February 12, 2025

Subtle Medical, Inc.
℅ Jared Seehafer
Regulatory Consultant
Enzyme Corporation
611 Gateway Blvd
Ste 120
South San Francisco, California 94080

Re: K243250
Trade/Device Name: SubtleHD (1.x)
Regulation Number: 21 CFR 892.2050
Regulation Name: Medical Image Management And Processing System
Regulatory Class: Class II
Product Code: QIH
Dated: January 13, 2025
Received: January 13, 2025

Dear Jared Seehafer:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

FDA's substantial equivalence determination also included the review and clearance of your Predetermined Change Control Plan (PCCP). Under section 515C(b)(1) of the Act, a new premarket notification is not required for a change to a device cleared under section 510(k) of the Act, if such change is consistent with an established PCCP granted pursuant to section 515C(b)(2) of the Act. Under 21 CFR 807.81(a)(3), a new premarket notification is required if there is a major change or modification in the intended use of a device, or if there is a change or modification in a device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process. Accordingly, if deviations from the established PCCP result in a major change or modification in the intended use of the device, or result in a change or modification in the device that could significantly affect the safety or effectiveness of the device, then a new premarket notification would be required consistent with section 515C(b)(1) of the Act and 21 CFR 807.81(a)(3). Failure to submit such a premarket submission would constitute adulteration and misbranding under sections 501(f)(1)(B) and 502(o) of the Act, respectively.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these

requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Daniel M. Krainak, Ph.D.
Assistant Director
Magnetic Resonance and Nuclear Medicine Team
DHT8C: Division of Radiological
Imaging and Radiation Therapy Devices
OHT8: Office of Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 07/31/2026
*See PRA Statement below.*

Submission Number *(if known)*

K243250

Device Name

SubtleHD (1.x)

Indications for Use *(Describe)*

SubtleHD is an image processing software that can be used for image enhancement of all body parts MRI images. It can be used for noise reduction and increasing image sharpness.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

***DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.***

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
*PRAStaff@fda.hhs.gov*

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*

## SubtleHD 510(k) Summary

**Table 1. Contact Details and Device Name**

| | |
|---|---|
| **Date Summary Prepared:** | 2025-02-10 |
| **Contact Details:** | |
| **Applicant Name:** | Subtle Medical, Inc. |
| **Applicant Address:** | 883 Santa Cruz Ave, Suite 205<br>Menlo Park, CA 94025 United States |
| **Applicant Contact:** | Ms. Ronny Elor |
| **Applicant Contact Telephone:** | (925) 324-8467 |
| **Applicant Contact Email:** | ronny@subtlemedical.com |
| **Correspondent Name:** | Enzyme Corporation |
| **Correspondent Address:** | 611 Gateway Blvd, Ste 120<br>South San Francisco, CA 94080 United States |
| **Correspondent Contact:** | Mr. Jared Seehafer |
| **Correspondent Contact Telephone:** | (415) 638-9554 |
| **Correspondent Contact Email:** | jared@enzyme.com |
| **Device Name:** | |
| **Device Trade Name:** | SubtleHD (1.x) |
| **Common Name:** | Medical image management and processing system |
| **Classification Name:** | System, Image Processing, Radiological |
| **Regulation Number:** | 892.2050 |
| **Product Code:** | QIH |
| **Device Class:** | Class II |
| **Legally Marketed Predicate Devices:** | **Primary Predicate #**: K230854<br>**Predicate Trade Name**: SwiftMR<br>**Predicate Manufacturer**: AIRS Medical Inc.<br><br>**Secondary Predicate #**: K223623<br>**Predicate Trade Name**: SubtleMR<br>**Predicate Manufacturer**: Subtle Medical, Inc. |

***Device Description Summary***

SubtleHD is Software as a Medical Device (SaMD) consisting of a software algorithm that enhances images taken by MRI scanners. As it only processes images for the end user, the device has no user interface. It is intended to be used by radiologists and technologists in an imaging center, clinic, or hospital. The SubtleHD software can be used with MR images acquired as part of standard of care and accelerated MRI exams as the input. The outputs are the corresponding images with enhanced image quality. Original DICOM images are passed onto the SubtleHD software as an input argument and the enhanced images are saved in the designated location prescribed when running the SubtleHD software. The functionality of SubtleHD (noise reduction and sharpness enhancement) is identified from the DICOM series description and/or through configuration. Configuration is specified as configuration files and OS environment variables.

SubtleHD software implements an image enhancement algorithm using a convolutional neural network based filtering. Original images are enhanced by running through a cascade of filter banks, where thresholding and scaling operations are applied. A single neural network is trained for adaptive noise reduction and sharpness increase. The parameters within the neural network were obtained through an image-guided optimization process. Additional nonlocal mean based denoising and unsharp masking based sharpening filters are applied to the deep learning processed image.

The software operates on DICOM files, enhances the images, and sends the enhanced images to any desired destination with an AE Title (e.g., PACS, MR device, workstation, and more). Enhanced images coexist with the original images.

***Intended Use / Indications for Use***

SubtleHD is an image processing software that can be used for image enhancement of all body parts MRI images. It can be used for noise reduction and increasing image sharpness.

***Intended Use / Indications for Use Comparison***

SubtleHD and its predicates are all intended to denoise and sharpen MRI images of various input protocols, imaging scanners, and anatomical regions.

***Technological Comparison***

SubtleHD and its predicates are all used for image enhancement. They operate on DICOM files, enhance the images, and send the enhanced images to any desired destination. The receipt of original DICOM image files and delivery of enhanced images as DICOM files depends on other software systems. Both subject and predicate devices use convolutional neural network based filtering. Original images are enhanced by running through a cascade of filter banks, where thresholding and scaling operations are applied. The software performs noise reduction and sharpness increase. The parameters within the software are obtained through an image-guided optimization process. Additional pre- and post-processing is applied to configure desired perceived image quality.

The following table provides a detailed description of the technological characteristics of subject and predicate devices.

**Table 2. Comparison of Technological Characteristics**

| Comparison | SubtleHD (Subject Device) | SwiftMR (Primary Predicate Device) (K230854) | SubtleMR (Secondary Predicate Device) (K223623) | Noted Differences |
|---|---|---|---|---|
| Workflow | The software operates on DICOM files, enhances the images, and sends the enhanced images to any desired destination with an AE Title (e.g., PACS, MR device, workstation, and more). Enhanced images coexist with the original images. | The software operates on DICOM files, enhances the images, and stores the enhanced images on PACS or on a MR device. Enhanced images coexist with the original images. | The software operates on DICOM files on the file system, enhances the images, and stores the enhanced images on the file system. The receipt of original DICOM image files and delivery of enhanced images as DICOM files depends on other software systems. | SubtleHD can send enhanced images to any destination as long as it is associated with an IP and AE Title. SubtleMR by default is intended to send enhanced images to PACS, but can be configured to other destinations. SwiftMR can send enhanced images to PACS or an MR Device. Substantially Equivalent. |
| Product Code | QIH | LLZ | LLZ | Substantially Equivalent. |
| Physical Characteristics | Software package Operates on a virtual machine | Same | Same | Same |
| Intended User | Radiologists | Same | Same | Same |
| Intended Location | Medical facility (hospitals, clinics, imaging center, etc.) | Same | Same | Same |
| Modalities | MRI | Same | Same | Same |
| Operating System / Computer | Linux Compatible; PC or Mac | PC Compatible | Same | SubtleHD and SubtleMR are PC or Mac, while SwiftMR is only PC. Substantially Equivalent. |
| Rx or OTC | Rx | Same | Same | Same |
| User Interface | None | Same | Same | Same |
| DICOM Standard Compliance | The software processes DICOM-compliant image data. | Same | Same | Same |

| Comparison | SubtleHD (Subject Device) | SwiftMR (Primary Predicate Device) (K230854) | SubtleMR (Secondary Predicate Device) (K223623) | Noted Differences |
|---|---|---|---|---|
| Image Enhancement Algorithm Description | SubtleHD software implements an image enhancement algorithm using a convolutional neural network based filtering. Original images are enhanced by running through a cascade of filter banks, where thresholding and scaling operations are applied. A single neural network is trained for adaptive noise reduction and sharpness increase. The parameters within the neural network were obtained through an image-guided optimization process. Additional nonlocal mean based denoising and unsharp masking based sharpening filters are applied to the deep learning processed image. | SwiftMR implements an image enhancement algorithm using convolutional neural network-based filtering. Original images are enhanced by running through a cascade of filter banks, where thresholding and scaling operations are applied. Neural network-based filters that perform noise reduction and/or sharpening are obtained. The parameters of the filters were obtained through an image-guided optimization process. Sharpening filter is additionally applied to the deep learning processed image. | SubtleMR software implements an image enhancement algorithm using convolutional neural network based filtering. Original images are enhanced by running through a cascade of filter banks, where thresholding and scaling operations are applied. Separate neural network based filters are obtained for noise reduction and sharpness increase. The parameters of the filters were obtained through an image-guided optimization process. | Substantially Equivalent. |
| Model Architecture | Single SRE/DNE model with filters/ pre/post-processing. | DNE is a model; SRE is achieved via multiple filters | SRE is a model, DNE is a model, with filters/ pre/post-processing | Deep-learning algorithm and processing steps for noise reduction and sharpness enhancement. Substantially Equivalent. |
| Function | Combined SRE and DNE for all anatomies. | Combined SRE and DNE, can turn either off as an option. | Separate, DNE head, spine, neck, abdomen, pelvis, prostate, breast, and musculoskeletal, SRE head only. | Substantially Equivalent. |
| Enhancement levels | Optional high denoising level and optional high sharpening level. | Denoising level from level 0 to level 8, Sharpness level from level 0 to level 5. | No levels (single level). | SubtleHD and SwiftMR are substantially equivalent. SubtleMR has a single SRE and DNE option. |
| Performance Validation | Endpoints and acceptance criteria using retrospective clinical images for both noise reduction and sharpness increase functions. | Same | Same | Same |

***Predetermined Change Control Plan (PCCP)***

SubtleHD has a Predetermined Change Control Plan (PCCP), which details planned device modifications, the associated methodology to develop, validate, and implement those modifications, and an assessment of the impact of those modifications. In general, Subtle Medical utilizes PCCPs for planned modifications that aim to improve customer satisfaction with respect to perceived image quality, generalizability, and flexibility of the product.

The SubtleHD PCCP contains one planned modification: to add more denoising and sharpening levels as a configuration option. This modification is intended to provide additional flexibility for the user. Prior to release, the software verification and validation and performance validation described in this summary shall be re-executed with the same endpoints and validation dataset as those used to support this submission, with the acceptance criteria for the new configurable levels of denoising and sharpness being adjusted to have increasing stringency. Re-executing the software verification and validation and performance validation will ensure substantial equivalence is maintained following the modification. The algorithm will be locked with fixed model parameters prior to release.

This modification shall be performed as a part of Subtle Medical's Design Change Control process in a Quality Management System that is ISO 13485:2016 and MDSAP certified. It shall be accompanied by a software version-specific Customer Release Notes describing the change along with software version-specific User Manual. The updated labeling shall be delivered to users by Subtle Medical customer success personnel.

***Non-Clinical and/or Clinical Tests Summary & Conclusions***

Subtle Medical conducted the following performance testing:

- Software Verification and Validation testing (unit, integration, and system testing) to demonstrate that software requirements are implemented. These tests passed.
- Standalone image quality metric testing to report the Least Absolute Deviations (L1 loss), Structural Similarity (SSIM), and peak signal-to-noise ratio (PSNR) values. This testing demonstrated significant reduction in L1 loss and significant increase in SSIM and PSNR.
- Performance Validation testing utilizing retrospective clinical data to demonstrate the software enhanced image quality in MR images via a reduction of noise or sharpness enhancement. These tests passed.
- A Reader Study utilizing retrospective clinical data to demonstrate the software enhanced image quality in MR images via a reduction of noise or sharpness enhancement. These tests passed.

**Standalone Image Quality Metric Testing:**

A subset of our performance validation set, which is detailed below, where standard-of-care (SOC) images were acquired, was used to create a paired test set for evaluating L1 loss, SSIM, and PSNR. To enhance the spatial alignment between the two separately acquired images, affine registration was applied to the accelerated images (i.e., inputs) to align them with the SOC images. However, perfect alignment of image pairs was not achievable due to inter-scan motions (e.g., non-rigid respiratory/pulsation). Additionally, slight image contrast differences in focal regions between the two scans (e.g., non-repeatable blood/CSF suppression, protocol adjustment-induced minor contrast changes) were possible. Furthermore, the acquired SOC images may not have all been of high quality, with residual noise and image blurring potentially persisting on the SOC images. All of these factors could induce additional errors (beyond the performance of the SubtleHD algorithm) when measuring pixel-wise

metrics using the SOC images as the reference. To eliminate residual noise and reduce blurring on SOC images, the metrics were also calculated using the SubtleHD-enhanced SOC as the reference, and then metric analysis was performed between the input and SubtleHD enhanced input.

The following selection criteria was used for the paired test data:

- Not used for algorithm training.
- Split between all anatomies (abdomen, ankle, brain, breast, C-spine, foot, hand, hip, knee, L-spine, neck, pelvis, prostate, shoulder, t-spine, and wrist).
- Have pediatric data:
    - 20 children (ages 2 to 11)
    - 22 adolescents (ages 12 to 21)
- Have 0%, 20%, 30%, 40%, 50%, 60%, 70%, and 80% time reduced images.
- Have axial, coronal, and sagittal orientations.
- Have 2D and 3D acquisitions.
- Have the following protocols: DWI, FLAIR, GRE, MRA, PD, RADIAL, STIR, SWI, T1, T2, and MIP
- Contrasted and non-contrasted images
- Have various Acceleration Method Distribution.
- Have 3.0T, 1.5T, and low field strengths.
- Have a variety of imaging scanner vendors and models.
- Have some data from sites that did not also supply training data.
- More than 50% of data is from sites in the United States.
- Have various clinical conditions and normal.
- Reconstruction Matrix (Image Sizes) up to 512 x 448

This selection criteria represents a well characterized clinically-relevant reference dataset.

In addition to a paired test set, an aligned test set was also evaluated. The purpose of the aligned test set was to better facilitate pixel-wise metrics analysis, which necessitates spatially aligned ground truth reference data. Any misalignment could contribute to metrics that do not reflect the model's performance. Furthermore, the quality of input images should align with the accelerated clinical protocols to ensure that the test results closely approximate practical scenarios. For this test set, therefore, the low-quality input images and high-quality ground truth images were paired and derived from the same undersampled k-space data. Undersampling was performed using commercially available acceleration methods on each vendor's MRI scanner. This ensures that low-quality input images are representative of the types of images that would be processed by these devices in real-world clinical scenarios, where acceleration techniques are frequently used to improve workflow efficiency. The high-quality ground truth images were reconstructed using the vendor's commercially available deep learning pipeline and represent standard-of-care image quality. Importantly, these pairs have perfect spatial alignment, which better facilitates pixel-wise metric analysis, such as L1 loss, SSIM, and PSNR. This alignment is critical for accurately assessing the performance of the image enhancement algorithm.

The following selection criteria was used for the aligned test data:

- Not used for algorithm training.
- Inputs (low-quality images) and targets (high-quality images) are spatially aligned to support the pixelwise based metrics (e.g. L1 loss, SSIM, PSNR) analysis
- Split between all anatomies (abdomen, ankle, arm, brain, extremity, knee, l-spine, pelvis, shoulder, spine)
- For known ages, have a variety of age ranges (28 years old - 80 years old)
- Have axial, coronal, and sagittal orientations.

- Have 2D acquisitions.
- Have the following protocols: DWI, PD, STIR, T1, T1 FLAIR, T2, T2 FLAIR, T2 STIR.
- The quality of inputs are aligned with the quality of accelerated clinical protocols
- Have 3.0T, 1.5T, and low field strengths.
- Have various acceleration factors: 1.0 - 6.0
- Have GE and Siemens scanners with various models.
- Have US and OUS data.

Each of the paired test sets (SOC as reference, SubtleHD-enhanced SOC as reference) had 97 samples for statistical comparison. The aligned test set had 471 samples. For each test pair, each metric was evaluated across all 2D slices and then averaged across slices to obtain the metric value for that test pair. The mean and standard deviation were calculated for L1 loss, SSIM, and PSNR.

The following table summarizes the results of this testing.

**Table 3. Standalone Image Quality Metric Summary**

| Test Set | Study Test | Result (mean ± std dev) | T-Test P-Value |
|---|---|---|---|
| Paired Test Set (Unaligned SOC as the Reference) | L1 Loss | 9.993% ± 92.487% | 0.189 |
| | SSIM | 0.0115 ± 0.0403 | 0.001 |
| | PSNR | -0.307 dB ± 2.863 dB | 0.150 |
| Paired Test Set (Unaligned SubtleHD-enhanced SOC as the Reference) | L1 Loss | -6.908% ± 22.422% | 0.022 |
| | SSIM | 0.0210 ± 0.0448 | <0.0001 |
| | PSNR | 0.583 dB ± 2.754 dB | <0.0001 |
| Aligned Test Set | L1 Loss | -38.837% ± 15.469% | <0.0001 |
| | SSIM | 0.0367 ± 0.0219 | <0.0001 |
| | PSNR | 3.844 dB ± 2.172 dB | <0.0001 |

**Performance Validation & Reader Study Dataset Characteristics:**

To represent the patient population and use of MRI in the field, the SubtleHD performance validation test dataset consists of:

- Body (breast, abdomen, prostate, and pelvis), Cardiac, Neuro (head, neck, and cervical, lumbar, and thoracic spine), and Musculoskeletal (shoulder, wrist, hand, hip, knee, foot, and ankle) anatomical regions
- DIXON, DWI, FLAIR, GRE, MRA, PD, RADIAL, STIR, SWI, T1, T2, T2*, and MIP input protocols
- Contrasted and non-contrasted images
- Axial, coronal, and sagittal orientations
- 2D and 3D acquisition types
- 0.25T, 0.30T, 0.50T, 0.55T, 0.60T, 1.16T, 1.50T, and 3.0T field strengths

- ASG Superconductors, ESAOTE, FONAR, Toshiba/Canon, Philips Medical Systems, Hitachi/Fujifilm, GE MEDICAL SYSTEMS, and SIEMENS imaging scanner vendors
- Reconstruction Matrix (Image Sizes) up to 1344x1344
- Standard-of-care data and time reduced data (up to 80% time reduction)
- Even distribution of subject sex (53% female, 47% male)
- Pediatric and Adult subject ages (ranging from 3 to 94 years old)

To show that the performance of the device is not hindered by site variability, in the validation dataset, data was selected from sources not included in the training dataset (36.50% of the dataset is from non-training sources). The majority of performance data comes from sources in the United States (65%).

**Performance Validation:**

Three Regions of Interest (ROIs) were drawn on each image in the SubtleHD performance validation test dataset by a Subtle Medical employee with an MD and/or PhD in a clinically-relevant field. Two rectangular ROI were drawn in homogeneous regions to compare the Signal-to-Noise ratio (SNR) before and after SubtleHD processing. One ROI line was drawn across a tissue interface or anatomy to compare image intensity change along the line before and after SubtleHD processing in terms of slope for all images and full width half max (FWHM) for brain images. A board-certified radiologist reviewed the ROI for acceptability for use in the performance validation study design.

The following are the endpoints, acceptance criteria, results, and conclusions from the SubtleHD Performance Validation:

**Table 4. Performance Validation Summary**

| Endpoint | Acceptance Criteria | SubtleHD Mode | Result | Conclusion |
|---|---|---|---|---|
| Denoising (SNR) Primary Endpoint | SNR shall improve by at least 40% in homogenous ROI regions for at least 90% of the dataset. | Default | **PASS** | SubtleHD performs denoising, in terms of improved SNR, MRI images. |
| | SNR shall improve by at least 40% in homogenous ROI regions for at least 95% of the dataset. | High Denoising | **PASS** | |
| Sharpness (Image Intensity Change) Primary Endpoint | Slope in a line ROI is increased for at least 90% of the dataset. | Default | **PASS** | SubtleHD sharpens, in terms of improvement in visibility of the edge at a tissue interface by image intensity slope measure, MRI images. |
| | Slope in a line ROI is increased for at least 95% of the dataset. | High Sharpening | **PASS** | |
| Sharpness (Image Intensity Change for Brains) Secondary Endpoint | Thickness, in terms of FWHM in a line ROI, is reduced for at least 90% of the dataset. | Default | **PASS** | SubtleHD sharpens, in terms of improvement in visibility of an anatomical structure by image intensity FWHM measure, MRI images. |
| | Thickness, in terms of FWHM in a line ROI, is reduced for at least 95% of the dataset. | High Sharpening | **PASS** | |
| Sharpness and Over Smoothing (Gradient Entropy) Primary Endpoint | At least 90% of cases demonstrate a lower gradient entropy value after SubtleHD processing. | Default | **PASS** | SubtleHD does not result in over-smoothed images, in terms of improvement in gradient entropy. |
| | At least 95% of cases demonstrate a lower gradient entropy value after SubtleHD processing. | High Sharpening | **PASS** | |

| Endpoint | Acceptance Criteria | SubtleHD Mode | Result | Conclusion |
|---|---|---|---|---|
| | There is a statistically significant improvement in gradient entropy when comparing the original and SubtleHD enhanced images across the performance dataset per a two-sided paired t-test. | Default and High Sharpening | **PASS** | |

**Reader Study:**

This study utilized human data gathered under the auspices of IRB-approved clinical protocols. 410 image series (205 input and 205 SubtleHD enhanced) were anonymized and randomized prior to the reader study. Readers were blind to the image processing method.

Both the input images and the SubtleHD enhanced images were ranked by board-certified radiologists for perceived SNR, Overall Image Quality / Diagnostic Confidence, Small Structure Visibility, and Imaging Artifacts, utilizing a 4 point Likert scale.

The following are the endpoints, acceptance criteria, results, and conclusions from the SubtleHD Reader Study:

**Table 5. Reader Study Summary**

| Endpoint | Endpoint Description | Acceptance Criteria | Result | Conclusion |
|---|---|---|---|---|
| Denoising (Primary Endpoint) | Signal-to-Noise Ratio | Statistically significantly better with p-value < 0.05 or not statistically significantly different in a Wilcoxon signed rank test | **PASS** | SubtleHD performs denoising, in terms of improved SNR, for MRI Images. |
| | Overall Image Quality / Diagnostic Confidence | Statistically significantly better with p-value < 0.05 or not statistically significantly different in a Wilcoxon signed rank test | **PASS** | |
| Sharpness (Primary Endpoint) | Visibility of Small Structures | Statistically significantly better with p-value < 0.05 or not statistically significantly different in a Wilcoxon signed rank test | **PASS** | SubtleHD performs sharpening and does not over-smoooth images, in terms of improved visibility of small structures, for MRI images. |

| Endpoint | Endpoint Description | Acceptance Criteria | Result | Conclusion |
|---|---|---|---|---|
| Artifacts (Secondary Endpoint) | Artifact Introduction | SubtleHD-enhanced images do not contain artifacts that could impact diagnosis or b) both input and SubtleHD-enhanced images are deemed to contain artifacts that could impact diagnosis. | **PASS** | SubtleHD does not introduce artifacts into MRI images. |

**Conclusion:**

These results demonstrate that SubtleHD is substantially equivalent to the predicate devices.