

AWARD NUMBER: W81XWH-19-1-0043

TITLE: Development of Virtual Surgery Technology Platform for Obstructive Sleep Apnea

PRINCIPAL INVESTIGATOR: Goutham Mylavarapu

CONTRACTING ORGANIZATION: Children's Hospital, Cincinnati

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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Obstructive sleep apnea (OSA) is a serious medical condition with long-term health effects including cardiovascular risks, diabetes, metabolic syndromes, and decreased quality of life. It is associated with partial or complete obstruction of the pharyngeal airway during sleep. Non-surgical treatments for OSA such as continuous positive airway pressure (CPAP) are not tolerated by most patients and do not offer a complete cure. Most OSA patients eventually opt for surgery. However, the success rates for most OSA surgical interventions are poor. Often, surgical planning is guided by the experience of the clinical team and hence, subjective. The objective of this work is to address this subjective component in surgical planning, replacing it with more scientific decision-making. To that end, we proposed to develop a **virtual surgery platform** for personalized OSA surgical planning and validate its clinical use. This novel tool has the potential to evaluate different OSA surgical plans, **non-invasive** using computer models with minimal patient interaction from patient scans alone. The technology, methodology developed in this work will be used to pursue our long-term goals of improving clinical outcomes for patients with OSA.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Obstructive sleep apnea, Upper airway, Pulmonary, Magnetic Resonance Imaging (MRI), Virtual surgery, Tonsillectomy, adenoidectomy, glossectomy, Computational Fluid Dynamics, Clinical outcomes, Software development, Technology development

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: To develop a visualization rendering software for performing virtual OSA intervention(s)

Major task 1: Obtain upper airway scans of OSA patients

Subtask 1 [100%]: Submit documents for IRB approval; (Target: Month 1; Submitted in Month 2; All regulatory approvals received in Month 7. Submitted and received continuing IRB approvals for 2021-22)
Subtasks 2 & 3 [67%]: Recruit 15 patients for the study and complete pre-op and post-op scanning (Target: Months 2-15; Subtask start: Month 8. Current status: Recruited all target 15 patients by Nov 2020. Performed pre-operative MRI scans on all 15 patients. Performed post-operative scans on 5/15 study participants.) Recruited another 2 additional subjects and performed pre-operative scans as some subjects were untraceable to complete post-operative scans.

Major task 2: Design and develop visualization software for virtual surgery

Subtask 1 [100%]: Write code for extracting centerlines of the airway (Target: Months 1-2)

Subtask 2 [100%]: Create endoscopy view to look inside the airway (Target: Months 2-3)

Subtask 3 [60%]: Add haptic interface for realistic surgical experience (Target: Months 3-4)

Subtask 4 [100%]: Add tools for performing virtual surgery (Target 4-7)

Major task 3: [27%] Perform virtual surgeries (Target: Months 6-14; Due to the covid pandemic situation, this task is extremely delayed. Started in May 2021 See section 5).

Specific Aim 2: To test and validate the virtual surgery system for predicting OSA surgical outcomes

Major task 1: Perform morphological and CFD data analysis in 15 patients

Subtask 1 [63%]: Obtain morphometrics of airway size and shape changes before and after virtual surgery (Target: Months 8-15; Status: Obtained airway measurements in 15/15 pre-op airways, 4/15 post-op airways;)

Subtask 2 [50%]: Perform CFD simulations on pre-op, post-op and post-virtual airways (Target: Months 8-16; Status: Completed pre-op imaging and corresponding CFD simulations. Completed post-op MRI in 5/15 subjects. Yet to perform post-op airway CFD simulations.)

Subtask 3 [0%]: Statistical analysis for intra-observer and inter-observer reliability of virtual surgeries (Target: Month 16). Waiting to complete post-op imaging on all study participants.

Major task 2: Add upper airway functional metrics to the software

Subtask 1 [100%]: Display CFD flow features on scans (Target: Months 8-10). working code completed.

Subtask 2 [80%]: Add display boxes on the GUI based on the clinical team feedback (Target: Months 9-10). Added a new module to display pre and post-surgery airway metrics.

Major task 3: Predict surgical outcomes

Subtasks 1 & 2 [0%]: Predict outcomes in 15 OSA patients based on morphological and functional data. Compare actual and predicted outcomes (Target: Months 13-15; Status: didn't start. waiting to complete post-op imaging on all participants.)

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

- 1. Major activities:** (1) The year 1 of this project focused on obtaining all regulatory approvals and writing working codes for centerline extraction, endoscopic view, graphical interface design, and working code for to display CFD simulated results of pressure and velocities on the patient scans. In year 1, we enrolled 4 of the target 15 subjects and obtained pre-op imaging. (2) Due to pandemic and ongoing difficulties in patient recruitment and subsequent wait-times for surgeries on these patients, we sought a 1- year no-cost-extension. (3) In the last year, we reached our target enrollment of 15 subjects. We obtained pre-op imaging on all 15 subjects, obtained sleep studies. 7/15 undergone surgeries so far and we scheduled post-op MRI on 5/15 subjects. (4) We have a working software model. Received feedback from clinicians. (5) 2 surgeons had performed surgeries on 5/15 patients.
- 2. Specific objectives:** The objectives of this study from Specific Aims 1 & 2 can be summarized into (A) Regulatory approvals, (B) Patient recruitment, (C) Virtual surgery software development, (D) Analysis: Perform virtual surgery and predict outcomes.

3. Significant results

(A) Regulatory approvals: We obtained continuing renewal regulatory approvals from local IRB which is valid until 05/24/2022.

(B) Patient recruitment: After an initial HRPO approval on 12/16/2019, we began enrolling patients briefly in Jan-Mar 2020 only to be suspended between Mar-June 2020 due to pandemic. Even after clinical operations resumed at our center, patients returning was slow. Despite these challenges, we completed enrollment of our target enrollment of 15 subjects by Nov 2020 and obtained pre-operative imaging. Due to covid, the clinical decisions for surgery on these patients were delayed. Only 7/15 subjects has surgeries. We had scheduled (6/15) and/or obtained post-operative imaging on 5/15 subjects. See below Table 1. for chronological scheduling of the target 15 subjects.

Study ID	Pre op MRI	Post op MRI	Pre-op AHI	Post-op AHI	Surgery Date
<u>VSOSA_01</u>	01/17/20	10/16/20	10.6	5.6	5/18/2020
<u>VSOSA_02</u>	03/13/20	07/26/21	85		8/3/2020
<u>VSOSA_03</u>	07/09/20		4.3	6.2	8/17/2020
<u>VSOSA_04</u>	07/16/20		9	1.7	
<u>VSOSA_05</u>	08/20/20		14.2	3.2	
<u>VSOSA_06</u>	09/03/20		98.9		
<u>VSOSA_07</u>	09/03/20		9.4		
<u>VSOSA_08</u>	10/19/20		12.5		
<u>VSOSA_09</u>	10/23/20	05/17/21	28.9		2/23/2021
<u>VSOSA_10</u>	11/05/20	07/19/21	12.2		6/7/2021
<u>VSOSA_11</u>	03/20/19		47.2		
<u>VSOSA_12</u>	11/13/20		10.6		
<u>VSOSA_13</u>	11/13/20	06/28/21	17.2		1/5/2021
<u>VSOSA_14</u>	11/20/20		23.1		1/29/2021
<u>VSOSA_15</u>	01/08/21		55.6		

Table 1: Chronological events for scheduling preoperative and post-operative MRI.

(C) Virtual surgery software development.

While we were waiting to complete both the preoperative and postoperative imaging on the study participants, we made significant progress towards the virtual surgery software.

We have created 6 modules for the ‘virtual surgery’ application using ‘Slicer’ opensource medical visualization software framework. The 5 modules created are (1) CenterlineCurveExtraction, (2) Endoscopy (3) SegmentEdit (4) Segmentation Tools (virtual surgery tools) (5) Analytics (6) Lights. The graphical interface looks as shown in Figure 1.

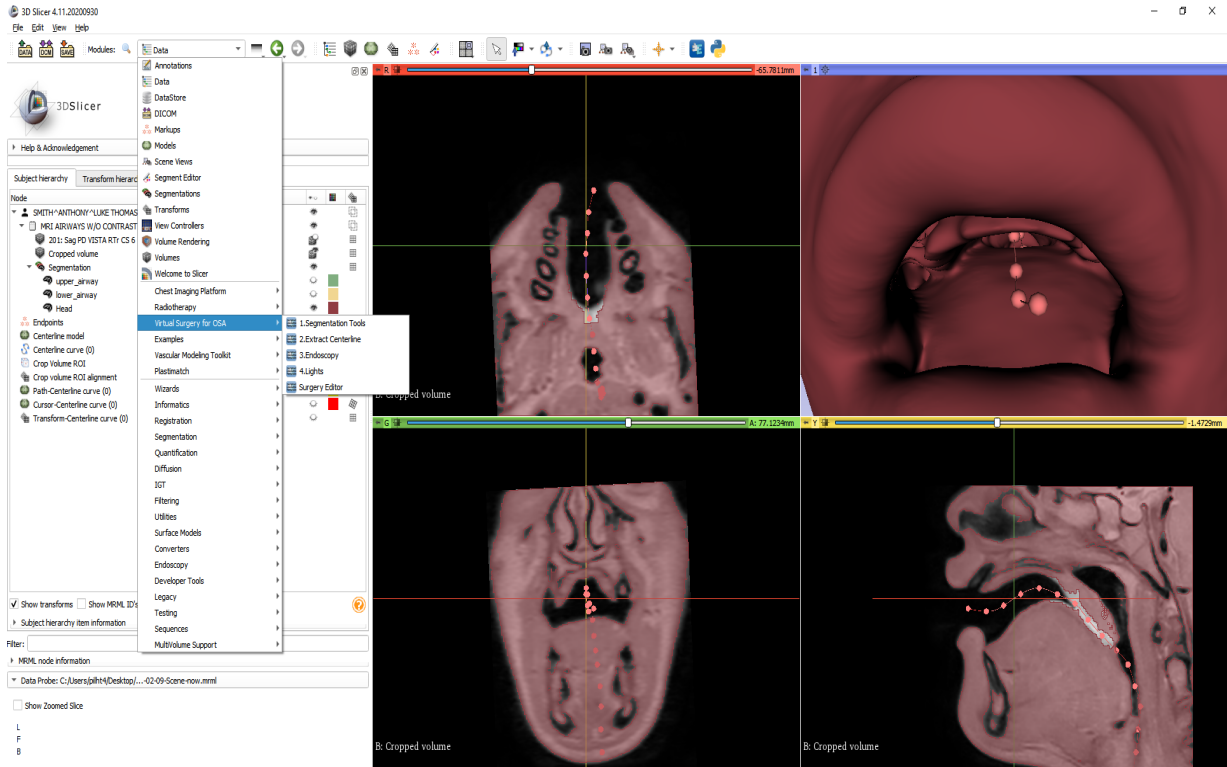


Fig. 1: Virtual Surgery Software Graphical User Interface (GUI).

The workflow is designed as follows:

STEP 1: Load MRI scans; Use SegmentEdit module to create segment the upper airway (oral and pharyngeal airways), a block segment. 3D models of airway and block are created. A tissue model (block - airway) is automatically created at this step. See Fig. 2 for examples.

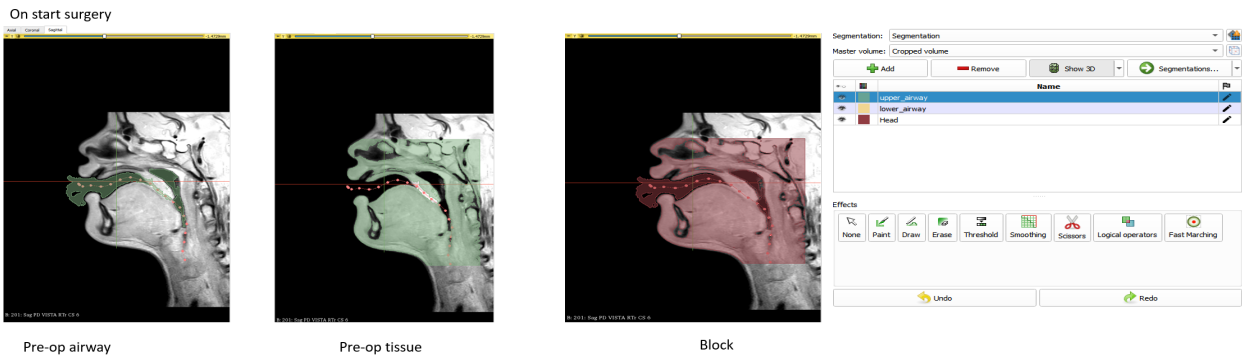


Fig. 2: Example of segmented airway, tissue in one of the study participants and GUI for this module.

STEP 2: Create centerlines in the airway to guide endoscopy and pan fly-through view of the airway.

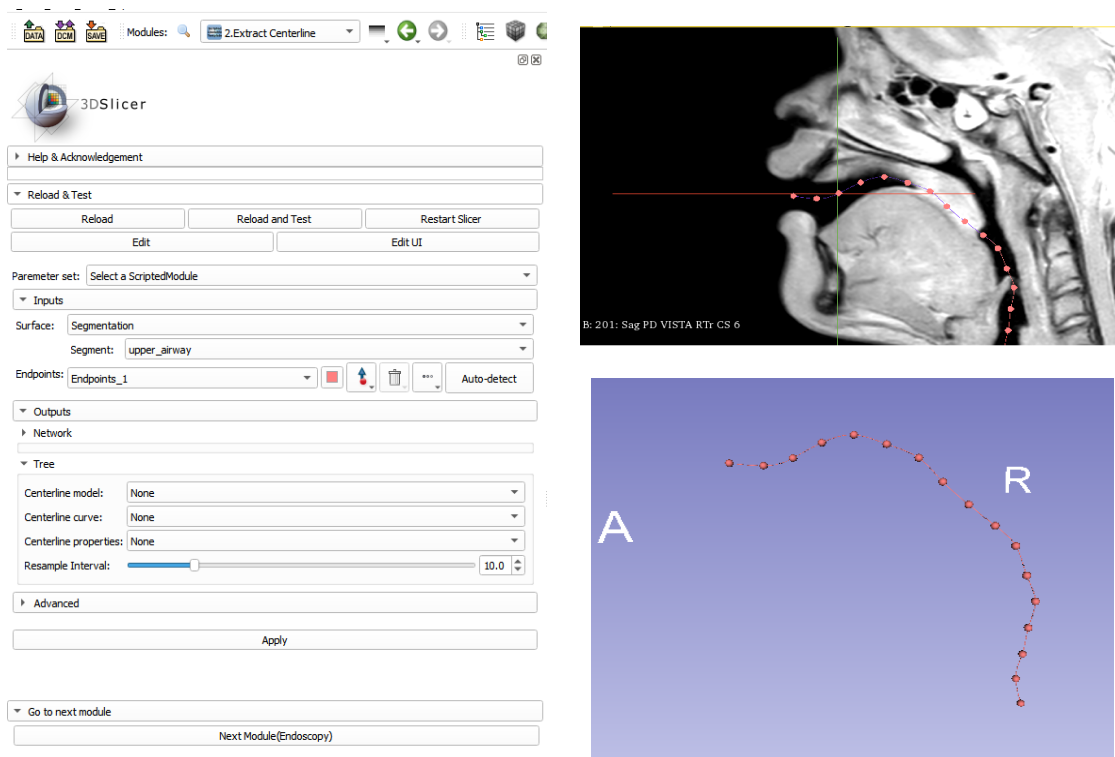


Fig. 3: GUI for centerline extraction module and extracted centerlines in a subject.

STEP 3: A fly-through endoscopic module to see “inside” the airway and step in/out along the centerlines

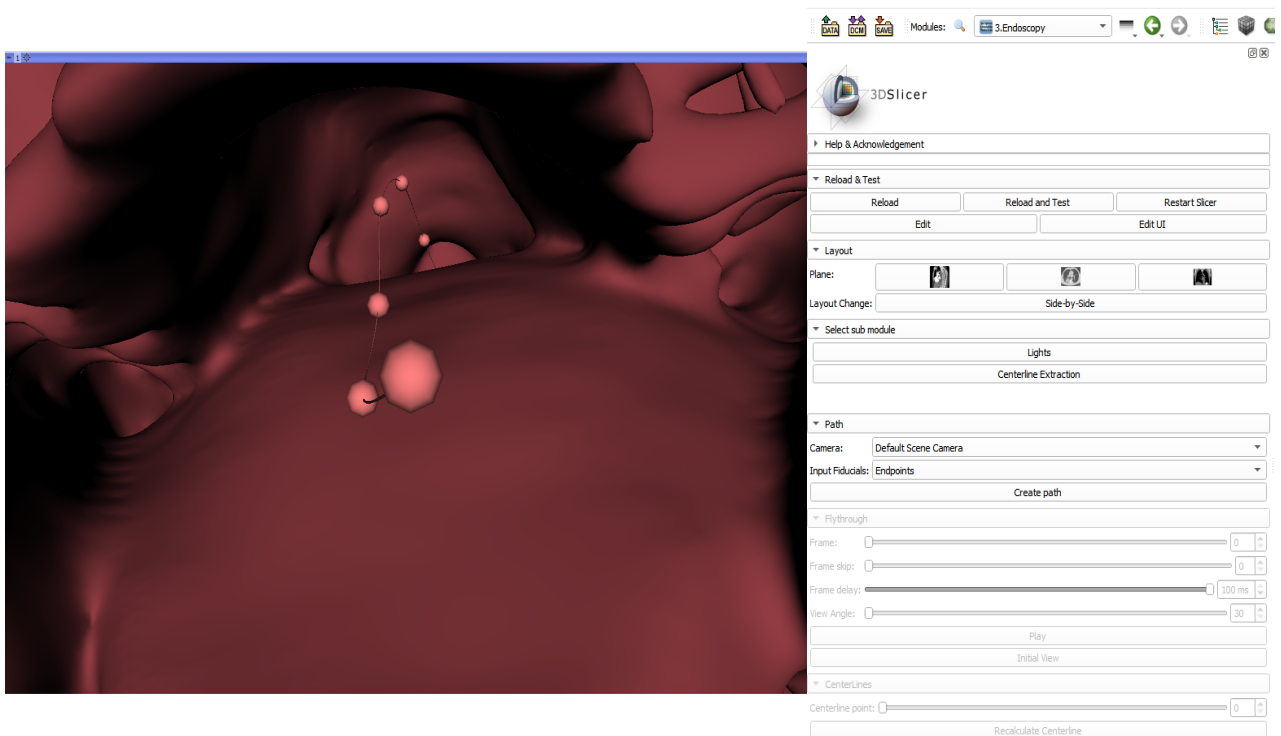


Fig. 4: An endoscopic view of airway in a study participant and corresponding module GUI.

STEP 4: We added a lights module for the surgeons to experience a more realistic shading and rendering of anatomy while performing virtual surgery. Fig. 5 shows the GUI

STEP 5: A ‘surgical tools’ module is developed to aid surgeons in performing virtual surgery on the preoperative tissue model. After this operation, when ‘finish surgery’ is clicked, post-operative airway, postoperative tissue is created. See Fig. 6 and 7.

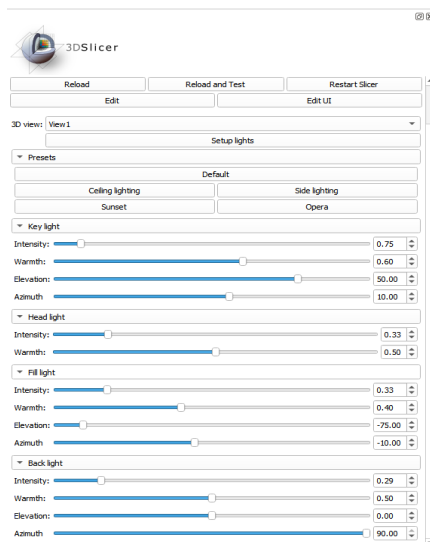


Fig 5: GUI for ‘lights’ module

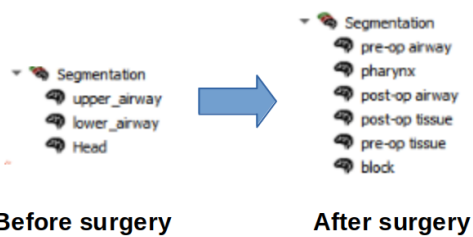
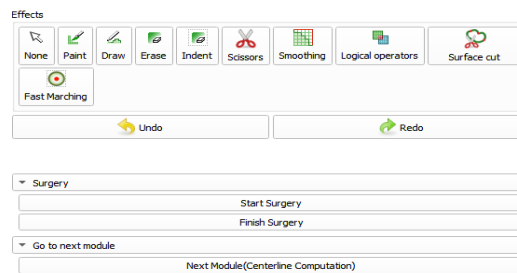


Fig. 6: Surgery Tools

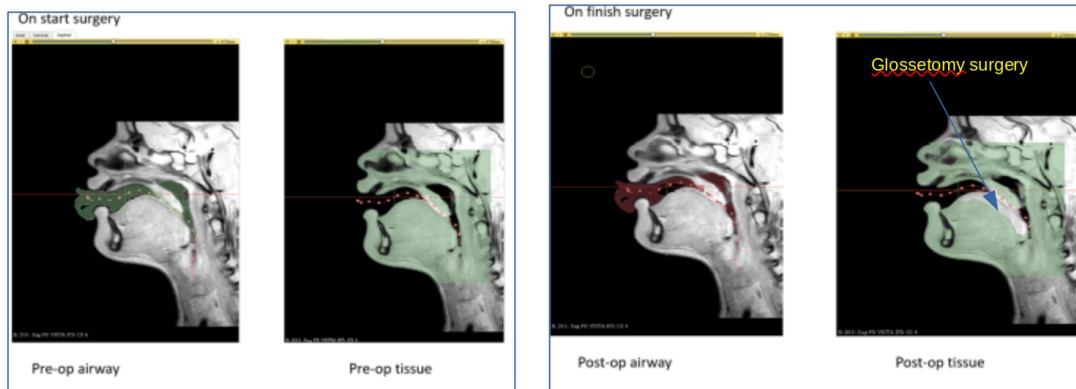


Fig. 7: Virtual glossectomy surgery performed in one of the study participants.

STEP 6: We developed an ‘Analytics’ module which would with a click of a button, compares the changes in airway measures of cross-sectional areas, volumes before and after surgery. The data could be exported to a CSV file for further analysis.

4. Discussion of stated goals not yet met.

Due to the covid situation, we had significant delays in patient recruitment. Even after reaching the target 15 subjects and completing preoperative scans. We have practical challenges in completing postoperative scans, as 8/15 subjects did not had surgery due to covid scheduling and the clinical decisions impacted postponing the surgeries. We could not complete the virtual surgeries and statistical analysis comparing before/after surgery. We have only 5/15 subjects with both time points and these number are low to perform stats and for predicting outcomes. We plan to perform an intermediate analysis when we complete post-operative imaging and sleep studies in about at least 10 subjects.

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

PI and/or CRC discussed the study objectives with the help of visual aids and a demo of the software in the development with the parents of some of the study participants. Patient families expressed interest in learning about the final outcome of this study. Dr. Ishman, one of the co-investigators in this study along with her colleagues in the division conducts an annual *Upper Airway Clinic* community outreach program for OSA patients. This program has been canceled during this award period due to covid. Investigators are planning to give a demonstration of the software and its application to the OSA community at the next opportunity for enhancing the understanding of this disease and technology advancements with the patients, families, and other caregivers.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to report

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

OSA is a common, yet a serious sleep disorder with unsatisfactory surgical intervention outcomes. With the funding support from DoD, our team could develop a software to perform and test personalized surgical plans in patients with OSA. We were able to generate software for generating centerlines through anatomical models, *see inside* the airways using fly-through views along the centerlines. This software program provides the surgeon, a field of view of a patient’s airway similar to his/her experience while performing actual surgery. Other tools to perform *virtual surgery* on a patient’s airway and comparing functional outcomes before and after surgery scenarios, should help optimize surgical planning by the clinical team.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Although the software scripts were written with the primary goal of developing virtual surgery software for OSA interventions, the centerline and endoscopy modules developed as part of this study are of great use in my other research to study lung airways and pulmonary vascular trees. The endoscopy module can be tested to develop a *virtual bronchoscopy* software with some additional work involving accurate segmentation of airways in the lung. Similarly, these tools can be used to study other tubular structures such as large and small vessels in the aorta, brain, lungs, etc. as well as the nasal and lower airways.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Once tested and validated, this software can be used for training clinical residents and educating patients with OSA, and their families into making informed decisions about OSA surgical plans.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:*

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Delay 1: Although clinical and research operations resumed from July 2020 at our institution after a suspension for 4 months in 2020 due to covid, patients did not return to the clinics immediately. Scheduling took a few months to recover and the surgical decisions were and are even today, still heavily influenced considering the safety of patients, families, and caregivers safety. Many were no-shows and a few study participants are hesitant to come to the hospital given the ongoing delta variant situation.

Action 1: We coordinated with the scheduling services and actively recruited the target 15 patients for this study and completed pre-operative imaging by Jan 2021. Only 7/15 subjects had surgeries so far. We have been actively pursuing and scheduled 6/7 for post-operative scans and 5/7 completed post-operative scans. We have been waiting for surgery schedules on 8/15 study participants, whose surgeries were delayed, postponed and had been on CPAP therapy due to the covid situation. Since we cannot intervene with the clinical decision-making, we have been actively pursuing their status every week. We have blocked MRI scan hours for our study every month and had been in touch with the patient’s families and caregivers.

Delay 2: Testing the virtual surgery software was delayed as we were waiting for a sizable number of study participants with both pre and post-operative scans. At present we have 5/15 study participants who completed both pre/pst-operative imaging. We could not perform statistics with these low numbers.

Action 2: We had surgeons test the software and perform virtual surgeries on these 5/15 patients. We will complete the virtual surgeries part of the study in batches, as and when patients had actual surgeries. We will perform intermediate stats as soon as we have 50% of samples collected.

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

No changes to report

Significant changes in use or care of vertebrate animals

No changes to report

Significant changes in use of biohazards and/or select agents

No changes to report

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

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periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

https://github.com/gunnups/Airway_Project.git

An open-source Slicer based module for performing virtual OSA surgical interventions.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Software technology to perform and evaluate virtual surgeries for OSA in individual patients using their MRI scans.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- data or databases;
- physical collections;
- audio or video products;
- software;
- models;
- educational aids or curricula;
- instruments or equipment;
- research material (e.g., Germplasm; cell lines, DNA probes, animal models);
- clinical interventions;
- new business creation; and
- other.

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.

Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name:	Goutham Mylavarapu – no change
Project Role:	Principal Investigator
Name:	Stacey Ishman – no change
Project Role:	Co-Investigator
Name:	Raouf Amin – no change
Project Role:	Co-Investigator
Name:	Robert Fleck – no change
Project Role:	Collaborator

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Goutham Mylavarapu (PI) has 40% effort in this DoD funded study. Since January 2020 and until December 2022, 60% of his remaining effort time is supported by an active grant from Cystic Fibrosis Foundation (CFF). Dr. Mylavarapu is a co-investigator on the CFF funded study and this does not impact his 40% effort in this project.

Raouf Amin (Co-I) – no change

Stacey Ishman (Co-I) – no change

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner's contribution to the project (identify one or more)

- Financial support;
- In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
- Facilities (e.g., project staff use the partner's facilities for project activities);
- Collaboration (e.g., partner's staff work with project staff on the project);
- Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and
- Other.

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.