Surgical Information Sciences, Inc.                                                   March 19, 2019
℅ Ms. Janice M. Hogan
Regulatory Counsel
Hogan Lovells US LLP
1735 Market Street, 23rd Floor
PHILADELPHIA PA  19103

Re: K183019
   Trade/Device Name:  SIS Software version 3.3.0
   Regulation Number:  21 CFR 892.2050
   Regulation Name:  Picture Archiving and communications system
   Regulatory Class:  Class II
   Product Code:  LLZ
   Dated:  February 15, 2019
   Received:  February 15, 2019

Dear Ms. Hogan:

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 (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
located 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.

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 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); 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 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). 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 (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

[Signature]

Thalia Mills, Ph.D.
Director
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure
Indications for Use

SIS Software (version 3.3.0)

SIS Software is an application intended for use in the viewing, presentation and documentation of medical imaging, including different modules for image processing, image fusion, and intraoperative functional planning where the 3D output can be used with stereotactic image guided surgery or other devices for further processing and visualization. The device can be used in conjunction with other clinical methods as an aid in visualization of the subthalamic nuclei (STN).

Typical users of the SIS Software are medical professionals, including but not limited to surgeons, neurologists and radiologists.

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.

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Surgical Information Sciences, Inc.’s SIS Software

Trade Name of Device: SIS Software version 3.3.0

Common or Usual Name/Classification Name: System, Image Processing, Radiological  (Product Code: LLZ; 21 C.F.R. 892.2050)

Regulatory Class: Class II

Predicate and Reference Devices

Predicate device: Surgical Information Sciences SIS Software version 1.0 (K162830)
Reference device: Merge Healthcare’s Merge PACS™ (K173475)

Intended Use / Indications for Use

SIS Software is an application intended for use in the viewing, presentation and documentation of medical imaging, including different modules for image processing, image fusion, and intraoperative functional planning where the 3D output can be used with stereotactic image guided surgery or other devices for further processing and visualization. The device can be used in conjunction with other clinical methods as an aid in visualization of the subthalamic nuclei (STN).

Typical users of the SIS Software are medical professionals, including but not limited to surgeons, neurologists and radiologists.

Technological Characteristics

SIS Software uses machine learning and image processing to enhance standard clinical images for the visualization of the subthalamic nucleus (“STN”). The SIS Software supplements the information available through standard clinical methods, providing adjunctive information for use in visualization and planning stereotactic surgical procedures. SIS Software provides a patient-specific, 3D anatomical model of the patient’s own brain structures that supplements other clinical information to facilitate visualization in neurosurgical procedures. The version of the software that is the subject of the current submission (Version 3.3.0) can also be employed to co-register a post-operative CT scan with the clinical scan of the same patient from before a surgery (on which
the software has already visualized the STN) and to segment in the CT image (where needed), to further assist with visualization.

The software makes use of the fact that some structures in the brain are better visualized using high-resolution and high-contrast 7T MRI than via 1.5T or 3T clinical MRI. The methodology relies on a reference database of high-resolution brain images (7T MRI) and standard clinical brain images (1.5T or 3T MRI). The algorithm uses the 7T images from a database to find regions of interest within the brain (e.g., the STN) on a patient’s clinical (1.5 or 3T MRI) image.

With regard to the updated functionality to process post-operative CT images, co-registration of the clinical MR and CT images allows alignment of the spatial positioning of the brains, and segmentation of objects (e.g., when an electrode is present) is performed to ensure that the software accurately reflects their proper position.

STN visualization, image co-registration and the optional additional CT segmentation, are incorporated in the standard-of-care clinical workflow protocols. Use of the device does not require any additional visualization software or hardware platforms.

The subject and predicate devices rely on the same core technological principles. The only major differences between the two are that version 3.3.0 (the subject device) includes the added optional functionality to process post-operative CT images as well as incorporates a user interface. The user interface/labeling has also been enhanced to clarify this optional follow-on process for the clinician.

**Performance Data**

**STN Visualization**

Pivotal validation testing of the subject device was completed to confirm performance with device modifications. A set of 68 STNs (from 34 subjects) were scanned with both clinical MRI (1.5T and 3T) and High Field (7T) MRI. None of the 68 STNs were part of the company’s database for algorithm development and none were used to optimize or design the company’s software. Thus, this validation data set was completely separate from the data set that was used for development. The software development was frozen and labeled before tested on this validation set.

Three measurements were used to compare the SIS visualization via the subject software and ground truth STNs (manually segmented clinical images and 7T images superimposed): (1) Center of mass distance; (2) Surface distance; and (3) Dice coefficient values.

In sum, 90% of the center of mass distances and surface distances were below 1.66mm and 0.63mm, respectively. Specifically, 98.3% of the center of mass distances and 100% of the surface distances were not greater than 2.0mm. Thus, the study met the pre-specified criteria of 90% of center of mass distances and surface distances not greater than 2.0mm. Furthermore, the proportion of visualizations not greater than 2.0mm was conservatively estimated from the literature to be 20%. Therefore, the rate of successful visualizations from SIS Software (98.3% of the center of mass distances not greater than 2.0mm) is significantly greater than the standard of care (p<0.0001). The corresponding two-sided confidence intervals are as follows:
(a) 90% of the center of mass distances and surface distances were below 1.66mm and 0.63mm, respectively (95% CI: 79.5 – 96.2%);
(b) 98.3% of the center of mass distances were not greater than 2.0mm (95% CI: 91 – 100%);
(c) 100% of the surface distances were not greater than 2.0mm (95% CI: 94 – 100%).

In addition, the Dice coefficient in this dataset was 0.69, which was expected given the small size of the STN and substantially similar to the predicate device. In sum, the SIS Software performed as intended and clinical validation data results observed were as expected.

Co-Registration

To ensure that 3D transformation to the CT is accurate, SIS collected 5 MR series and 1 CT series of a phantom brain. For each of the 5 MR series, 6 fiducial points were marked by an expert. Marking the fiducial points allowed SIS to test 30 points of reference. These points were used as reference points in the image series.

If the distance between the fiducial points was smaller than 2 mm, the test passed. This criterion was justified based on SIS’ maximum acceptable slice thickness for MRI scans of 2mm. SIS success criteria is to show 95% confidence that 90% of the registrations will have corresponding reference point distances below 2 mm.

The table below summarizes the test data. For each of the MR images, the 6 distances were recorded. The average of all distances and its standard deviation are detailed in the table below:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean of Maximum Error</th>
<th>STD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>5</td>
<td>0.242 mm</td>
<td>0.062 mm</td>
</tr>
</tbody>
</table>

Based on the results from the table above the tolerance interval was calculated. SIS demonstrated it can register MR images to the CT space. SIS statistics shows there is 95% confidence that the error will be below 0.454 mm 90% of the time.

Segmentation

In addition to the above testing, to validate the optional segmentation feature to ensure any present leads are accurately represented with the co-registered 3D output, SIS used 26 post-surgical CT scans that contained leads with a total sample size of 45 electrodes. For each of the CT scans, ground truth segmentations were generated by 2 experts. To generate the ground truth data, the experts used the same set of 3D components (STL files) that are used by SIS Software version 3.3.0.

First, the experts segmented the electrode(s) from each CT image. Second, the 3D components were aligned manually to the segmentation from step one (ground truth). Once the system generated the segmentations of the electrode components, and calculated the location and orientation of these components, the differences between the ground truth and the automated objects were calculated:
• Distance between center of mass (COM) of the electrode tip and contacts of the ground truth and the corresponding automatically segmented objects. If the COM distance was less than 1 mm, the test passed, else it was declared as failure.

• Angle between the orientation of contacts in the ground truth and the corresponding automatically segmented orientation. If the difference between the orientations relative to the ground truth electrode shaft was less than 5 degrees, the test passed, else it was declared as failure.

These acceptance criteria of 1 mm and 5 degrees were justified based on SIS’ maximum acceptable slice thickness of the image, which is 1 mm. SIS success criteria for the tests is to show 95% confidence that 90% of the segmentations will have center of mass distances below 1 mm and orientation differences below 5 degrees.

The table below summarizes the test data:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Average Mean</th>
<th>STD</th>
</tr>
</thead>
<tbody>
<tr>
<td>COM</td>
<td>45</td>
<td>0.30 mm</td>
<td>0.12 mm</td>
</tr>
<tr>
<td>Orientation</td>
<td>45</td>
<td>1.00 Degrees</td>
<td>0.90 Degrees</td>
</tr>
</tbody>
</table>

SIS uses the following tolerance intervals formula to calculate the upper tolerance limit for the 2 measurements:

• For the center of mass distance, SIS shows there is a 95% chance that 90% of the cases will be lower than 0.491 mm from the center of mass of the real contact.

• For the difference in orientation, SIS shows there is a 95% chance that 90% of the cases will be lower than 2.486 degrees from the real orientation of the lead.

In both cases the criteria of 1 mm and 5 degrees are met with a high level of confidence.

**Modified Anomaly Detection**

The functionality of this Anomaly Detection component is the same as the original SIS Software version 1.0.0, and while the implementation of that functionality has been modified, the validation testing methodology is identical to what was used in the original version and the results were similarly acceptable.

Briefly, two separate commonly used outlier detection machine learning models were trained using the brains from the training set, from which the same brain geometry characteristics were extracted as described below:

• One of these models is an elliptic envelope, which defines a volume in feature space based on the distributions of feature values from the training set; visualizations with characteristics (features) that fall outside the envelope will be considered anomalies.

• The second model is an isolation forest, which contains a population of decision trees
based on random partitioning of the training set. The scores from each of these models is combined to yield an overall anomaly score, with a threshold separating anomalous from non-anomalous classifications. The anomaly detection in SIS 1.0.0 used a single random forest classifier.

During system verification and validation (V&V) testing, there are 4 possible outcomes:

- True Positive (TP) – Inaccurate visualization that was classified as anomaly.
- True Negative (TN) – Accurate visualization that was classified as non-anomaly.
- False Positive (FP) – Accurate visualization that was classified as anomaly.
- False Negative (FN) – Inaccurate visualization that was classified as non-anomaly.

SIS’ approach for improving the anomaly detection component was to further minimize the number of False Negatives, which would represent inaccurate STN predictions and be reported out to the physician user (i.e., not be flagged as an anomaly). As such, the Sensitivity and Specificity of the anomaly detection component, as well as the overall visualization success of the system, are the criteria used to demonstrate the acceptable performance of this component.

These data demonstrate that more true anomalies were identified with the Version 3.3.0, such that sensitivity was improved, and specificity was only marginally decreased. The tables below demonstrate that the overall performance of version 3.3.0 is improved by the anomaly detection component compared to the original functionality of version 1.0.0.

### Table 1: Anomaly Detection Analysis

<table>
<thead>
<tr>
<th>Version</th>
<th>Total cases</th>
<th>Successful visualizations &lt; 2mm</th>
<th>Failed visualizations &gt; 2 mm</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0.0</td>
<td>68</td>
<td>65</td>
<td>3</td>
<td>0</td>
<td>60</td>
<td>5</td>
<td>3</td>
<td>0.00%</td>
<td>92.31%</td>
</tr>
<tr>
<td>3.3.0</td>
<td>68</td>
<td>66</td>
<td>2</td>
<td>1</td>
<td>59</td>
<td>7</td>
<td>1</td>
<td>50.00%</td>
<td>89.39%</td>
</tr>
</tbody>
</table>

### Table 2: Overall System Performance

<table>
<thead>
<tr>
<th></th>
<th>Success without AD</th>
<th>Success with AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0.0</td>
<td>95.59%</td>
<td>95.24%</td>
</tr>
<tr>
<td>3.3.0</td>
<td>97.06%</td>
<td>98.33%</td>
</tr>
</tbody>
</table>
STN Smoothing Functionality

SIS validated the smoothed STN visualizations that were produced by the system, based on Center of Mass (COM), Dice Coefficient (DC) and Surface Distance (SC). Testing produced acceptable results.

In addition, SIS also analyzed the results of the difference between the smoothed STN visualization and the non-smoothed STN visualizations to compare the effect of this change at a unit level. The shapes of the visualized targets from the verification and validation accuracy testing were compared using COM, SD and DC. The results demonstrated significant correlation between the smoothed and non-smoothed STN objects. These results, in addition to the overall system accuracy, demonstrate that the overall system performance remains in line with the verification criteria for the predicate device.

Substantial Equivalence

Both the subject and predicate versions of the SIS Software are applications used for visualization, presentation and documentation of medical imaging, including different modules for image processing, image fusion, and intraoperative functional planning where the 2D or 3D output can be used with stereotactic image guided surgery or other devices for further processing and visualization. In addition, the SIS Software, like the identified predicate and reference devices, use proprietary algorithms to generate 3D segmented anatomical models from patient’s MRI scans. The subject device additionally segments post-operative CT scans (when needed) of a patient whose pre-operative MR has already been processed by the software, and enables co-registration of the two images. These additional functionalities serve the same fundamental purpose as those carried over from the predicate – to assist the clinician in surgical case management. Finally, the new features of version 3.3.0 as compared to the version 1.0 predicate device are supported by other cleared PACS systems, which perform image registration/fusion including CT and MR, such as the reference device (K173475), as well as validation testing. The table below provides a summary comparison between the SIS Software and the predicate and reference devices.

### SIS Software Technological Characteristics Comparison Table

<table>
<thead>
<tr>
<th>Feature</th>
<th>SIS Software version 3.3.0 (subject)</th>
<th>SIS Software version 1.0 (K162830)</th>
<th>Merge PACS (K173475)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allows for importing of digital imaging sets</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Uses proprietary software algorithm for 3D image processing</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Allows for review and analysis of data in various 2D and 3D presentation formats</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Performs image fusion of datasets using automated or manual image matching technique</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Segments structures in</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear from publicly</td>
</tr>
<tr>
<td>Feature</td>
<td>SIS Software version 3.3.0 (subject)</td>
<td>SIS Software version 1.0 (K162830)</td>
<td>Merge PACS (K173475)</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Images with manual and automated tools and converts them into 3D objects for display</td>
<td>Available information; but these features are already supported by the predicate.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creates hybrid datasets by filling in segmented regions slice-by-slice on anatomical datasets</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Results can be uploaded to planning system</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Segmentation of CT scan to identify structures in relation to those visualized on MR</td>
<td>Yes</td>
<td>No</td>
<td>Processes images to enable cross-registration or cross-referencing.</td>
</tr>
<tr>
<td>Cross-registration of two multi-modality images and creation of 3D (fused) model</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Uploading and viewing images via web-based portal or directly via separately cleared PACS</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Anomaly Detection</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>STN Smoothing Functionality</td>
<td>Yes; supported by testing demonstrating new feature does not alter device output compared to predicate device</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Conclusions**

The updated SIS Software (version 3.3.0) is as safe and effective as the version previously cleared in K162830 (predicate device). The subject device has the same intended use and indications for use as the predicate, and very similar technological characteristics and principles of operation, with minor differences supported by clearance of the reference device (K173475), as well as performance validation testing demonstrating that the subject device is as safe and effective as the predicate device and performs as intended. Thus, the minor technological differences between SIS Software (version 3.3.0) and its predicate device raise no new issues of safety or effectiveness, and the updated SIS Software (version 3.3.0) is substantially equivalent.