openwater will utilize an updated phantom that is similar to Figure 15 but includes additional channels to simulate flow at different depths. Specifically, the phantom includes an array of tubes at different depths so that both volume and flow rates can be modified. The phantom design is based on experiments in Racheli et al., 2012 and Choe R., 2005. The phantom will be designed to match the optical properties of tissue, i.e., the scattering and absorbing properties, characterized by μ_s (reduced scattering coefficient) and μ_a (absorption coefficient) respectively.

The solid part of the phantom would have a base material of acrylic, with a scatter of titanium dioxide, and absorber of carbon black. Matcher et al [Matcher, SJ, 1997] reports human forehead $\mu_a = 0.16 \pm 0.01$ cm^{-1} and $\mu_s = 9.4 \pm 0.7$ cm^{-1} at 800 nm for 14 adult subjects (Jacques SL, 2013)[1], while Jacques2013 reports $\mu_s = 10$ cm^{-1} at 800 nm. The target for the phantom with the materials noted above are $\mu_a = 0.16$ cm^{-1}, $\mu_s = 10$ cm^{-1}. The blood mimicking fluid used in the phantom is proposed to have a base material of water, a scatterer of half and half (i.e., whole milk and cream), and an absorber of India ink, whose amounts can be varied.

[1] https://omlc.org/news/dec14/Jacques_PMB2013/Fig_brain.jpg

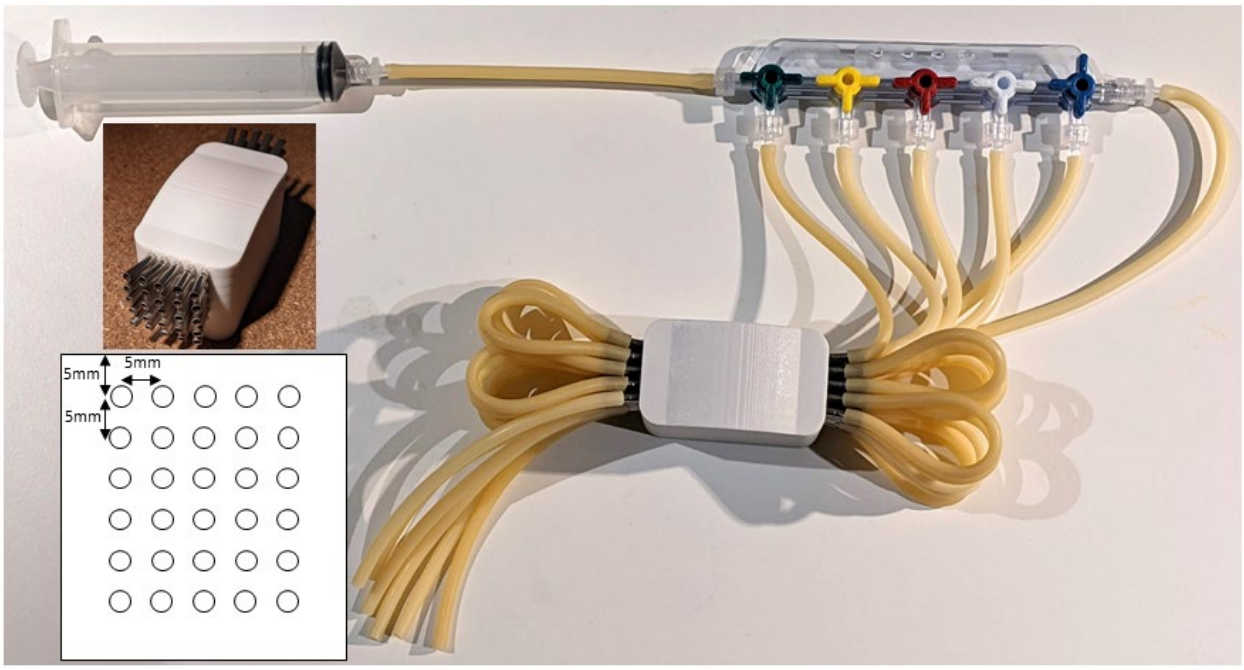


Figure 16: Photograph of the proposed tissue mimicking phantom. A syringe pump (only the syringe is shown) is used to pump a fatty emulsion to a 1x6 switch which guides the fluid to one of six layers in the tissue simulating phantom where the fluid is routed back and forth through 5 tubes at a single depth before exiting the system. All 30 tubes in the phantom are filled with the emulsion before beginning the experiment. A module from the headset consisting of a light source and sensors is placed on top of the phantom, and then the emulsion is pumped through the tubes in one of the layers which vary in depth from 5-30 mm. Top inset is a photo of one end of the phantom without the tubbing attached. Bottom inset is a schematic of the phantom cross section showing the grid of tubes with 5 mm spacing.

The testing includes the following evaluations:

- Sensitivity to changes in blood flow at different depths, by simulating blood flow different rates in a calibrated manner at various depths,
- Sensitivity to changes in volume by using a fluid that matches the scattering properties of human tissue at 785 nm. The change in volume is simulated by increasing the concentration of chromophores in the mimicking fluid.
- Simulation of skin tone by adding neutral density filters to attenuate the signal and its capture and performing the flow and volume experiments.

In addition to the measurement of accuracy, Openwater proposes to utilize the calibrated phantom model to perform repeated measurements to demonstrate the repeatability and reproducibility of the blood flow and volume indices measured by the device.

7.2 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.

7.3 Cleaning

Given that the device's wearable headset is intended to contact intact skin on the head, the device will include instructions to clean the headset. The device will not require high level disinfection or sterilization. Validation that the device can be cleaned will be conducted including an assessment that afterwards, the device continues to perform as intended.

7.4 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 predicate device's "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.

7.5 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. Based on the guidance noted above, Openwater assessed the level of concern in the tables below and concluded that the device has a "Moderate" level of concern.

Table 1: FDA Guidance Table 1: Major Level of Concern

Question	Response	Notes
1. Does the Software Device qualify as Blood Establishment Computer Software?	No	Openwater Headset does not qualify as Blood Establishment Computer Software.
2. Is the Software Device intended to be used in combination with a drug or biologic?	No	Openwater Headset is not intended to be used in combination with a drug or biologic.
3. Is the Software Device an accessory to a medical device that has a Major Level of Concern?	No	The Openwater Headset is not an accessory to another medical device.
4. Prior to mitigation of hazards, could a failure of the Software Device result in death or serious injury, either to a patient or to a user of the device?	No	Openwater Headset is intended to measure the blood flow and volume that is an input as part of a clinical workup but may not be used as the sole basis for diagnosis or therapy, as will be noted in the device labeling including instructions to utilize other modalities to confirm a critical diagnosis. The device is not intended for active patient monitoring. The failure of the device

Table 1: FDA Guidance Table 1: Major Level of Concern

Question	Response	Notes
		could not directly lead to death or serious injury per risk analysis and risk mitigation.
a. Does the Software Device control a life supporting or life sustaining function?	No	Openwater Headset is not intended to control a life supporting or sustaining function.
b. Does the Software Device control the delivery of potentially harmful energy that could result in death or serious injury, such as radiation treatment systems, defibrillators, and ablation generators?	No	Openwater Headset is intended control delivery of a laser energy device, but the energy output is limited in hardware at a Class I laser level. As a result, a failure in the device software cannot result in the delivery of potentially harmful energy that could result in death or serious injury.
c. Does the Software Device control the delivery of treatment or therapy such that an error or malfunction could result in death or serious injury?	No	Openwater Headset is not intended to control delivery of treatment or therapy.
d. Does the Software Device provide diagnostic information that directly drives a decision regarding treatment or therapy, such that if misapplied it could result in serious injury or death?	No	Openwater Headset is intended to measure the blood flow and volume that is an input as part of a clinical workup but may not be used as the sole basis for diagnosis or therapy, as will be noted in the device labeling including instructions to utilize other modalities to confirm a critical diagnosis. The device is not intended for active patient monitoring. It does not provide diagnostic information that directly drives a decision regarding treatment or therapy, such that if misapplied it could result in serious injury or death.
e. Does the Software Device provide vital signs monitoring and alarms for potentially life-threatening situations in which medical intervention is necessary?	No	Openwater Headset is not intended for active patient monitoring and is not intended to monitor vital signs or provide alarms in potentially life-threatening situations.

Conclusion: Openwater Headset is <u>not</u> a Major Level of Concern software.

Table 2: FDA Guidance Table 2: Moderate Level of Concern

Question	Response	Notes
1. Is the Software Device an accessory to a medical device that has a Moderate Level of Concern?	No	Openwater Headset is not a component of other medical devices.

Table 2: FDA Guidance Table 2: Moderate Level of Concern

Question	Response	Notes
2. Prior to mitigation of hazards, could a failure of the Software Device result in Minor Injury, either to a patient or to a user of the device?	Yes	Prior to mitigation of hazards, failure of the software in Openwater Headset could cause minor injury.
3. Could a malfunction of, or a latent design flaw in, the Software Device lead to an erroneous diagnosis or a delay in delivery of appropriate medical care that would likely lead to Minor Injury?	Yes	A software malfunction or latent design flaw could result in an inaccurate information presented to the HCP. This can lead to an erroneous diagnosis or a delay in delivery of appropriate medical care that would likely lead to Minor Injury.

Conclusion: Openwater Headset is a Moderate Level of Concern software.

7.6 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.

7.7 Clinical Testing

Based on the intended use and the methods of verification utilized by the predicate, Openwater believes that clinical testing would not be required for the subject device and that substantial equivalence could be established using testing on the phantom (see Section 7.1). Specifically, the device does not provide oximetry and thus regulation 21 CFR 870.2700, "Oximeter" is not applicable. As a result, Openwater does not intend apply test methods equivalent to ISO 80601-2-61, "Medical electrical equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment"

7.8 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 Specific Questions for Discussion

Openwater requests that feedback on the following topics:

Regulatory Strategy Questions

1) Does FDA agree that the proposed regulatory pathway is appropriate for Openwater Headset? Specifically,
    a. Does the FDA agree that based on the regulatory strategy provided and the device's risk profile, the subject device may be classified as a Class II device?
    b. Does the FDA agree that based on the regulatory strategy provided, that a 510(k) pathway may be appropriate for the subject device that utilizes the DPW, "Flowmeter, Blood, Cardiovascular" product code under regulation 870.2100, "Cardiovascular blood flowmeter"?
    c. For a future 510(k) for the subject device, Openwater proposes to use the K150268, CerOx Model 3215FOP as a predicate, with the K200203, Infrascanner Model 2500 as a reference predicate. Does the FDA have any concerns with the predicate device proposed or recommendations for alternative predicates or references?

Performance Testing Questions

2) Does the FDA have any comments on the proposed testing to assess device performance, as described in Section 7, for a future device submission?
    a. Does the FDA agree that the proposed testing of the proprietary blood flow and volume indices utilizing a phantom model, like the predicate K150268, would be an appropriate method to characterize device performance as well as establish substantial equivalence? Are there any specific considerations for testing with the phantom model that Openwater should additionally include in its test plans?
    b. Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that clinical or animal performance testing data is not needed to support a future 510(k)?
    c. Does FDA agree that the Openwater Headset software is a "moderate" level of concern and that the level of documentation that will be included in an upcoming marketing submission is consistent with FDA's recommendations provided in FDA's guidance entitled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" as part of the upcoming device submission?

Other considerations

3) Does the FDA have any other concerns or topics they would like Openwater to consider for Openwater Headset's premarket notification?

9 Mechanism of Feedback

In addition to written feedback, Openwater is requesting an in-person 1-hour long teleconference meeting to discuss the questions listed in Section

Materials needed during meeting:

- Conference bridge to share information and slides

Suggested FDA staff who should attend the meeting:

- Lead Reviewer
- Assistant Director for the reviewing branch

Proposed dates:

Openwater proposed the following dates for the meeting. Per FDA guidelines, these dates are proposed 60-75 dates from the submission date.

- Any business day between Jan 31, 2022 to Feb 15, 2022, between 11am – 5pm EST

Openwater Attendees:

The following Openwater personnel and its consultants will attend this meeting:

Name	**Title**
Maurizio Vecchione	President, Openwater
Achal Singh Achrol, MD	Chief Medical Officer, Openwater
Soren Konecky, Ph.D.	Chief Technology Officer, Openwater
Casey Trubo	Senior Staff Program Manager, Openwater
Prabhu Raghavan	Regulatory Consultant to Openwater

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