PROTOCOL TITLE:
Controlling **R**apid **A**trial-Fibrillation with **D**exmedetomidine (**C-RAD**) Randomized Double-Blind Controlled Trial

PROTOCOL VERSION/AMENDMENT: 0.01

NCT04042727

DATE: 9/21/2020

STUDY PERSONNEL:

Andreas Kalogeropoulos, MD MPH PhD	Associate Professor, Department of Medicine (Cardiology)
Elliott Bennett-Guerrero, MD (Co-I)	Professor and Vice Chair for Clinical Research (Dept of Anesthesiology)
Ibrahim Almasry, MD (Co-I)	Cardiac Electrophysiology Attending (Div of Cardiology/Dept of Medicine)
Roberto Thomas Sanchez, BS (Co-I)	
Jamie Romeiser, MPH (Co-I)	Study datamanager and statistician
Brittney Ayala, MS	Clinical Research Coordinator

1.1 OBJECTIVES

1.2 Describe the purpose, specific aims, or objectives of this research. Specifically, explain why it is important to do the study.

The purpose of this trial is to assess the ability of Dexmedetomidine (Dex), a commonly used sympatholytic, to improve heart rate control in patients with rapid Atrial Fibrillation (AF) through a pragmatic, randomized, double blind study comparing the addition of Dexmedetomidine or placebo to standard of standard of care (SOC) treatment.

This trial is the first of its kind to use bradycardia, a common side effect of Dexmedetomidine, for therapeutic purposes in an attempt to control heart rate in rapid Atrial Fibrillation. The aim is to study whether Dexmedetomidine can help improve rate control for patients with rapid-AF in the critical care setting – a setting in which the management of AF is often challenging due to co-morbidities and organ dysfunction.

1.2 State the hypothesis to be tested, if applicable. NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Addition of Dexmedetomidine administration to patients with atrial fibrillation already receiving standard of care results in improved heart rate control compared to the standard of care plus placebo arm.

2.0 SCIENTIFIC/SAFETY ENDPOINTS

2.1 *Describe the scientific endpoint(s), the main result or occurrence under study. NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw*

conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should not be a date.

Primary Endpoints:
The primary end point will be to assess the degree of heart rate control (mean ventricular heart rate <100 bpm), in the Dexmedetomidine plus SOC arm compared to the placebo plus SOC arm. Heart rate will be calculated from 6-second rhythm strips obtained every 15-minutes from the hospital's electronic medical record. Heart rate will be recorded 1-hour prior to the study drug administration, for 8-hours during study drug infusion and for 2-hours post cessation of the study drug infusion (a total of 44 rhythm strips).

Key Secondary Endpoints:
1) Time to heart rate control (HR <100 bpm) in the Dexmedetomidine plus SOC arm vs. Placebo plus SOC arm.
2) Percentage of rhythm strips with heart rate <100 bpm.
3) Percentage of rhythm strips with conversion to sinus rhythm. An attending cardiologist (Dr. Almasry- CoI), who is blinded to study drug assignment, will adjudicate all rhythm strips for determination of heart rhythm.

Exploratory Endpoints:
Descriptive assessment of rate control, and vasoactive medications used in both arms during the 8-hour study drug infusion.

Safety Endpoints:
1) Percentage of patients requiring pausing or discontinuation of study drug.
2) Episodes of hypotension defined as two consecutive values of SBP <90 mm Hg requiring intervention.
3) Episodes of bradycardia requiring cessation of infusion (persistent heart rate <50 bpm).

3.0 BACKGROUND AND RATIONALE:

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute/fill in gaps to existing knowledge.

Atrial fibrillation (AF) is the most common arrhythmia, affecting nearly 2.2 million Americans[1-7]. Approximately 25% of men and women over 40 will develop AF in their lifetime[7]. AF is characterized by a rapid irregular atrial activation, or "quivering", resulting in loss of atrial systole, ineffective ventricular filling and a lack of distinct P-waves with repetitive RR-interval patterns on electrocardiogram (ECG). Rapid, irregular ventricular contraction rates can develop in AF and result in decreased cardiac output, increase myocardial oxygen demand, and atrial appendage thrombus formation[1,8-12]. AF can result in decompensated heart failure[13], myocardial infarction (MI)[14-17], systemic embolization[18], and increased overall morbidity[19] and mortality[13,18,20-25]. AF increases cardiovascular-associated mortality[26,27] and acute myocardial infarction (AMI) risk increases 2-fold[14,15]. AF management strategies initially require a rapid reduction in ventricular rate in order to prevent these complications and improve symptoms. Long term strategies usually revolve around rate control +/- rhythm control.

Initiation and maintenance of AF is affected by the autonomic nervous system (ANS)[28] and may be promoted by heightened vagal and sympathetic tone[29,30]. Excessive adrenergic stress has been implicated in adverse events including direct myocardial damage[31,32]. Since excessive sympathetic drive is implicated in the development of rapid AF, then the use of a sympatholytic-agent may have a role in the treatment of rapid AF in the acute setting.

Dexmedetomidine, a centrally acting alpha-2 agonist (sympatholytic), was approved by the FDA in 1999 for anxiolysis and sedation in both intubated and non-intubated patients[33-40]. It is one of the most commonly used medications in ICUs, therefore, there is extensive knowledge about its safety profile. It is generally regarded as a safe drug. Common side effects of Dexmedetomidine are bradycardia and hypotension[33], yet it causes less hypotension than other sedatives such as Propofol, and benzodiazepines[34].

Several studies have suggested a role for Dexmedetomidine with ventricular arrhythmias[26,35-39]. The role of Dexmedetomidine for patients with rapid atrial tachyarrhythmias remains unknown. Our proposed study is the first of its kind to evaluate whether Dexmedetomidine, an anxiolytic/sedative agent, can be used to lower the heart rates of patients with AF. We hypothesize that its sympatholytic properties will lead to improved rate control over standard of care management. We believe this study could have important clinical therapeutic implications for use in patients with rapid AF and expand the armamentarium available for treating rapid AF in the critical care setting.

3.2 Include complete citations or references:

1. Perula-de-Torres LA, Martinez-Adell MA, Gonzalez-Blanco V, et al. Opportunistic detection of atrial fibrillation in subjects aged 65 years or older in primare care: a randomised clinical trial of efficacy. DOFA-AP study protocol. *BMC family practice.* 2012;13:106.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama.* 2001;285(18):2370-2375.
3. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *The American journal of cardiology.* 1994;74(3):236-241.
4. Curry SJ, Krist AH, Owens DK, et al. Screening for Atrial Fibrillation With Electrocardiography: US Preventive Services Task Force Recommendation Statement. *Jama.* 2018;320(5):478-484.
5. Welton NJ, McAleenan A, Thom HH, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health technology assessment (Winchester, England).* 2017;21(29):1-236.
6. England PH. Atrial Fibrillation Prevalence Estimates in England: Application of Recent Population Estimates of AF in Sweden. *London: Public Health England.* 2015.
7. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation.* 2004;110(9):1042-1046.
8. Pritchett EL. Management of atrial fibrillation. *The New England journal of medicine.* 1992;326(19):1264-1271.
9. Atrial fibrillation: current understandings and research imperatives. The National Heart, Lung, and Blood Institute Working Group on Atrial Fibrillation. *Journal of the American College of Cardiology.* 1993;22(7):1830-1834.
10. Lip GY, Metcalfe MJ, Rae AP. Management of paroxysmal atrial fibrillation. *The Quarterly journal of medicine.* 1993;86(8):467-472.
11. Disch DL, Greenberg ML, Holzberger PT, Malenka DJ, Birkmeyer JD. Managing chronic atrial fibrillation: a Markov decision analysis comparing warfarin, quinidine, and low-dose amiodarone. *Annals of internal medicine.* 1994;120(6):449-457.
12. Jonas DE, Kahwati LC, Yun JDY, Middleton JC, Coker-Schwimmer M, Asher GN. Screening for Atrial Fibrillation With Electrocardiography: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama.* 2018;320(5):485-498.
13. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98(10):946-952.

14. Soliman EZ, Safford MM, Muntner P, et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA internal medicine.* 2014;174(1):107-114.
15. Smolina K, Wright FL, Rayner M, Goldacre MJ. Incidence and 30-day case fatality for acute myocardial infarction in England in 2010: national-linked database study. *European journal of public health.* 2012;22(6):848-853.
16. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *European heart journal.* 2009;30(9):1038-1045.
17. Garg RK, Jolly N. Acute myocardial infarction secondary to thromboembolism in a patient with atrial fibrillation. *International journal of cardiology.* 2007;123(1):e18-20.
18. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983-988.
19. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database. *BMJ open.* 2011;1(2):e000269.
20. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation.* 2004;109(12):1509-1513.
21. Andersson T, Magnuson A, Bryngelsson IL, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *European heart journal.* 2013;34(14):1061-1067.
22. Raju NC, Hankey GJ. Dabigatran etexilate in people with atrial fibrillation. *BMJ.* 2010;341:c3784.
23. Hannon N, Sheehan O, Kelly L, et al. Stroke associated with atrial fibrillation--incidence and early outcomes in the north Dublin population stroke study. *Cerebrovascular diseases (Basel, Switzerland).* 2010;29(1):43-49.
24. Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *European heart journal.* 2007;28(19):2346-2353.
25. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *The American journal of medicine.* 2002;113(5):359-364.
26. Chrysostomou C, Sanchez-de-Toledo J, Wearden P, et al. Perioperative use of dexmedetomidine is associated with decreased incidence of ventricular and supraventricular tachyarrhythmias after congenital cardiac operations. *The Annals of thoracic surgery.* 2011;92(3):964-972; discussion 972.
27. Chen LY, Sotoodehnia N, Buzkova P, et al. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. *JAMA internal medicine.* 2013;173(1):29-35.
28. Workman AJ. Cardiac adrenergic control and atrial fibrillation. *Naunyn-Schmiedeberg's archives of pharmacology.* 2010;381(3):235-249.
29. Herweg B, Dalal P, Nagy B, Schweitzer P. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. *The American journal of cardiology.* 1998;82(7):869-874.
30. Coumel P. Autonomic influences in atrial tachyarrhythmias. *Journal of cardiovascular electrophysiology.* 1996;7(10):999-1007.
31. Singer M. Catecholamine treatment for shock--equally good or bad? *Lancet (London, England).* 2007;370(9588):636-637.
32. Dunser MW, Hasibeder WR. Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *Journal of intensive care medicine.* 2009;24(5):293-316.
33. Research CfDEa. Precedex Approval Package. 2010.
34. Hoy SM, Keating GM. Dexmedetomidine: a review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. *Drugs.* 2011;71(11):1481-1501.
35. Ling X, Zhou H, Ni Y, Wu C, Zhang C, Zhu Z. Does dexmedetomidine have an antiarrhythmic effect on cardiac patients? A meta-analysis of randomized controlled trials. *PloS one.* 2018;13(3):e0193303.

36. Herr DL, Sum-Ping ST, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. *Journal of cardiothoracic and vascular anesthesia.* 2003;17(5):576-584.
37. Ren J, Zhang H, Huang L, Liu Y, Liu F, Dong Z. Protective effect of dexmedetomidine in coronary artery bypass grafting surgery. *Experimental and therapeutic medicine.* 2013;6(2):497-502.
38. Corbett SM, Rebuck JA, Greene CM, et al. Dexmedetomidine does not improve patient satisfaction when compared with propofol during mechanical ventilation. *Critical care medicine.* 2005;33(5):940-945.
39. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology.* 2009;111(5):1075-1084.
40. Zientara A, Mariotti S, Matter-Ensner S, et al. Fast-Track Management in Off-Pump Coronary Artery Bypass Grafting: Dexmedetomidine Provides Rapid Extubation and Effective Pain Modulation. *The Thoracic and cardiovascular surgeon.* 2018.

4.0 STUDY DESIGN

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, and observational). Indicate if there is randomization, blinding, control group, etc. If randomizing, explain how this will be achieved.

Prospective, randomized, controlled, double-blind placebo controlled study.

5.0 LOCAL NUMBER OF SUBJECTS

5.1 Indicate the total number of subjects who will be enrolled or records that will be reviewed through Stony Brook.

This is a single center pilot study designed to enroll 60 subjects, 30 per arm.

5.2 If this study is only being conducted through Stony Brook, provide statistical justification (i.e. power analysis) for the number of subjects provided in 5.1 above. If qualitative research, so state, and provide general justification for the total number of subjects proposed.

Based on prior clinical experience, we anticipate the average heart rate in the Standard of Care (SOC) treatment plus placebo arm will be higher (mean ventricular rate of about 100 bpm), with more relative variability (standard deviation of 20). We believe the SOC plus Dexmedetomidine group will have a lower average heart rate (mean ventricular heart rate of about 85 bmp) with less variability (standard deviation of 15). Because of the uncertainty in these estimates, a range of power estimations were calculated by using a target goal of 60 participants (30 per group) [see table below]. The power estimations were carried out using PASS 12 Software (Kaysville, Utah). Using a two sample t-test allowing for unequal variance, and a range of standard deviations, we will have between 81.5% - 99.4% power to detect a difference between the two groups.

Numeric Results for Two-Sample T-Test Allowing Unequal Variance

Alternative Hypothesis: H1: $\delta = \mu1 - \mu2 \neq 0$

Power	N1	N2	N	δ	σ1	σ2	Alpha
0.99395	30	30	60	15	15	10	0.05
0.96771	30	30	60	15	15	15	0.05
0.89745	30	30	60	15	15	20	0.05
0.94849	30	30	60	15	20	10	0.05
0.89745	30	30	60	15	20	15	0.05

0.81497	30	30	60	15	20	20	0.05

5.3 If applicable, indicate your screen failure rate, i.e., how many subjects you expect to screen to reach your target sample

We anticipate a screen failure rate of approximately 10-15%, which is reasonable for a trial of this type. Therefore, we expect to screen ~70 patients.

5.4 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

There are approximately 65 adult Critical Care beds at Stony Brook University Hospital. Patients in adult ICUs or ICRs who meet the eligibility criteria below will be screened daily for entry into the study by study personnel with the help of the PIand Dr. Bennett-Guerrero, a Co-I, who is an intensivist in the CTICU. We anticipate that 5%-10% of the daily ICU population will be in AFIB. We plan to enroll approximately 1 patient each day to achieve our target of 60 patients.

We will also consider enrolling patients - who are not in need of life support - in the Medical ICR and the CACU, as they can also present rapid AF in these critical care settings while bearing fewer comorbidities. They are less sick than patients in the ICUs, the nurse to patient ratio in these units is 4:1, arterial lines (A-lines) are the standard for patient heart rate (HR) and blood pressure (BP) monitoring, and we believe that these patients may also benefit from being included in this study.

6.0 INCLUSION AND EXCLUSION CRITERIA

6.1 Inclusion Criteria:

- Adult patients in a Stony Brook University Hospital ICU or ICR with rapid atrial fibrillation (with ventricular rates >100 bpm)
- Patients with and without capacity to consent will be screened. Consent will be acquired either from the patient directly or from the Legal Authorized Representative when the patient is not able to consent, as is consistent with most ICU studies.
- Patients that are mechanically ventilated as well as those that are not.

6.2 Exclusion Criteria:

- <18 years of age.
- Anticipated ICU or ICR length of stay of less than 11-hours.
- Patients with a permanently paced heart rhythm.
- Patients with known 2nd and 3rd degree heart blocks, junctional rhythms
- Known pregnancy
- Patients with known allergy to Dexmedetomidine.
- Patients receiving Dexmedetomidine prior to onset of study
- Non-intubated patients with a Glasgow Coma Scale (GCS) <8.
- Patients who weigh more than 400 pounds (182 kg) (protocol dosing restriction).
- Patients with untreated, symptomatic hypotension (sustained SBP <90 mm Hg).
- Patients who have received amiodarone, lidocaine, or mexiletine within 4-hours prior to consent.

6.3 Describe how individuals will be screened for eligibility. Upload all relevant screening documents with your submission (screening protocol, script, questionnaire). Identify who will certify that subjects meet eligibility requirements.

Dr. Kalogeropoulos, Associate Professor Department of Medicine, Dr. Bennett-Guerrero (a Co-I, who is an intensivist in the CTICU), and other study personnel will make rounds in the various ICUs and ICRs throughout the day to determine if there are patients who are potentially eligible for the trial. In addition, clinicians (RNs, MDs) will also be encouraged to refer patients with rapid-AF to our attention for consideration. Study personnel will use the IRB approved inclusion/exclusion checklist to determine and confirm eligibility.

6.4 Indicate whether you are specifically recruiting or targeting any of the following special populations in your study using the checkboxes below. (You will be asked for additional information in Section 7 if you check any of these boxes)

N/A

6.5 Indicate if you will include minorities (American Indians, Alaskan Native, Asian, Native Hawaiian, Pacific Islander, Black [not of Hispanic origin] and Hispanic) as Federal mandates require that you include minorities unless you can justify their exclusion

☒ Yes
☐ No, Justify:

6.6 Indicate whether you will include non-English speaking individuals in your study. Provide justification if you will specifically exclude non-English speaking individuals. Review http://research.stonybrook.edu/human-subjects-standard-operating-procedures/policy-non-english-speakers-research-subjects for SBU policy on inclusion of non-English speakers. Upload any translated materials (consent, questionnaires, etc).

We will not include individuals who do not speak English in this study.

7.0 Vulnerable Populations

7.1 For research that involves pregnant women, review, complete and upload Supplemental Form A: Pregnant Women, Fetuses, Non-Viable Neonates, or Neonates of Uncertain Viability.

☐ Confirmed
☒ N/A: This research does not involve pregnant women.

7.2 For research that involves neonates of uncertain viability or non-viable neonates, review, complete and upload Supplemental Form A: Pregnant Women, Fetuses, Non-Viable Neonates, or Neonates of Uncertain Viability.

☐ Confirmed
☒ N/A: This research does not involve non-viable neonates or neonates of uncertain viability.

7.3 For research that involves prisoners, review, complete and upload Supplemental Form H: Prisoners

☐ Confirmed
☒ N/A: This research does not involve prisoners.

7.4 For research that involves minors (under 18 years), review, complete and upload Supplemental Form F: Minors

☐ Confirmed

☒ N/A: This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

7.5 For research that involves adults who cannot consent for themselves, you will be asked additional information in Section 25 ("Informed Consent")

☒ Confirmed

☐ N/A

7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.

vulnerable populations will be targeted.

☒ N/A

8.0 Eligibility Screening

8.1 Describe screening procedures for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.

Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaires) as attachments.

Dr. Kalogeropoulos, Associate Professor Department of Medicine, and other study personnel will make rounds in the various ICUs and ICRs throughout the day to determine if there may be patients who are potentially eligible for the trial. In addition, if clinicians (RNs, MDs) bring patients with rapid-AF in an adult ICU or ICR to our attention, these patients will also be screened for eligibility. The patient's medical record, telemetry monitoring and ECGs (when available) will be reviewed to ascertain that the patient is in fact in rapid-AF. Study personnel will use the IRB approved inclusion/exclusion checklist to determine and confirm eligibility.

☐ N/A: There is no screening as part of this protocol.

9.0 Recruitment Methods

☐ N/A: This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections, including date range for records that will be reviewed.

9.1 Describe source of subjects: When, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. These may include, but are not limited to: ResearchMatch.org, physician referral, Office of Clinical Trials database, West

Campus departmental pools, reviewing medical charts, Research Participant Groups/help groups, advertising companies, call centers, in person announcements / presentations

Dr. Kalogeropoulos, Associate Professor Department of Medicine, and other study personnel will make rounds in the various ICUs and ICRs throughout the day to determine if there may be patients who are potentially eligible for the trial. In addition, if clinicians (RNs, MDs) bring patients with rapid-AF in an adult ICU or ICR to our attention, these patients will also be screened for eligibility. The patient's medical record, telemetry monitoring and ECGs (when available) will be reviewed to ascertain that the patient is in fact in rapid-AF. Study personnel will use the IRB approved inclusion/exclusion checklist to determine and confirm eligibility. If a patient appears to be eligible we will discuss the study with them or with their LAR.

9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process. NOTE: Privacy refers to an individual's right to control access to him or herself. This is NOT asking about confidentiality of data.

We will speak to patients or their LAR in a private setting.

9.3 Identify/describe any materials that will be used to screen/recruit subjects and upload copies of these documents with the application. They may include, but are not limited to Telephone scripts for calling, flyers, Questionnaires, Posters, Letters or written material to be sent or emailed, pamphlets, posted advertisements, email invitations.

N/A

10.0 RESEARCH PROCEDURES

Provide a detailed description of all research procedures or activities being performed on the research subjects. ***This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research.*** *For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response. Be sure to include:*

- *Procedures being performed to monitor subjects for safety or to minimize risks.*
- *All drugs and devices used in the research and the purpose of their use, and their regulatory status*

ROUTINE CARE: All patients (ie in both study arms) will receive routine standard of care (SOC) treatment of their atrial fibrillation per the discretion of their treating physicians. This typically includes correction of electrolyte abnormalities (K^+, Mg^{2+}) and administration of beta blockers, calcium channel blockers, and Digoxin, etc. in order to achieve rate control and prevent complications associated with rapid ventricular rates. Our trial will record details of this care but does not control nor limit what SOC is used in the treatment of the patient's rapid-AF.

SUMMARY OF RESEARCH PROCEDURES: From the perspective of the subject, the only additional aspects of the trial that are not routine will be the following:

1) Patient's rhythm will be confirmed by reviewing telemetry and available ECGs. Patients deemed to be in rapid-AF will be consented and randomized in a 1:1 fashion to receive placebo (normal saline infusion),
   or the study drug Dexmedetomidine. A patient who is no longer in rapid-AF at time of consent will be screen failed
   (see Statistical Methods section for details).
2) An order for the study drug will be entered into the Electronic Medical Record (EMR) as a Therapeutic Non-Formulary (TNF) request per Stony Brook's Investigational Pharmacy's standard operating procedure. The Investigational Pharmacy will prepare the blinded study drug with appropriate labeling as either 250 mL of normal saline (placebo) or

Dexmedetomidine (1200 µg/250 mL). The study drug will be delivered to the patient's bedside. The patient's nurse will scan the medication using the hospital's routine bar code technology and administer the drug via infusion pump.

Study drug administration and monitoring:

a. Study drug will be infused at 1 µg/kg/hr with maximum rate of 150 µg/hr for a period of 8 hours from the initial start of study drug administration. This dosing regimen is consistent with routine use of Dexmedetomidine at Stony Brook and in numerous clinical studies (see RISKS section).
b. Heart rate will be continuously monitored via telemetry, as is routine in ICU patients. Per the study protocol, blood pressure will be measured every 15 minutes during study drug administration either non-invasively by cuff or via an indwelling arterial catheter (placed for routine care).
c. If HR is < 50 bpm, SBP < 80 mm Hg, or RASS< -2 for non-intubated patients, or a patients clinically decompensates, the study drug infusion will be paused for 1 hour. The study drug will then be restarted at half the dose (i.e. 0.5 µg/kg/hr) once the patient is stable and no longer hypotensive or bradycardic. If the infusion is not restarted then the patient will be assessed hourly to determine if it is safe to resume the infusion once the above pausing criteria have been resolved.

3) Concomitant medications: The study prohibits the use of Dexmedetomidine during the study drug administration period for sedation.

4) As described in Endpoints, rhythm strips will be printed from the hospital EMR every 15 minutes for assessment of cardiac rhythm and rate.

5) Routinely collected demographic and patient related variables (e.g. date of birth, age, race, ethnicity, sex, height, weight, medical history, comorbidities: type 2 diabetes, smoker; pre-existing conditions: coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease; APACHE 3 variables: AaDO2 or PaO2, temperature, MAP, pH arterial, heart rate, respiratory rate, sodium (serum), potassium (serum), creatinine, hematocrit, white blood cell count, Glasgow Coma Scale; date and time of ICU admission, admitting diagnosis, RASS score, mechanical ventilation, systolic and diastolic blood pressure, heart rate, date of last echocardiogram, left ejection fraction, left atrial size, concomitant medications (e.g. vasopressors, beta-blockers)) will be recorded from the EMR.

10.1 Describe what data, including long-term follow-up, will be collected. NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

As described above, we will collect rhythm strips 1-hour before and 2-hours after the study drug administration period, and during the 8-hour study drug administration period. The investigational team will print out 4 rhythm strips per hour- amounting to a total of 44 rhythm strips. This information will be included and ordered sequentially into the patients study's folder. An attending cardiologist (Dr. Almasry- CoI), who is blinded to study drug assignment, will adjudicate all rhythm strips for determination of heart rhythm.

Routinely collected demographic and patient related variables (e.g. date of birth, age, race, ethnicity, sex, height, weight, medical history, comorbidities: type 2 diabetes, smoker; pre-existing conditions: coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease; APACHE 3 variables: AaDO2 or PaO2, temperature, MAP, pH arterial, heart rate, respiratory rate, sodium (serum), potassium (serum), creatinine, hematocrit, white blood cell count, Glasgow Coma Scale; date and time of ICU admission, admitting diagnosis, RASS score, mechanical ventilation, systolic and diastolic blood

pressure, heart rate, date of last echocardiogram, left ejection fraction, left atrial size, concomitant medications (e.g. vasopressors, beta-blockers)) will be recorded from the EMR.

List, and upload, any instruments or measurement tools used to collect data (e.g. survey, scripts, questionnaire, interview guide, validated instrument, data collection form).

10.2 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records) and include the date range for records that will be accessed.

Electronic medical records will be used to collect demographic information, patient related variables (e.g. date of birth, age, race, ethnicity, sex, height, weight, medical history, comorbidities: type 2 diabetes, smoker; pre-existing conditions: coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease; APACHE 3 variables: AaDO2 or PaO2, temperature, MAP, pH arterial, heart rate, respiratory rate, sodium (serum), potassium (serum), creatinine, hematocrit, white blood cell count, Glasgow Coma Scale; date and time of ICU admission, admitting diagnosis, RASS score, mechanical ventilation, systolic and diastolic blood pressure, heart rate, date of last echocardiogram, left ejection fraction, left atrial size, concomitant medications (e.g. vasopressors, beta-blockers)) will be recorded from the EMR.

Additionally, heart rate (HR) will be calculated from 6-second rhythm strips obtained every 15-minutes. Heart rate will be recorded 1-hour prior to the study drug administration, during the 8-hours of the study drug infusion and for 2-hours post cessation of the study drug infusion (a total of 44 rhythm strips). An attending cardiologist (Dr. Almasry- CoI), who is blinded to study drug assignment, will adjudicate all rhythm strips for determination of heart rhythm.

10.3 Indicate whether or not the results for individual subjects, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.

Not applicable as no results will be shared during the course of the study.

10.4 Indicate whether or not generalized study results will be shared with subjects or others, and if so, describe how these will be shared.

We plan to disseminate study results in a published manuscript.

11.0 Study Timelines

11.1 Describe the anticipated duration of the study needed to enroll all study subjects.

It is expected to take approximately 3 months to enroll all study subjects.

11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

The duration of an individual subject's participation in the study will be approximately 11-hours. This is to ensure the collection of heart rate data which will be recorded for 1-hour prior to the study drug administration, for 8-hours during the study drug infusion, and for 2-hours post cessation of the study drug infusion.

11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Full study completion is expected within 6 months.

12.0 Research Setting

12.1 Describe all facilities/sites/locations where you will be screening and conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

Example: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Stony Brook University Hospital, a fully accredited tertiary care institution within New York State with badge access,"

Adult Intensive Care Units and ICRs at SBU Hospital are secure and private facilities within the hospital.

12.2 For research procedures being conducted, for this study, external to SBU and its affiliates (e.g., in schools, out-of-state, internationally, etc.) describe:

- *Site-specific regulations or customs affecting the research*
- *The composition and involvement of any community advisory board*
- *Local scientific and ethical review structure outside the organization.*
- *Local issues affecting the research and rights of research subjects.*

NOTE: This question is not referring to multi-center research. If this research is being conducted internationally, Supplemental Form C must be completed and uploaded.

N/A

☒ N/A: This study is not conducted outside of SBU or its affiliates.

13.0 Resources and Qualifications

13.1 The Principal Investigator (PI) must confirm, in consultation with Chair and Dean as applicable, that adequate resources are present to conduct and complete the study compliantly and safely. Specifically:

☐ **NO** ☒**YES** *The proposed subject population(s) are available in sufficient numbers to meet the study requirements.*

☐ **NO** ☒**YES** *Sufficient funds are available to conduct and complete the study compliantly and safely.*

☐ **NO** ☒**YES** *The PI and study team have sufficient time to conduct and complete the study compliantly and safely.*

☐ **NO** ☒**YES** *The PI has determined that the named study team is qualified to conduct the research compliantly and to monitor the safety and welfare of the enrolled research subjects effectively.*

☐ **NO** ☒**YES** *The PI ensures that the study team is fully aware of his/her involvement in this study and the details of the study protocol.*

☐ **NO** ☒**YES** *The PI ensures that the study teams will only be involved in research procedures for which they have been trained, and are currently certified and/or licensed, if required.*

13.2 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable. (e.g, "on-call availability of a counselor or psychologist for a study that screens subjects for depression").

Patients will be continuously monitored in an ICU or ICR setting, with bedside nurses and physicians immediately available should the need arise due to unanticipated consequences.

13.3 Describe your process to ensure that all study team members are updated on the progress of the research and the regulatory requirements (including enrolled subjects, unanticipated problems etc.)

The study team will have regular (e.g. weekly) meetings to discuss and review any issues that may arise.

14.0 Other Approvals

14. List approvals that will be obtained prior to commencing the research (e.g., University Hospital sign-offs per the UH Application, Cancer Center Scientific review, school, external site, funding agency, laboratory, Radiation Safety, IBC, SCRO, IACUC, RDRC).

Investigational Pharmacy: We have already consulted with Stony Brook's Investigational Pharmacy (Richard Connor, RPh). He has been extremely helpful and given us guidance on randomizing patients in the pharmacy, purchasing the study drug, setting up the procedures to order the study drug, and having the pharmacy prepare the study-drug, all of which have been incorporated into our study design. The IRB application will be sent to the Department of Medicine for approval as per routine.

☐ N/A: This study does not require any other approvals.

15.0 Provisions to Protect the Privacy Interests of Subjects

15.1 Describe how you will protect subjects' privacy interests during the course of this research and any steps you will take to make the subject feel at ease.

NOTE: Privacy refers to an individual's desire/right to control access to or to place limits on whom they interact with or whom they provide personal information. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a private office setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

All meetings with participants, or their LAR, and study personnel will occur in private settings where no one can overhear these discussions of patient information.

16.0 Data Management and Analysis

16.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

All statistical procedures/analyses will be performed by the trial's biostatistician using SAS 9.4 (SAS Institute Inc., Cary, NC).

Randomization: Randomization lists will be generated by the study's statistician using block randomization with random permuted block sizes of 2 and 4 will be used to ensure a similar number of patients in each group over time. Patients will be stratified at randomization on 2 factors (mechanically ventilated yes/no, receiving an inotropic agent, i.e. dopamine, dobutamine, epinephrine, or milrinone yes/no). From these 4 randomization lists 4 sets of sealed envelopes will be created with randomization assignments to maintain allocation concealment, and the Investigational Pharmacy will store and open these sealed envelopes consecutively to randomize each patient. All eligible patients who are consented, randomized, and received the treatment/placebo will be included in the analyses, consistent with a modified intent-to-treat (mITT) principle.

Data management:

Collection of CRF documents and rhythm strips values will occur on paper forms as source documents. These documents will be stored in a locked office and the transferred/matched/merged to the electronic data capture system (Redcap) for complete record storage.

Sample size/Power Calculation:

Based on prior clinical experience, we anticipate the average heart rate in the Standard of Care treatment (placebo) will be higher (mean ventricular rate of about 100 bpm), with more relative variability (standard deviation of 20). We believe the Dexmedetomidine group will have a lower average heart (mean ventricular heart rate of about 85 bmp) with less variability (standard deviation of 15). Because of the uncertainty in these estimates, a range of power estimations were calculated by using a target goal of 60 participants (30 per group) [see table below]. The power estimations were carried out using PASS 12 Software (Kaysville, Utah). Using a two sample t-test allowing for unequal variance, and a range of standard deviations, we will have between 81.5% - 99.4% power to detect a difference between the two groups.

Numeric Results for Two-Sample T-Test Allowing Unequal Variance
Alternative Hypothesis: H1: $\delta = \mu1 - \mu2 \neq 0$

Power	N1	N2	N	δ	σ1	σ2	Alpha
0.99395	30	30	60	15	15	10	0.05
0.96771	30	30	60	15	15	15	0.05
0.89745	30	30	60	15	15	20	0.05
0.94849	30	30	60	15	20	10	0.05
0.89745	30	30	60	15	20	15	0.05
0.81497	30	30	60	15	20	20	0.05

Primary Endpoints:
The primary end point will be the difference in mean ventricular heart rate between the Dexmedetomidine plus SOC arm compared to the placebo plus SOC arm during the last 4-hours of study drug administration. Each individual will have a total of 16 mean ventricular heart rate measures taken during the last 4-hours of study drug administration. These measures will be averaged for each person. Using this measure, the two groups will be compared using independent t-tests.

To further understand variability in heart rate between the two groups, a standard deviation will be calculated for each individual's 16 measurements. Multivariable linear regression will be used to model the outcome of SD, with the primary predictor of randomization group. We will control for the subject's mean value in this analysis. These analyses will be performed at the $p \leq 0.05$ level.

Key Secondary Endpoints:
Time to heart rate control (HR <100 bpm) in the Dexmedetomidine plus SOC arm vs. Placebo plus SOC arm will be analyzed using an exact stratified log-rank test (i.e., a time to event survival analysis). An exploratory analysis, cox's proportional hazard model may be used to compare time to event after adjusting possible confounding factors that might be imbalanced between the two groups.

Percentage of rhythm strips with heart rate <100 bpm (last 4-hours) and percentage of rhythm strips with conversion to sinus rhythm (last 4-hours) will be calculated for each individual. Wilcoxon Rank Sum tests will be used to assess differences in these two outcomes between the two study groups. Secondary analyses will be performed at the $p \leq 0.025$ level.

16.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Please see above.

17.0 Confidentiality

A. Confidentiality/Security of Study Data

Describe the local procedures for maintenance of security and confidentiality of **study data and any records that will be reviewed for data collection.**

17.1 Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, certificates of confidentiality, and separation of identifiers and data, as applicable. Include physical (e.g. paper) and electronic files.

All paper study documents will be stored in a locked room, e.g. the research coordinators office.

We will use a Stony Brook SBMIT RedcAP database to store study data. Only study personnel will have log in access to this study specific RedcAP database. Additional study data, e.g. Master Log, will be stored on a study specific folder created by SBMIT on the "w" drive of the Department of Anesthesiology, and similar to all our other studies only study personnel will have access (granted by SBMIT) to this study specific folder.

17.2 How long will the data be stored?

Data will be stored for 6 years.

17.3 Who will have access to the data?

Only study personnel will have access to the data. All study personnel will provide evidence of their appropriate CITI training certifications.

17.4 Who is responsible for receipt or transmission of the data?

Not applicable for this study.

17.5 How will the data be transported/transmitted?

Not applicable for this study.

B. Confidentiality of Study Specimens

Describe the local procedures for maintenance of confidentiality of study specimens.

☒ **N/A:** No specimens will be collected or analyzed in this research.
(Skip to Section 18.0)

17.6 Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response: N/A

17.7 How long will the specimens be stored?

Response: N/A

17.8 Who will have access to the specimens?

Response: N/A

17.9 Who is responsible for receipt or transmission of the specimens?

Response: N/A

17.10 How will the specimens be transported?

Response: N/A

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects OR is limited to records review procedures only OR is a minimal risk study

18.1 Describe the plan to evaluate the data periodically regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

The study's PI and its Independent Safety Monitor (see below) will review all Safety Endpoints (see below) and study related AEs on an ongoing basis. Given the extensive use and knowledge of this drug (approved by FDA in 1999) and the short duration of exposure (only 8 hours), the lack of bolus dosing, and the provision to lower the dose if needed, we believe this is an appropriate strategy.

18.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Safety Endpoints:
1) Percentage of patients requiring pausing or discontinuation of study drug.
2) Episodes of hypotension defined as two consecutive values of SBP <90 mm Hg requiring intervention.
3) Episodes of bradycardia requiring cessation of infusion (persistent heart rate <50 bpm).
4) Any study related AEs.

18.3 Describe any primary or secondary safety endpoints.

Safety Endpoints:
1) Percentage of patients requiring pausing or discontinuation of study drug.
2) Episodes of hypotension defined as two consecutive values of SBP <90 mm Hg requiring intervention.
3) Episodes of bradycardia requiring cessation of infusion (persistent heart rate <50 bpm).
4) Any study related AEs.

18.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Case Report Forms with data entered into a RedcAP database.

18.5 Describe the frequency of safety data collection, including when safety data collection starts.

Safety data collection starts after initiation of study drug since there is no risk related to study procedures, e.g. printing out baseline rhythm strips, that occur before this time.

18.6 Describe who will review the safety data.

The PI and Dr. Aaron Sasson, an attending physician at Stony Brook and its Chief of Surgical Oncology, who will independently review and monitor the data for safety and will review all serious adverse events that may be related to the study on an ongoing basis.

18.7 Describe the frequency or periodicity of review of cumulative safety data.

The study's PI and Independent Safety Monitor will review all Safety Endpoints (see below) and study related AEs on an ongoing basis and at least on a monthly basis.

18.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Given the small size of this pilot study (only 30 subjects per arm) there are no formal test for analyzing the safety data consistent with most clinical trials of this size.

18.9 Describe any conditions that trigger an immediate suspension of the research.

No specific conditions.

19.0 Withdrawal of Subjects

☐ N/A: This study is not enrolling subjects. This section does not apply.

19.1 Describe anticipated circumstances under which subjects may be withdrawn from the research without their consent.

Before a subject is randomized if they are no longer in AF then we will screen fail them. If the patients do not tolerate the study drug, we have procedures to pause it and if necessary, terminate the study drug infusion.

]*19.2 Describe any procedures for orderly termination.*

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: N/A

19.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: As there is nothing sensitive collected in this study, we will continue to confidentially store the available study data until the study is concluded, and all data are destroyed per Stony Brook IRB guidelines on maintenance of study records.

19.4 Describe what will happen to data already collected.

Response: We will continue to confidentially store the available study data until the study is concluded, and all data are destroyed.

20.0 Risks to Subjects

20.1 In your opinion, what is the overall risk (physical and nonphysical) to research subjects in this study (minimal, greater than minimal or unknown)

More than minimal risk.

20.2 Describe if any subjects are withdrawn from therapeutic procedures or drugs (e.g., washout periods) prior to, or during, their participation in the study.

N/A

20.3 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

The table found below is part of the original FDA labeling document for Dexmedetomidine HCl describing the adverse reactions associated with the drug:

Table 2: Adverse Reactions* in Clinical Trials of Dexmedetomidine HCl for Adult Procedural Sedation

Adverse Reaction	Dexmedetomidine HCl (N = 318) (%)	Placebo (N = 113) (%)
Hypotension[1]	54%	30%
Respiratory Depression[2]	37%	32%
Bradycardia[3]	14%	4%
Nausea	3%	2%
Dry Mouth	3%	1%

* Adverse reactions that occurred at an incidence of greater than 2% of patients receiving dexmedetomidine HCl and at an incidence greater than placebo

[1] Hypotension was defined in absolute and relative terms as systolic blood pressure of less than 80 mmHg or less than or equal to 30% lower than pre-study drug infusion value, or diastolic blood pressure of less than 50 mmHg.

[2] Respiratory depression was defined in absolute and relative terms as respiratory rate (RR) less than 8 beats per minute or greater than 25% decrease from baseline.

[3] Bradycardia was defined in absolute and relative terms as less than 40 beats per minute or less than or equal to 30% lower than pre-study drug infusion value.

The following table is part of the 2016 FDA labeling for Dexmedetomidine HCL which includes postmarketing adverse reactions:

Table 2: Adverse Reactions with an Incidence >2%— Adult Intensive Care Unit Sedation Population <24 hours*				
Adverse Event	All Dexmedetomidine HCl (N = 1007) (%)	Randomized Dexmedetomidine HCl (N = 798) (%)	Placebo (N = 400) (%)	Propofol (N = 188) (%)
Hypotension	25%	24%	12%	13%
Hypertension	12%	13%	19%	4%
Nausea	9%	9%	9%	11%
Bradycardia	5%	5%	3%	0
Atrial Fibrillation	4%	5%	3%	7%
Pyrexia	4%	4%	4%	4%
Dry Mouth	4%	3%	1%	1%
Vomiting	3%	3%	5%	3%
Hypovolemia	3%	3%	2%	5%
Atelectasis	3%	3%	3%	6%
Pleural Effusion	2%	2%	1%	6%
Agitation	2%	2%	3%	1%
Tachycardia	2%	2%	4%	1%
Hyperthermia	2%	2%	3%	0
Chills	2%	2%	3%	2%
Hyperglycemia	2%	2%	2%	3%
Hypoxia	2%	2%	2%	3%
Post-procedural Hemorrhage	2%	2%	3%	4%
Pulmonary Edema	1%	1%	1%	3%
Ventricular Tachycardia	<1%	1%	1%	5%
*26 subjects in the all dexmedetomidine HCl group and 10 subjects in the randomized dexmedetomidine HCl group had exposure for greater than 24 hours.				

Adverse reaction information was also derived from the placebo-controlled, continuous infusion trials of dexmedetomidine HCl for sedation in the surgical intensive care unit setting in which 387 adult patients received dexmedetomidine HCl for less than 24 hours.

We consider the first table to be more applicable to the study that we have designed given the dosing algorithm that we have created, the absence of a bolus or loading dose, and the reduced timeframe of the study drug infusion (far shorter than the infusion timeframe of 15.9 hours seen in the latter table of adverse effects).

Dexmedetomidine, approved by the FDA in 1999, is used commonly in the ICU setting. The most common side effects associated with Dexmedetomidine use (>2%) are hypotension, bradycardia, and dry mouth[1]. For that reason, Dexmedetomidine should only be administered to patients who are in a continuously monitored setting such as in an intensive care unit. Treatment of hypotension and bradycardia may necessitate decreasing or stopping the Dexmedetomidine infusion, intravenous fluid administration, and the use of pressors. The intravenous administration of anticholinergic agents (e.g. glycopyrrolate or atropine) can also be administered to modify vagal tone.

To test the maximum safely tolerated dose of Dexmedetomidine, a study used doses 13 times greater than the upper limit of Dexmedetomidine's therapeutic range. In this case, the most significant effects were seen in two patients who received the highest doses of Dexmedetomidine. The first patient presented first-degree atrioventricular (AV) block- which showed no hemodynamics compromise- while the other patient presented a second-degree heart block- which was resolved in one minute[2]. Within this same study, it was noted that giving patients twice the recommended loading dose of

Dexmedetomidine (2µg/kg/hr for the first 10 minutes) did not present any adverse symptoms for the majority of subjects in the Dexmedetomidine cohort. However, two of the patients did experience bradycardia and hypotension.

Other researchers have determined the importance of avoiding the initial bolus/ loading dose of Dexmedetomidine. Notably when Jakob et al. avoided the provision of a loading dose and did not exceed the 1.5µg/kg/hr dose of Dexmedetomidine, SAEs were seen in equivalent frequencies when comparing the SOC and the Dexmedetomidine cohorts[1]. Therefore, many clinicians support the implementation of this safety administration measure, which ensures a reduction in bradycardia and hypotension Dexmedetomidine-associated SAEs[3].

Transient hypertension has been occasionally described, primarily during the loading dose. Owing to the peripheral vasoconstrictive effects of Dexmedetomidine. Treatment of the transient hypertension has generally not been necessary in studies, although reduction of the loading infusion rate may be considered.

Dexmedetomidine does not cause bradypnea the way Propofol, benzodiazepines or opiates do. It however, can cause decreases in respiratory rate as part of its sympatholytic/anxiolytic mechanism of action. As such, Precedex is used frequently and safely used in non-intubated patients in conjunction with benzodiazepines without concern for respiratory compromise[4-20].

Rare side effects that have been reported with infusions > than 24 hrs include ARDS, respiratory failure, agitation, sinus arrest and death. Bradycardia and hypotension are more frequently observed in patients with high vagal tone, or those receiving prolonged infusions, with high doses and with bolus administration.

Dexmedetomidine infusion in this study will run for only 8 hrs and be well within the FDA's recommended 24 hrs infusion limit. The maximum dosage in this study will be 1µg/kg/hr, which is significantly less than the 1.5µg/kg/hr infusion maximum allowed by standard dosing regimens. No bolus will be given in this study to further decrease the risks of hypotension. Blood pressures will be checked manually every 15 minutes non-invasively or continuously in patients who have arterial catheters.

References:

1. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *Jama.* 2012;307(11):1151-1160.
2. Research CfDEa. Precedex Approval Package. 2010.
3. Dasta JF, Kane-Gill SL, Durtschi AJ. Comparing dexmedetomidine prescribing patterns and safety in the naturalistic setting versus published data. *The Annals of pharmacotherapy.* 2004;38(7-8):1130-1135.
4. Herr DL, Sum-Ping ST, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. *Journal of cardiothoracic and vascular anesthesia.* 2003;17(5):576-584.
5. Ren J, Zhang H, Huang L, Liu Y, Liu F, Dong Z. Protective effect of dexmedetomidine in coronary artery bypass grafting surgery. *Experimental and therapeutic medicine.* 2013;6(2):497-502.
6. Zientara A, Mariotti S, Matter-Ensner S, et al. Fast-Track Management in Off-Pump Coronary Artery Bypass Grafting: Dexmedetomidine Provides Rapid Extubation and Effective Pain Modulation. *The Thoracic and cardiovascular surgeon.* 2018.
7. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. *Jama.* 2000;283(11):1451-1459.
8. MD CVZ. Fibrilación auricular: -Guías Clínicas. Fisterra. http://www.fisterra.com/guias2/fa.asp. Published 2009. Accessed.
9. Testa LD, Tobias JD. Pharmacologic drugs for controlled hypotension. *J Clin Anesth.* 1995;7(4):326-337.
10. Zhang YH, Zhu J, Song YC. Suppressing sympathetic activation with clonidine on ventricular arrhythmias in congestive heart failure. *International journal of cardiology.* 1998;65(3):233-238.

11. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. *European journal of pharmacology.* 1988;150(1-2):9-14.
12. Khalil MA, Abdel Azeem MS. The impact of dexmedetomidine infusion in sparing morphine consumption in off-pump coronary artery bypass grafting. *Seminars in cardiothoracic and vascular anesthesia.* 2013;17(1):66-71.
13. Tsujikawa S, Ikeshita K. Low-dose dexmedetomidine provides hemodynamics stabilization during emergence and recovery from general anesthesia in patients undergoing carotid endarterectomy: a randomized double-blind, placebo-controlled trial. *Journal of anesthesia.* 2019;33(2):266-272.
14. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet (London, England).* 2010;375(9719):985-997.
15. Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. *British journal of anaesthesia.* 2009;102(4):442-452.
16. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. *Proceedings (Baylor University Medical Center).* 2001;14(1):13-21.
17. Talke P, Chen R, Thomas B, et al. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesthesia and analgesia.* 2000;90(4):834-839.
18. Guler G, Akin A, Tosun Z, Eskitascoglu E, Mizrak A, Boyaci A. Single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation. *Acta anaesthesiologica Scandinavica.* 2005;49(8):1088-1091.
19. Tufanogullari B, White PF, Peixoto MP, et al. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. *Anesthesia and analgesia.* 2008;106(6):1741-1748.
20. McCutcheon CA, Orme RM, Scott DA, Davies MJ, McGlade DP. A comparison of dexmedetomidine versus conventional therapy for sedation and hemodynamic control during carotid endarterectomy performed under regional anesthesia. *Anesthesia and analgesia.* 2006;102(3):668-675.

20.4 Describe procedures performed to minimize the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

There are numerous procedures to minimize risks to study subjects including:

1) The Investigational Pharmacy will prepare the study drug, and an order for the study drug will be entered into the Electronic Medical Record (EMR) as a Therapeutic Non-Formulary (TNF) per Stony Brook's Investigational Pharmacy's standard operating procedure. The patient's nurse will scan the medication using the hospital's routine bar code technology.

2) We will not bolus study drug, which is most associated with adverse events with this drug.

3) Heart rate is already continuously monitored in ICU and ICR patients. Per the study protocol blood pressure will be measured every 15 minutes during study drug administration either by an indwelling arterial catheter (placed for routine care) or non-invasively by cuff.

4) If HR is < 50 bpm, SBP < 80 mm Hg, or RASS< -2 for non-intubated patients, or the patients shows significant evidence of decompensation, the study drug infusion will be paused for 1 hour, and then restarted at half the dose (i.e. 0.5 µg/kg/hr) if none of the pausing criteria still exist.

5) We will only enroll patients who are already in an ICU where there is immediate availability of supportive care.

6) We will monitor pre-specified Safety Endpoints on an ongoing basis:

<u>Safety Endpoints:</u>

1) Percentage of patients requiring pausing or discontinuation of study drug.
2) Episodes of hypotension defined as two consecutive values of SBP <90 mm Hg requiring intervention.
3) Episodes of bradycardia requiring cessation of infusion (persistent heart rate <50 bpm).
4) Any study related AEs.

20.5 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Administration of study drug (Dexmedetomidine) may have other (ie unforeseen) risks.

20.6 Indicate which research procedures, if any, may have risks to an embryo or fetus should the subject be or become pregnant.

☒ **N/A**

20.7 If you responded to 20.6 that there are such risks, how will you minimize the risk of a pregnancy occurring during the course of the study? (Select all that apply)

☐ Counseling on birth control and /or abstinence

☐ Pregnancy test during the study

☐ Pregnancy test prior to initiation of the study

☐ Other _____

☒ **N/A**

20.8 If applicable, describe possible risks to others who are not subjects.

N/A

21.0 Potential Benefits to Subjects

21.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits.

The potential benefit of Dexmedetomidine use in patients with rapid-AF is better and faster heart rate control.

21.2 Indicate if there is no direct benefit.

NOTE: Compensation cannot be stated as a benefit.

Indicate if there is a potential benefit to others, future science or society.

There is a need for improved methods of heart rate control in patients with rapid-AF so learning if Dexmedetomidine is usefull for this could potentially benefit others.

22.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury. This section does not apply.

22.1 If the research procedures carry a risk of research related injury, describe the available compensation to subjects in the event that such injury should occur.

None per standard Stony Brook approved IRB approved investigator initiated research.

22.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with different language regarding research related injury, you must modify your response here and submit an amendment to the IRB for review and approval.

N/A

23.0 Economic Burden to Subjects

23.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

There are no additional financial costs to the subject. The study team will pay for the study drug.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

24.0 Compensation for Participation

☒ **N/A:** There is no compensation for participation. This section does not apply.

24.1 Describe the amount/nature and timing/scheduling of any compensation to subjects, including monetary, course credit, or gift card compensation. Describe any prorated payments based on participation.

N/A

24.2 Justify the amount and scheduling of payments described above to ensure that they are reasonable and commensurate with the expected contributions of the participant. If multiple visits are involved payments should be prorated.

Note: If using West Campus Departmental pools, participation in studies may be offered for credit in class but students MUST be given other options for fulfilling the research component that are comparable in terms of time, effort, and education benefit. Please list alternative activities

N/A

25.0 Informed Consent

25.1 Will you be obtaining consent from subjects?

☒ ***Yes*** *(If yes, Provide responses to each question in this Section, and upload your consent documents where indicated in the electronic submission system)*

☐ ***No*** *(If no, Skip to next section)*

25.2 Describe how the capacity to consent will be assessed for all subjects. Review for guidance http://research.stonybrook.edu/human-subjects-standard-operating-procedures/determining-potential-adult-subjects-ability-consent:

We will be enrolling patients who have capacity to consent as evidenced by their ability to provide consent for routine medical care in the ICU and in the ICR and knowledge that the subject understands the following: 1) that the activity is research, not standard treatment, 2) the risks and benefits of a study, 3) the alternatives that are available if s/he does not participate; and 4) that, if s/he chooses not to participate, this decision will be accepted without penalty, i.e., without jeopardizing clinical care.
In addition, consistent with most ICU studies, we will also enroll patients without capacity to consent through their Legally Authorized Representative.

25.3 Describe the consent process that will be conducted to ensure that subject is fully informed regarding study details and subject rights. Include where the consent process will take place, with consideration of the need to protect the subject's right to privacy.

The study will be discussed in a private setting or in the patient's hospital room. Subjects (or their LAR) will be provided with enough time to have their questions answered, and discuss the study with family members if appropriate.

25.4 Describe how you will ensure that subjects are provided with sufficient time to consider taking part in the research study. Detail if there is there any time period expected between informing the prospective subject and obtaining the consent.

NOTE: It is respectful to the prospective subject to ensure that sufficient time is given to have their questions answered and to consider their participation

Same as above.

25.5 Describe the process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

If a subject (or LAR) voices any concern about continued participation in the study, they will be reminded that they have the ability to withdraw from the study.

Non-English Speaking Subjects

☒ *N/A: This study will not enroll Non-English speaking subjects.*

25.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

N/A

25.7 If subjects who do not speak English will be enrolled, describe the process to consent the subjects, as well as the process to be used to ensure their understanding of research procedures throughout the conduct of the study. Review SOP's section 17.8 for important policies in this regard: http://research.stonybrook.edu/human-

subjects-standard-operating-procedures/policy-non-english-speakers-research-subjects for SBU policy on inclusion of non-English speakers.

N/A

Adults Unable to Consent

☐ **N/A:** This study will not enroll adults unable to consent.

25.8 Justify why it is necessary to include adult subjects who are unable to consent.

Consistent with most ICU studies, we will also enroll patients without capacity to consent through their Legally Authorized Representative. This is necessary since many patients in the ICU do not have capacity to consent so studies in ICU patients cannot be practically done without the option for using an LAR approach.

25.9 Describe how you will identify Legally Authorized Representatives (LAR) for the subjects that will be consistent with the NYS Family Health Care Decisions Act (FHCDA; see http://research.stonybrook.edu/human-subjects-standard-operating-procedures/definitions-2). Indicate why it is necessary to include subjects who are unable to consent.

Note: For research conducted outside of New York State, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research.

We will confirm through review of the medical chart and discussion with medical staff who the subjects LAR is. Consistent with most ICU studies, we will enroll patients without capacity to consent through this LAR. This is necessary since many patients in the ICU do not have capacity to consent so studies in ICU patients cannot be practically done without the option for using an LAR approach.

25.10 Describe the process for obtaining assent from the adult subjects

Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.

No assent will be obtained.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Assent is usually not required for ICU studies in patients who lack capacity due to the affects of critical illness and/or ongoing sedation.

25.11 Describe whether assent of the adult subjects will be documented and the process to document assent.

Response: N/A

25.12 Describe how you will obtain consent from a subject to use their data if they later become capable of consent. How will competence be assessed and by whom?

Given the short duration of this study (less than 12 hours), we do not see how a patient without capacity is likely to develop capacity during this short period.

26.0 Waiver or Alteration of Consent Process

Complete this section if:

- Informed consent will not be obtained at all
- Informed consent will be obtained, but not documented, or
- consent will be obtained, but not all required information will be disclosed (e.g., in deception research)

☒ **N/A:** A waiver or alteration of consent is not being requested.

26.1 Review, complete, and upload SUPPLEMENTAL FORM G: Consent Waivers

☐ Confirmed

26.2 If the research involves a waiver of the consent process for planned emergency research, please contact the Office of Research Compliance for guidance regarding assistance in complying with federal regulations governing this activity (see: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24)

27.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not a multi-site study. This section does not apply.

27.1 If this is a multi-site study where SBU is the lead site and/or the IRB of record, describe the processes to ensure communication among sites. Include:

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

N/A

27.2 Describe the method for communicating to engaged participating sites:

- *Problems*
- *Interim results*
- *Study closure*

N/A

*27.3 Indicate and statistically justify the total number of subjects that will be enrolled or records that will be reviewed **across all sites**.*

N/A

28.0 Banking Data or Specimens for Future Unspecified Use

☒ **N/A:** This study is not storing data or specimens for research outside the scope of the present protocol. This section does not apply.

IMPORTANT: If you are proposing to bank specimens for future use, you may be subject to licensure requirements under the NYS Department of Health, and must be covered under the SBU license. See SOPs at http://research.stonybrook.edu/human-subjects-standard-operating-procedures/data-tissue-registries-banks

28.1 If data will be banked for research outside of the scope of the present protocol, describe where the data will be stored, how long they will be stored, how will they be accessed, and who will have access to the data

NOTE: Your response here must be consistent with the information provided to subjects in your Consent Documents

N/A

28.2 If specimens will be banked (stored) for research outside of the scope of the present protocol, describe where the specimens will be stored, how long they will be stored, identifiers that will be associated with each specimen, how will they be accessed, and who will have access to the specimens

NOTE: Your response here must be consistent with the information provided to subjects in your Consent Documents

N/A

28.3 Describe the procedures to release banked data and/or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

N/A

29.0 Drugs and Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

29.1 Does this study involve use of radiopharmaceuticals? ☐ Yes ☒ No

29.2 For investigational devices (including marketed devices being used off label), Provide the following information below:

Where will the device(s) be stored? Note that the storage area must be within an area under the PI's control Describe the security of the storage unit/facility

Provide full detail regarding how the dispensing of the device(s) will be controlled (accountability of removal/return of used devices, and disposition of remaining devices at the conclusion of the investigation) and documented (accounting records/logs)

The Investigational Pharmacy will store, prepare, and dispense the study drug using their routine procedures. Per FDA guidance our study meets all criteria for IND exemption.

29.3 For investigational drugs (including humanitarian use devices, and marketed drugs being used off label), will the services of the Investigational Drug Pharmacy be used for storage, dispensing, accounting the drug (required for research conducted at UH, HSC, Cancer Center, and Ambulatory Surgery Center)?

☒ **Yes**

☐ **No** →PI Provide the following information below:

- *Where will the drugs/biologics be stored? Note that the storage area must be within an area under the PI's control*
- *Describe the security of the storage unit/facility:*
- *Provide full detail regarding dispensing of the drugs(s), how labeled, controlled (accountability, disposition of unused drug at the conclusion of the investigation) and documented (accounting records/logs):*

N/A

30.0 Sharing of Results with Subjects

30.1 Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.