Complex And Simple Appendicitis: REstrictive or Liberal post-operative Antibiotic eXposure (CASA RELAX) Using Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR) – A Randomized Controlled Trial

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NCT number: 05966454

Under the direction of the Principal Investigator (NCT 05002829), participating site separately registered this study to clinical trials.gov given separate overseeing IRB submission at UCSF.

1) Protocol Title

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2) IRB Review History

N/A

3) Objectives

To demonstrate the safety, efficacy, and feasibility of short-course post-operative antibiotic treatment for simple and complicated appendicitis

Hypothesis

We hypothesize that a restricted course of post-operative antibiotics results in a higher desirability of outcome ranking (DOOR) compared to a liberal course of post-operative antibiotics for simple and complicated appendicitis.

4) Background

The treatment of acute appendicitis in the United States is primarily surgical, with the vast majority undergoing a laparoscopic approach to appendectomy. While the post-operative treatment of simple acute appendicitis is relatively straightforward, the same cannot be said for complicated (eg. perforated or gangrenous) appendicitis. One could argue that in the presence of an established complicated intra-abdominal infection (cIAI), a more prolonged duration of post-operative antibiotic treatment is warranted as a therapeutic measure. On the other hand, in the presence of gross contamination, it is arguable how effective prolonged antibiotic treatment will be once source control has been established.

In 2015, Sawyer et al. published the STOP-IT trial comparing outcomes of two treatment strategies after source control of cIAI: a short-course (four days) versus a “standard-course” (approximately eight days) [1]. There were no significant differences detected in the primary composite endpoint of surgical-site infection, recurrent intra-abdominal infection, or death within 30 days leading the investigators to conclude that a 4-day course was non-inferior to a longer course of post-operative antibiotic treatment. The MUSTANG (Multicenter Study of the Treatment of Appendicitis in North America: Acute, Perforated, and Gangrenous) study was an observational study of 29 centers in the United States, enrolling 3,597 subjects from January 2017 to June 2018 [2]. Of the subjects with simple (non-perforated) appendicitis, 612 (28%) received post-operative antibiotics [3]. Post-operative antibiotics were not associated with improved clinical outcomes at index hospitalization or within 30 days after discharge. Of the MUSTANG subjects with intraoperative findings of complicated (gangrenous or perforated) appendicitis (n=407), 17% did not receive post-operative antibiotics [4]. Of those who received post-operative antibiotics, 12% received < 24h while the remainder received ≥ 24h, with the most common (mode) duration being 4 days. A post-hoc analysis revealed no significant benefit of 4 days of antibiotics compared to < 24h of antibiotics in the

following outcomes: index hospital length of stay (LOS), infectious complications during index hospitalization, total complications during index hospitalization, 30-day Emergency Department (ED) visits, 30-day hospital readmission rates, 30-day infectious complications, or 30-day total complications. Although underpowered and non-randomized, all trends seemed to favor short-course (< 24h) antibiotic treatment (Table), though a selection bias is highly likely. A recently published multicenter observational study from The Netherlands also confirms the treatment variability of post-operative antibiotics after appendectomy for complicated appendicitis and also did not demonstrate a clinical benefit associated with prolonged antibiotic therapy [5].

Table – Comparing Outcomes for <24 h vs. 4 Days of Postoperative Antibiotics for Complicated Appendicitis

	<24 h (n=38)	4 days (n=54)	p
Index hospital LOS (days)	1.4	3.3	<0.001
Composite infectious complications (index hospitalization)	0 (0%)	3 (5%)	0.143
Composite complications (index)	3 (8%)	14 (25%)	0.031
30 day ED visit	2 (7%)	10 (21%)	0.092
30 day hospital readmission	2 (6%)	6 (13%)	0.409
30 day Cumulative composite infectious complications	2 (5%)	10 (18%)	0.068
30 day Cumulative composite all complications	6 (16%)	22 (40%)	0.012

Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)

The desirability of outcome ranking (DOOR) ranking system analyzes trial participants according to the desirability of their overall outcome and distributions of DOOR are compared between strategies [6]. Within categories, subjects have similar overall clinical outcomes, whereas subjects in different categories have clinically relevant differences in patient-centered outcomes. Additionally, the subjects will be ranked according to the Response Adjusted for Duration of Antibiotic Risk (RADAR), a version of DOOR designed for trials comparing strategies to optimize antibiotic use. The underlying principle of RADAR is that less antibiotic exposure is better but must not come at the expense of clinical outcomes. Thus, within DOOR categories, subjects are ranked according to duration of antibiotic exposure, with shorter durations receiving a higher rank when comparing patients with similar overall clinical outcomes. Within this

rules-based system, a subject with a worse clinical outcome cannot have a higher rank than a subject with a better clinical outcome, no matter how short the antibiotic exposure. This novel analysis is pragmatic and compares two strategies in a way similar to how clinicians and patients actually weigh treatment decisions, by considering all clinical consequences, incorporating competing risks, and accounting for patient outcome preferences.

Once the DOOR distributions for the two strategies have been determined, then the probability of a randomly selected control patient will have a better DOOR (if assigned to the other experimental strategy) is calculated with confidence intervals. Assuming no difference (null hypothesis) in strategies, then the probability will be approximately 50%. However, if the experimental strategy has a benefit in clinical outcome, shorter antibiotic exposure, or both, then the probability will be proportionally and significantly higher than 50%. For the purposes of sample size calculation, we propose the alternative hypothesis, ie that the short-course strategy has a higher DOOR (ie, the probability that a randomly selected patient will have a better DOOR if assigned to the new strategy vs 4-day strategy is >50%.

References

1. Sawyer, R.G., et al., Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med, 2015. 372(21): p. 1996-2005.
2. Yeh, D.D., et al., *Multicenter Study of the Treatment of Appendicitis in America: Acute, Perforated, and Gangrenous (MUSTANG), an EAST Multicenter Study.* Ann Surg, 2019.
3. Lawless, R.A., et al., *Antibiotics after Simple (Acute) Appendicitis are not Associated with Better Clinical Outcomes: A Post-Hoc Analysis of an EAST Multi-Center Study.* Surg Infect (Larchmt), 2021. **22**(5): p. 504-508.
4. Bou Zein Eddine, S., et al., *Complicated Appendicitis: Are Extended Antibiotics Necessary? A Post Hoc Analysis of the EAST Appendicitis "MUSTANG" Study.* J Surg Res, 2020. **247**: p. 508-513.
5. van Rossem, C.C., et al., *Antibiotic Duration After Laparoscopic Appendectomy for Acute Complicated Appendicitis.* JAMA Surg, 2016. **151**(4): p. 323-9.
6. Evans, S.R., et al., Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). Clin Infect Dis, 2015. 61(5): p. 800-6.

4) Inclusion and Exclusion Criteria

Included are all patients admitted to the hospital that meet the following criteria:
- Age ≥ 18 years
- Planned appendectomy (laparoscopic or open)
- Working telephone number or reliable method to contact patient after hospital discharge

Excluded are patients who are:
- Unable to consent
- Pregnant Women

- Prisoners
- Immunocompromised as determined by clinical team, or patients actively receiving steroids, chemotherapy, or immunosuppressing medications (for example tacrolimus), or patients with active hematologic malignancy affecting the immune system, leukopenia, or end-stage AIDS
- Heart failure
- Allergy to bupivacaine
- Unlikely to comply with treatment or follow-up
- Inpatient consultation for appendicitis
- Clinically suspected of sepsis based on Sepsis-3 definition
- Current use of antibiotics for other indications
- Type 1 Diabetes or uncontrolled hyperglycemia
- Surgeon preference
- Patient preference
- Research team unavailable

5) Number of Subjects

Sample Size Required
2275 total subjects across all enrollment sites

Justification for Sample Size
This will be an "event-driven" power analysis, meaning that we will enroll subjects until the minimum number of primary endpoints necessary for clinically meaningful comparisons have occurred. This approach will guard against type 2 error if the actual incident rate is lower than expected (31.8%) and will also obviate the need for interim analyses. Because this is a multi-center trial, the effect of enrollment site must be taken into account and we have constructed a table with varying combinations of enrollment sites and subjects per site.

The EAST Appendicitis ("MUSTANG") observational study (Ann Surg, published online October 28, 2019) database was used to estimate incident rates of DOOR outcomes. From a total of 3597 enrolled subjects, 1:1 matching was utilized resulting in 479 match pairs from the MUSTANG dataset and diagnostics for matches were explored and it suggested that good matches were obtained. Below are the rates from the matched set, one observation was added to every cell to ensure that there were no zero probabilities in the assumptions.

All patients will be recruited into the study and they will be randomized in permuted blocks of 4 to 6 to one of two arms. Each arm will have two treatments which will be given to the patient depending on the case nature: acute or complicated. Comparisons in DOOR outcome will be compared only within the case nature strata by treatment; since the stratification criteria makes comparisons between strata not feasible.

Treatments	If simple:	If complicated:
Restrictive Arm	NO post-op antibiotics	Up to 24 h of post-op antibiotics

Liberal Arm	Up to 24 h of post-op antibiotics	4 days of postop antibiotics

Power analysis on DOOR outcome

In order to attempt to retrieve the expected rates of DOOR outcomes from a Randomized Controlled Trial (RCT) propensity score matching via the MatchIt algorithm was utilized. The issue being mitigated is that our patients were part of an observation where treatment was a byproduct of patient characteristics which would introduce selection into treatment bias and our direct estimates of DOOR outcomes would not be valid for powering an RCT. AAST clinical grade, body mass index, age, Charlson Comorbidity Index (CCI), and prior operations were used in the matching. 1:1 matching was utilized resulting in 479 match pairs from the MUSTANG dataset and diagnostics for matches were explored and it suggested that good matches were obtained. Below are the rates from the matched set, one observation was added to every cell to ensure that there were no zero probabilities in the assumptions.

DOOR	Matched Population	
Treatment	**<24**	**>24**
1	88.72%	70.83%
2	1.39%	11.11%
3	4.17%	1.39%
4	2.78%	8.33%
5	4.17%	4.17%
6	1.39%	2.78%
7	1.39%	1.39%

Once our expected rates of DOOR outcomes were developed, we simulated observations with roughly similar ICC values by drawing from a multivariate normal distribution and mapping it to a discrete uniform distribution using the above probabilities with an ICC of -0.001963853. The number of clusters and events per cluster were varied between 3 and 30 and 5 and 40, respectively. This process was replicated 1000 times at a 5% significance level to determine power. Powering was based on a signed rank test for clustered data to take into consideration correlation within clusters. Number of patients expected per cluster is taken from the rate of complicated cases in the MUSTANG dataset of 31.8%.

We will recruit patients until we see a sufficient number of complicated cases to be sufficiently powered for our comparison on treatment within the complicated strata. Since we expect fewer than 50% to be complicated cases, we expect a larger sample size to be available for analysis in the acute (simple) arm. Thus, we will be powered for an even larger effect size for simple appendicitis and if we do not find a statistically significant difference it is very likely that if there is a difference it would not be clinically meaningful. Also, since each analysis will depend on a mutually exclusive set of patients, we can consider these to be independent samples for which no adjustment for multiple testing is required.

Clusters	Events per cluster	Total Events	Patients per Cluster	Patients per Cluster +15% attrition	Power
30	15	300	48	55	0.84
20	20	400	63	72	0.804
25	20	500	63	72	0.876
30	20	600	63	72	0.906
15	25	375	79	91	0.809
20	25	200	79	91	0.842
25	25	625	79	91	0.927
15	30	450	95	109	0.857
10	35	350	111	128	0.818
15	35	525	111	128	0.916
10	40	400	126	145	0.836

Total events range from 300-625, and we will add 15% to account for loss-to-follow-up. Given that MUSTANG had an event rate of 31.8%, we expect to recruit up to 2275 patients.

Statistical Analysis Plan

Difference in DOOR score will be tested restrictive versus liberal strategies via proportional odds regression, accounting for enrollment site and age strata. The primary endpoint will be analyzed using an intention-to treat analysis. In case a significant difference is discovered, we plan to calculate the Fragility Index to determine the fragility of the study results. Significance will be determined at an alpha of 0.05. All analyses will be performed in R version 3.6.1 using the clusrank package.

Bayesian analysis

Bayesian analyses will be used to assess the probability of benefit with restrictive antibiotic use for appendicitis. Both primary and secondary outcomes will be assessed. Bayesian analyses combine prior beliefs (priors) and data obtained from the study (likelihood) to generate posteriors. Posteriors may then be utilized to generate posterior probabilities, which are statements indicating the probability that an effect of interest (or more extreme) is true, when considering both prior knowledge and the observed study data. The minimum clinically important difference in the primary outcome will be considered any increase in DOOR score (OR >1.0). To assess the primary and secondary outcomes, vague, neutral priors will be utilized. The neutral prior selected is based on a prior assumption that antibiotic administration does not affect DOOR score, however with notable uncertainty (OR 1.0, 95% CI 0.25 to 4.) Bayesian models will be built using the aforementioned criteria and will be adjusted for stratification variables which include clinical site and age group. All Bayesian analyses will utilize R with rstanarm package.

A priori interim analyses

Interim analyses will be conducted annually and presented to an independent data safety monitoring board comprised of members of the Surgical Infection Society

(SIS) Multicenter Trials committee at the annual meeting. A Bayesian interim analysis will be conducted as outlined above. The two arms (uncomplicated and complicated) will be analyzed separately and considered for early termination separately. Our stopping rule for safety will be a >95% posterior probability that a restrictive antibiotic strategy increases DOOR scores in either group. Our efficacy rule will be a >98% posterior probability that a restrictive antibiotic strategy decreases DOOR scores in either group. Finally, our stopping rule for futility will be a posterior probability between 45 and 55 that restrictive antibiotic strategy increased DOOR scores in either group after half the target sample size has been enrolled.

6) Study-Wide Site Recruitment Methods

This is a planned multicenter study and additional enrollment sites will be recruited through the Surgical Infection Society annual meeting and website. Additionally, we plan to promote this study on social media, specifically Facebook and Twitter.

7) Subject Recruitment Methods

Potential subjects will be identified by the clinical team (Acute Care Surgery) during the course of usual clinical care, and the clinical team will inform the subjects about the study and seek their verbal approval to being approached by the study research team. The patient will then be approached by the research team (in the emergency department, pre-operative holding area, or hospital ward) for detailed discussion about the study and for informed consent as outlined in the consent procedures below. If the subject consents to participate and agrees to be randomized, randomization will take place and the subject will be assigned to one of the two study groups (restricted or liberal). If the subject consents to participate but declines to be randomized, we will seek to enroll the patient in an observational arm; the clinician will decide the duration of post-operative antibiotic therapy and data will be collected from the subject's medical records and through a telephone call at approximately 1 month after hospital discharge. It is not possible to obtain consent to participate in this study on another day because if the patient has simple acute appendicitis (80% of cases), they are usually discharged home immediately after surgery or within 12 hours of surgery. For complicated appendicitis patients (20%), the restrictive arm is randomized to only 1 day of post-operative antibiotics and obtaining consent the following day would be too late to assign the subject to this arm.

Recruitment will not involve restrictions on socio-demographic factors including gender or ethnic characteristics. Recruitment will be devoid of any procedures which could be constructed as coercive. Study researchers and clinicians will stress that participation is voluntary, that patients are not obliged to participate, and that the decision not to participate in the study will not affect patient care.

8) Local Number of Subjects:

145 subjects at Jackson Memorial Hospital (JMH)

9) Study Timelines

The duration of an individual subject's participation in the study will be for approximately 1 month following appendectomy. The duration anticipated to enroll all study subjects is 2-3 years. The estimated date for the investigators to complete this study is July 2024.

10) Study Endpoints

All subjects will be contacted by telephone at approximately 1 month or later after the index operation and will be assigned to 7 mutually exclusive hierarchical (ie, ordinal) categories in decreasing order of desirability:

1. Cure; no adverse effects
2. Infectious/antibiotic complication requiring antibiotic treatment only or no specific treatment
3. Infectious/antibiotic complication requiring Emergency Department visit
4. Infectious/antibiotic complication requiring hospital readmission
5. Infectious/antibiotic complication requiring percutaneous drainage
6. Infectious/antibiotic complication requiring operative intervention
7. Death

The study endpoints will be reported as distribution across the above 7 groups for each arm.

11) Procedures Involved

This study is planned to be a multicenter trial and the University of Miami will be the primary pilot site as well as the overall data coordinating center. For the University of Miami, the Acute Surgery service at Jackson Memorial Hospital will identify potential subjects who will undergo for simple or complicated appendicitis. Upon patient consent, randomization will occur in permuted blocks of 4 to 6 and will be stratified according to center and age >65. Patients who agree to participate in the study but decline randomization will invited to enroll in an observational manner and their treatment will be determined by the clinician as appropriate.

12) Data and Specimen Banking

N/A

13) Data Management

Study subjects will be assigned unique study numbers that will be used in all study documents. No actual names will be used in the study. Only the researchers will know the actual names of the subjects. Study database and documents will be stored in a locked research office at Ryder Trauma Center Room T-215 and will only be accessible to the researchers. A copy of the de-identified data will be stored on REDCap.

Demographic data will include: age, sex, weight (kilograms), race and ethnicity, body mass index, date/time of ED triage, co-morbid medical conditions, CCI, steroids/ chemotherapy/other immunosuppressant, and tobacco use.

History of present illness data will include duration of symptoms in six-hour intervals up to 96 hours, and the presence/absence of: nausea, vomiting, anorexia, diarrhea, migration to the right lower quadrant (RLQ), and prior episodes.

Physical exam data collected included temperature (Celsius), heart rate, systolic blood pressure (SBP), Alvarado score, and the presence/absence of: RLQ tenderness, diffuse abdominal tenderness, RLQ rebound tenderness, diffuse abdominal rebound tenderness, Rovsing's sign, Obturator sign, and Psoas sign.

Laboratory data will include WBC, % polymorphonuclear cells, and % band cells. These tests are normally ordered by the subject's clinical team as part of their plan of care. No tests that are not part of the plan of care will need to be ordered for this study.

Radiographic data collected will include imaging type (none, ultrasound (US) only, computed tomography (CT) only), US and CT, magnetic resonance imaging (MRI) only, US and MRI, or other), and imaging findings.

The American Association for the Surgery of Trauma (AAST) severity grading scale for appendicitis will be recorded for the clinical, imaging, operative, and pathology dimensions.

Pathology data included intraoperative microbiological specimens and the final pathologic diagnosis: normal appendix, acute appendicitis, acute-on-chronic appendicitis, chronic appendicitis, gangrenous appendicitis, perforated appendicitis, adenocarcinoma, neuroendocrine (carcinoid) tumor, or other.

Operative data will include initial operative approach, final operative approach, intraoperative findings, intraoperative adverse events, operative duration, surgical drains, and post-operative antibiotics (class and duration).

Outcomes will be assessed for index hospitalization and at 30 days after appendectomy, including the presence/absence of complications defined when possible by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.5. The only Adverse Events of interest that will be collected for this study are: surgical site infection (SSI), intra-abdominal abscess (IAA), dehiscence, multiple organ failure, hospital acquired pneumonia, catheter-associated urinary tract infection (UTI), Clostridium difficile infection (CDI), sepsis defined according to Sepsis-3, postoperative ileus, supraventricular and nodal arrhythmia, ventricular arrhythmia, radiographically confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE), hemorrhage/bleeding, urinary retention, acute kidney injury (AKI), Clavien-Dindo complications, secondary interventions, hospital LOS, ED visits, appendicitis-related ED visits, hospital readmissions, and mortality. Any deviation from the expected recovery course will be assigned a severity grade according to the Clavien-Dindo system and the Comprehensive Complication Index will be calculated.

14) Provisions to Monitor the Data to Ensure the Safety of Subjects

We plan to establish a data safety monitoring board (DSMB), comprised of members of the Surgical Infection Society (SIS) Multi-Institutional Trials committee. The PI will prepare an annual interim analysis report comparing the study endpoints (see Section 9 above) between the two groups. The groups will be blinded in the interim analysis. The DSMB will review the report at the annual SIS scientific assembly and decide whether or not to continue the study or to prematurely terminate the study due to futility or safety. Efficacy will not be analyzed at interim analyses and will only be analyzed once at study completion or early termination as per the RADAR-DOOR group comparison (see Section 4 Background above).

Futility will be determined by the actual enrollment rate, which will vary according to overall number of participating sites as well as each individual site enrollment.

Safety information will be collected using case report forms (CRF) to be filled out by each site based on the telephone call to the subject at approximately 1 month. The CRF data will be uploaded to REDCap and the PI will review each case.

The frequency of review of cumulative data is once per year until study completion or early termination. There are no conditions that would trigger an immediate suspension of the research.

15) Withdrawal of Subjects

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.
In this trial, a subject may discontinue from study therapy but can continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent.

16) Risks to Subjects

Data suggest a therapeutic potential of a shorter duration of antibiotics, but its risks and benefits must be clearly and systematically defined with analysis. Results may lead to some study participants being at increased risk of infection and related complications. Clinical care will be at the discretion of the attending physician. Decision to resume or restart antibiotic treatment may be taken at any stage of the study by the attending physician.

17) Potential Benefits to Subjects

Based on encouraging results in studies on short periods of antibiotic treatment in cases of abdominal infections, we anticipate that the risk of adverse effects due to administration of antibiotics will be reduced in the study population with a shorter period of treatment. Therefore, this study will provide potential benefits to the study group as well as the general population of appendicitis patients who undergo appendectomy.

18) Vulnerable Populations

We will not enroll pregnant women, prisoners, children, or adults unable to consent.

19) Multi-Site Research

Communication to sites will be primarily by email and phone when possible.
All sites will have the most current version of the protocol, consent document, and HIPAA authorization. The required approvals will be obtained at each site (including approval by the site's IRB of record) as required for conducting the study at their site. The pertinent modifications will be communicated to sites to be approved (including approval by the site's IRB of record) before the modification is implemented. The participating sites are to safeguard data as required by local information security policies. The local site investigators are to conduct the study appropriately and all non-compliance with the study protocol or applicable requirements to be reported in accordance with local policy. Issues, problems, interim results, and closure of a study will be communicated to all sites as applicable.

20) Community-Based Participatory Research

N/A

21) Sharing of Results with Subjects

The results of this study will not be shared with subjects or other clinicians involved in the subject's care.

22) Setting: Jackson Memorial Hospital (JMH)

23) Resources Available

The Principal Investigator (PI) has experience conducting clinical research. All study researchers will be trained on the protocol by the investigator or designee and will complete required CITI trainings. Researchers who will be obtaining consent will also have prior experience communicating with patients.

24) Prior Approvals

N/A

25) Confidentiality

Data collected from JHS EMR and research participants will be stored in the secured JHS Sharepoint environment. De-identified data will be stored locally as follows:

✓ On a cloud-based storage system that is approved by the University of Miami
✓ JHS Secured SharePoint

The protected health information (PHI) collected for the purpose of this research study will be assigned a code number at the earliest opportunity and any obvious patient identifiers (name, social security number, medical record number) will be removed from this information. This information and any information linking the code numbers to the patients' identifiers will be stored in a secure manner (password-protected database) accessible only to study researchers. The health information and the information linking the code numbers to patients' identities will be stored separately.

Clinical data will be collected and include a phone call at approximately 1 month or later after hospital discharge. Data will be de-identified and stored on a password-protected network accessible only to study researchers. Data will be retained on this network for up to or after 2 years following conclusion of the study. The collected information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

25(a). Will the research collect protected health information or personally identifiable information from the EMR or from subjects at UHealth and/or JHS?

☒ Yes (If checked go to 26(b))

☐ No (If checked, go to Section 27)

25(b). Check the box next to the correct statement below

☒ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☐ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB.

25(c). How will the research store the data? (See Section 26(e) below)

☐ On a University of Miami electronic device (e.g. encrypted, password-protected computer)

☒ On a cloud-based storage system that is approved by the University of Miami

☒ On the secured JHS SharePoint environment (required for protected health information or identifiable information collected from JHS records without a waiver of authorization from an IRB.)

☐ Other, specify: Click here to enter text.

25(d) Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that does not include any indirect or direct identifiers (listed in the instructions for Section 26 of this protocol

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 26 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

25(e) Additional requirement for Jackson Health System Data:

☐ Not-applicable, no data will be acquired from JHS under a waiver of authorization.

☒ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research under a waiver of authorization shall only be stored on the secured JHS SharePoint environment made available by JHS. I and the Study Team members shall not copy or store the JHS sourced personally identifiable information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 26 of this protocol.

26) Biospecimens

☒ Not applicable. No biospecimens will be collected

☐ Bio-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☐ Bio-Specimens obtained for this research will be stored in a de-identified coded manner.

☐ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

27) Provisions to Protect the Privacy Interests of Subjects

Access to patients and their protected health information along with the collection and analysis is necessary in order to conduct this research study. Consistent with the "minimum necessary standard" of the HIPAA privacy rule, we will only access and collect the specific health information necessary to complete this research study.

Some of the study researchers who will access and use the protected health information may also be involved directly in the care of the study patients thus obviating privacy and confidentiality concerns.

The protected health information collected for the purpose of this research study will be assigned a code number and any obvious patient identifiers (name, social security number, medical record number) will be removed from this information. This information and any information linking the code numbers to the patients' identifiers will be stored in a secure manner (password-protected database) accessible only to study researchers.

27) Compensation for Research-Related Injury

Some study participants may be at increased risk of infection and related complications. No funds are available for compensation.

28) Economic Burden to Subjects

There are no costs that subjects may be responsible for because of participation in the research.

29) Consent Process

After giving verbal approval to the clinical team to being approached by the research team, potential identified patients will be approached in the pre-operative area or post-operatively within 24 hours of operation by a study researcher. Any of the researchers listed on the protocol will discuss risks and benefits of participation. If a researcher is not fluent in the patient's native language, they will use a translator to obtain informed consent in a document written in the patient's native language.

A patient will be given an informed consent form in their native language. They will be given time to review the form. Once they have agreed, they will be required to sign the consent before any study procedures can be started. A copy of the consent form will be given to the subject and one will be placed in the medical records. The original form will be kept in the subject's source documentation folder.

Patients who are incapacitated or unable to sign their own consent will not be enrolled in the study.

For non-English speaking subjects, a translated written informed consent form will be provided in a language that is understandable to them. This will be an accurate translation of the IRB-approved English version of the full informed consent form.

30) Process to Document Consent in Writing

Study researchers will document consent with a translated written informed consent document in a language understandable to the subject. If any patients who do not speak English are eligible, we will ensure that oral and written information provided to those patients will be in their own language translated by either research personnel fluent in that language or by an institutional translator. We will pursue approval of the consent documents in Spanish since a significant portion of the subject population may speak Spanish. We also request permission to utilize the short forms for documentation of consent and translation into any language other than English or Spanish for the rare circumstance that a subject cannot communicate in either of those languages.

31) Authorization for Use and Disclosure of Protected Health Information (HIPAA)

Confirm that you will destroy or de-identify the information you collect at the earliest opportunity.

✓ I confirm

Confirm that the information you collect will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.
✓ I confirm

✓ Not applicable. This research will not collect data from JHS record under a waiver of authorization

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified**, to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).

PI Signature: 

Date: 6/8/2021

32) Drugs or Devices

N/A