Northwell Health

RESEARCH PROTOCOL

Protocol Title:	ROIDS-Dose (Randomized Open Investigation Determining Steroid Dose)
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Guidelines for Preparing a Research Protocol

Instructions:

- You do not need to complete this document if you are submitting an *Application for Exemption* or *Application for a Chart Review*.
- Do not use this template if:
  - Your study involves an FDA regulated product. In this case, use the *Clinical Trial Protocol Template.*
  - Your study has a protocol from a sponsor or cooperative group. In this case, use the *Protocol Plus*.
  - Your study is a registry or repository for data and/or samples, In this case, use *Protocol Template – Registry Studies.* .
- If a section of this protocol is not applicable, please indicate such.
- Do not delete any of the text contained within this document.
- Please make sure to keep an electronic copy of this document. You will need to use it, if you make modifications in the future.
- Start by entering study information into the table above, according to these rules:
  - Protocol Title: Include the full protocol title as listed on the application.
  - Investigator: include the principal investigator's name as listed on the application form
  - Date Revised: Indicate the date at which the protocol was last revised
  - IRB Number: Indicate the assigned IRB number, when known. At initial submission, this row will be left blank.
- Once the table information in entered, proceed to page 2 and complete the rest of the form.

↓ Continue to next page to begin entering information about this study ↓

1. PREVIOUS STUDY HISTORY

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

☒ No ☐ Yes – if yes, please explain:

2. BRIEF SUMMARY OF RESEARCH

- *The summary should be written in **language intelligible to a moderately educated, non-scientific layperson**.*
- *It should contain a clear statement of the rationale and hypothesis of your study, a concise description of the methodology, with an emphasis on what will happen to the subjects, and a discussion of the results.*
- *This section should be ½ page*

Rationale: COVID-19 is associated with a marked inflammatory response, resulting in both systemic and pulmonary damage – the most devastating being Acute Respiratory Distress Syndrome (ARDS), which often results in invasive mechanical ventilation and higher mortality. Treatment for COVID-19 patients with respiratory failure has been vexing, but the use of steroids, which can help attenuate both the inflammatory and fibrotic process of lung injury, has shown promise. In a recent randomized control trial, dexamethasone 6 mg once daily showed a modest decrease in mortality among hospitalized COVID-19 patients with respiratory failure, which has been defined as patients who require oxygen supplementation or invasive mechanical ventilation. Thus, dexamethasone 6mg daily is being routinely used to treat COVID-19 patients.

Other trials have shown that the inflammatory response to COVID-19 can be further attenuated at higher dosages of dexamethasone. These higher dosages have not been well studied and have not been directly compared to the current standard dose of dexamethasone 6 mg daily. We propose that a higher dexamethasone dose, equivalent to methylprednisolone 1 mg/kg/day which is routinely used to treat other inflammatory conditions of the lungs, may be more effective than the current standard dose in reducing mortality in COVID-19 patients with respiratory failure.

Methodology: We will include hospitalized adult patients with COVID-19 infection with hypoxemia requiring oxygen supplementation. Eligible patients will be randomized in a 1:1 fashion to receive either standard dose of dexamethasone at 6 mg daily, or higher, weight-based dose of dexamethasone at 0.2 mg/kg/day (which is equivalent to methylprednisolone 1 mg/kg/day).

Outcomes: The primary outcome will be all-cause mortality at 28 days. The secondary outcomes will include need for ICU admission, ICU length of stay,

hospital length of stay, higher requirements of oxygen supplementation (e.g. venturi mask, non-rebreather mask, high-flow nasal cannula or non-invasive mechanical ventilation), invasive mechanical ventilation, duration of mechanical ventilation, tracheostomy, ECMO, subjective symptoms at 28 days, disposition upon discharge, oxygen supplementation upon discharge, development of secondary bacterial or fungal infections and development of clinically significant hyperglycemia.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*
- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*
- *Describe the importance of the knowledge expected to result*

The use of steroids in COVID-19 infection was initially controversial and was not recommended early in the pandemic. Later, observational, retrospective studies suggested a role for steroids in COVID-19. A subsequent randomized clinical trial (RECOVERY) showed clinical benefit with steroids. In particular, the study showed that the use of dexamethasone 6 mg once daily was associated with a decrease in mortality in COVID-19 patients requiring oxygen supplementation, particularly in those requiring invasive mechanical ventilation. However there was no benefit in those patients, who did not requiring oxygen supplementation. Since the findings were reported, the use of dexamethasone 6 mg once daily for 10 days in COVID-19 patients with respiratory failure has been routinely used in clinical practice. Other studies, however, suggest that a higher dose of dexamethasone may be beneficial. The CoDEX trial, a multicenter, randomized clinical trial conducted in Brazil, studied the effects of dexamethasone in patients with COVID-19 in moderate to severe ARDS requiring mechanical ventilation. Ultimately, the investigators found that the use of dexamethasone at a dose of 20 mg daily for 5 days followed by 10 mg daily for an additional 5 days was associated with increase in ventilator-free days compared to supportive care alone. Another randomized, single-blinded control trial using 250 mg of intravenous methylprednisolone showed significant decrease in mortality rate when compared to patients who did not receive steroids. The ideal dose of dexamethasone remains unclear, and to the best of our knowledge, there are no studies at this time comparing different doses of dexamethasone in this population.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

- *A concise statement of the goal(s) of the current study.*
- *The rationale for and specific objectives of the study.*
- *The goals and the hypothesis to be tested should be stated.*

The aim of the study is to compare the efficacy of dexamethasone at the current recommended dose versus a higher, weight-based dose. We hypothesize that the use of a higher, weight-based dose of dexamethasone equivalent to 1 mg/kg/day of methylprednisolone would be associated with a decrease in mortality in COVID-19 patients requiring oxygen supplementation.

Primary outcome:
- All-cause mortality at 28 days

Secondary outcomes:
- ICU admission
- ICU length of stay
- Hospital length of stay
- Need for higher oxygen supplementation including venturi mask, non-rebreather mask, high flow nasal cannula or non-invasive mechanical ventilation
- Invasive mechanical ventilation
- Duration of invasive mechanical ventilation
- ECMO
- Need for tracheostomy
- Development of secondary bacterial or fungal infections
- Development of clinically significant hyperglycemia, which will be defined as need for insulin drip or ICU admission to control hyperglycemia
- Oxygen supplementation upon discharge from the hospital
- Subjective symptoms at 28 days
- Disposition upon discharge (home, home with physical therapy, skilled nursing facility, long-term acute care facility, long-term care facility / nursing home, acute rehabilitation facility, hospice care, death)

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

- *Explain the feasibility of meeting recruitment goals of this project and demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period*
    - *How many potential subjects do you have access to?*
- *Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions*

COVID-19 cases are still prevalent in New York, and another surge is anticipated from March to May according to Infectious Disease experts. We have seen a significant increase in the number of admissions to the hospitals within our healthcare system during past surges. We project we would have access to at least 300 potential subjects.

All persons assisting with the trial will have access to the protocol, and meetings will be arranged to clarify trial related duties and functions via Microsoft Teams.

6. RECRUITMENT METHODS

- *Describe the source of potential subjects*
- *Describe the methods that will be used to identify potential subjects*
- *Describe any materials that will be used to recruit subjects. A copy of any advertisements (flyers, radio scripts, etc.) should be submitted along with the protocol.*
- *If monetary compensation is to be offered, this should be indicated in the protocol*

Recruitment of potential subjects will occur at 7 of the hospitals within the Northwell Health System including Long Island Jewish Medical Center, North Shore University Hospital, Plainview Hospital, Long Island Jewish Valley Stream Hospital, Lenox Hill Hospital, South Shore Hospital and Mather Hospital. Enrollment will first be done at North Shore University Hospital and Long Island Jewish Medical Center with phased-approach expansion to the other sites.

Patients that are admitted with COVID-19 infection within these institutions will be screened for eligibility. The principal investigator and co-investigators will be responsible in obtaining informed consent from those patients who meet eligibility criteria in order to participate in the study. A full discussion of the rationale of the study will be held with the patients and/or their surrogate decision makers to answer any study-related questions. The use of a printed/electronic version of the informed consent will be available for review. All research coordinators will be trained by the principal investigator on non-coercive recruitment approaches. Patients will be clearly informed that their medical care will be of the highest standards regardless of their decision to participate on the study.

No monetary compensation will be offered.

7. ELIGIBILITY CRITERIA

- *Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.*
- *Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol*
- *Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.*

Over 10,000 patients have been treated in the Northwell Health system with COVID-19 infection. The anticipated demographics of participants in this study will reflect that of severe COVID-19 which has been described to include 60% males and 70% non-white race/ethnicity – the majority of which are African American or Hispanic. Common comorbidities include hypertension, diabetes mellitus, obesity and/or preexisting lung disease.

Inclusion criteria:
- Adults ≥18 years
- COVID-19 infection confirmed by a positive PCR test
- Hypoxemia defined by an O2 saturation <94% or the need for supplemental oxygen

Exclusion criteria:
- Corticosteroid use for > 48h within the past 15 days prior to enrollment
- Use of steroids with doses higher than the equivalent to dexamethasone 6 mg
- Use of immunosuppressive drugs
- Pregnant women
    Dexamethasone is a fluorinated corticosteroid and has the potential to cause oral clefts or decreased birth weight. When corticosteroids are required in pregnancy, non-fluorinated corticosteroids (e.g. prednisone) is preferred. As we are specifically studying dexamethasone, we are excluding pregnant women to prevent potential harm.
- Chronic oxygen use
- Known history of dexamethasone allergy
- DNR / DNI
- Patient or proxy cannot consent

This study will not preclude participation in other ongoing COVID-19 trials.

8. NUMBER OF SUBJECTS

- *Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized and complete the research procedures.*
- *If your study includes different cohorts, include the total number of subjects in each cohort.*
- *If this is multisite study, include total number of subjects across all sites.*

We project screening 300 potential subjects and enrolling 142 patients - 71 in each arm of the study. Accounting for a potential 10% drop out, it will allow us to include at least 128 subjects to achieve statistical power.

9. STUDY TIMELINES

- *Describe the duration of an individuals participation in the study*
- *Describe the duration anticipated to enroll all study subjects*
- *The estimated date of study completion*

The duration of an individual's participation in the study will be 28 days or until hospital discharge, whichever occurs first.

The duration anticipated to enroll all study subjects is 6 months.

The estimated date of study completion is 12 months.

10. ENDPOINTS

- *Describe the primary and secondary study endpoints*
- *Describe any primary or secondary safety endpoints*

Primary study endpoint: all-cause mortality at 28 days.

Secondary study endpoints: need for ICU admission, ICU length of stay, hospital length of stay, higher requirements of oxygen supplementation (venturi mask, non-rebreather mask, high-flow nasal cannula or non-invasive mechanical ventilation), invasive mechanical ventilation, duration of invasive mechanical ventilation, ECMO, tracheostomy, subjective symptoms at 28 days, disposition upon discharge, and oxygen supplementation upon discharge.

The primary and secondary safety endpoints will include the development of secondary bacterial or fungal infections that is objectively identified based on culture data, and clinically significant hyperglycemia requiring ICU stay or insulin drip.

11. RESEARCH PROCEDURES

- *Include a detailed description of all procedures to be performed on the research subject and the schedule for each procedure.*
- *Include any screening procedures for eligibility and/or baseline diagnostic tests*
- *Include procedures being performed to monitor subjects for safety or minimize risks*
- *Include information about drug washout periods*
- *If drugs or biologics are being administered provide information on dosing and route of administration*
- *Clearly indicate which procedures are only being conducted for research purposes.*
- *If any specimens will be used for this research, explain whether they are being collected specifically for research purposes.*
- *Describe any source records that will be used to collect data about subjects*
- *Indicate the data to be collected, including long term follow-up*

All hospitalized patients with COVID-19 infection documented by a positive PCR test who require oxygen supplementation or have documented hypoxemia based on oxygen saturation <94% will be screened for eligibility. Baseline diagnostics tests will be as per standard of care and no additional testing is required for our research purposes. All patients will receive routine medical care as per most updated COVID-19 guidelines prior to randomization.

Eligible patients who agree to participate in the study will be randomized 1:1 into two groups. Randomization was set up in REDCap. Once the patient gives consent, the randomization form on REDCap will randomize to either of the groups. As the study is multi-site, the randomization will be stratified by each site.
The standard dexamethasone group will receive a dose of 6 mg daily. The higher dexamethasone group will receive a dose of 0.2 mg/kg/day with maximum dose of 20 mg per day. The route of administration will be IV for both groups. No patients will receive less than dexamethasone 6 mg. The duration of treatment in both arms will be a total of 10 days of steroids or until discharge, whichever comes first.

No procedures, blood draws, imaging or diagnostic testing will be performed on the participants other than those indicated for their medical care.

Data will be obtained from the medical electronic records and tabulated in REDCap. Patient will be de-identified and REDCap access will be limited to appropriate investigators involved in the trial to avoid HIPAA violations.

Data to be collected will include baseline demographic variables, need for higher requirements of oxygen supplementation (venturi mask, non-rebreather mask, high flow nasal cannula or non-invasive mechanical ventilation), ICU admission, invasive mechanical ventilation, duration of invasive mechanical ventilation, tracheostomy, ECMO, length of ICU stay, length of hospital stay, development of secondary bacterial or fungal infections, subjective symptoms at 28 days, development of clinically significant hyperglycemia, oxygen supplementation upon discharge and disposition upon discharge (home, home with physical therapy, skilled nursing facility, long-term acute care facility, long-term care facility / nursing home, acute rehabilitation facility, hospice care, death)

An interim safety and result analysis will be performed after the first 20 patients are enrolled in the study. Subsequent monitoring will occur when 50 and 100 patients are recruited. A designated committee from the study will be assigned for this purpose.

12. STATISTICAL ANALYSIS

- *Describe how your data will be used to test the hypotheses.*
- *State clearly what variables will be tested and what statistical tests will be used.*
- *Include sample size calculations.*

- *If this is a pilot study, state which variables will be examined for hypothesis generation in later studies.*

In general, baseline patient characteristics including demographics and clinical data will be summarized using descriptive statistics for all data combined and data by treatment arm. Specifically, continuous variables will be summarized using mean, standard deviation and median; categorical variables will be summarized using frequencies and percentage. No inferential comparison of treatment arms will be made with respect to baseline and demographic clinical data; such comparisons will be descriptive only. Unless otherwise specified, all results will be considered significant if $p<0.05$**.** All data analysis will be performed using SAS 9.4 (SAS institute Inc., Cary, NC). The intent-to-treat (ITT) principle will be employed, i.e all randomized patients in the groups to which they are randomly assigned will be included in the final analysis, regardless of the intervention they actually receive, and regardless of withdrawal from treatment or deviation from the protocol for any reason.

The primary endpoint is all-cause mortality at 28 days. It will be compared between the two treatment arms using chi-squared test or Fisher's exact test.
Among the secondary study endpoints, binary variables (need for ICU admission, need for higher oxygen supplementation including non-rebreather mask, high flow nasal cannula or non-invasive mechanical ventilation, need for invasive mechanical ventilation and need for oxygen supplementation upon discharge) will be compared using chi-squared test or Fisher's exact test between the two arms; continuous variables (ICU length of stay, hospital length of stay, duration of mechanical ventilation) will be compared between the two arms using Kaplan-Meier curve and log-ran test to take into account data censoring.

Sample size consideration: The sample size calculation was based on the hypothesis of primary endpoint. Our primary hypothesis is that the use of a higher dose of dexamethasone equivalent to 1 mg/kg/day of methylprednisolone would be associated with a decrease in mortality in COVID-19 patients requiring oxygen supplementation. A two group χ^2 test with a 5% two-sided significance level will have 80% power to detect the difference between the proportion of dexamethasone 6 mg group 23.3% and the proportion of dexamethasone weight based 5.9% (odds ratio of 0.206) when the sample size in each group is 64.

To account for 10% dropout rate, will be increasing recruitment to 142, with 71 in each arm to ensure 128 evaluable subjects.

Missing data: If there is less than 5% of an endpoint missing, complete case analysis will be used; if there is more than 5% missing, sensitivity analysis will be performed by assuming all the missing values of an endpoint to be either outcome if it is binary, or by assuming all the missing values of an endpoint to be either upper quartile or lower quartile of the available values if it is continuous, to see if the results are similar to those using complete case analysis.

13. SPECIMEN BANKING

- *If specimens will be banked for future research, describe where the specimens will be stored, how long they will be stored, how they will be accessed and who will have access to the specimens*
- *List the information that will be stored with each specimen, including how specimens are labeled/coded*
- *Describe the procedures to release the specimens, including: the process to request release, approvals required for release, who can obtain the specimens, and the information to be provided with the specimens.*

N/A

14. DATA MANAGEMENT AND CONFIDENTIALITY

- *Describe the data and specimens to be sent out or received. As applicable, describe:*
  - *What information will be included in that data or associated with the specimens?*
  - *Where and how data and specimens will be stored?*
  - *How long the data will be stored?*
  - *Who will have access to the data?*
  - *Who is responsible for receipt or transmission of data and specimens?*
- *Describe the steps that will be taken to secure the data during storage, use and transmission.*

Data will be obtained from the medical electronic records and tabulated in REDCap using adequate patient de-identifiers to avoid HIPAA violations. Only research staff (i.e. principal investigator, co-investigators and research coordinators) will have access to the database. The data will be stored up as required by regulatory guidelines.

Data is only being stored on REDCap which would be accessed only from a hospital computer. Only de-identified data will be exported and transmitted, minimizing risk of breaching patient confidentiality. All paper consent forms will be locked securely at 410 Lakeville Road.

15. DATA AND SAFETY MONITORING PLAN

A specific data and safety monitoring plan is only required for greater than minimal risk research. For guidance on creating this plan, please see the Guidance Document *on the HRPP website.*

Part I – this part should be completed for all studies that require a DSMP.
Part II – This part should be completed when your study needs a Data and Safety Monitoring Board or Committee (DSMB/C) as part of your Data and Safety Monitoring Plan.

Part I: Elements of the Data and Safety Monitoring Plan

- *Indicate who will perform the data and safety monitoring for this study.*
- *Justify your choice of monitor, in terms of assessed risk to the research subject's health and well being. In studies where the monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and rationale for selection*
- *List the specific items that will be monitored for safety (e.g. adverse events, protocol compliance, etc)*
- *Indicate the frequency at which accumulated safety and data information (items listed in # above) will be reviewed by the monitor (s) or the DSMB/C.*
- *Where applicable, describe rules which will guide interruption or alteration of the study design.*
- *Where applicable, indicate dose selection procedures that will be used to minimize toxicity.*
- *Should a temporary or permanent suspension of your study occur, in addition to the IRB, indicate to whom will you report the occurrence.*

Data and safety monitoring will be performed after the first 20 patients are enrolled in the study. Subsequent monitoring will occur when 50 and 100 patients are recruited. A designated committee from the study will be assigned for this purpose, and potential side effects such as secondary bacterial and fungal infections, as well as, clinically significant hyperglycemia as defined above will be assessed.

Part II: Data and Safety Monitoring Board or Committee

- *When appropriate, attach a description of the DSMB.*
- *Provide the number of members and area of professional expertise.*
- *Provide confirmation that the members of the board are all independent of the study.*

The DSMB is not an independent committee and includes coinvestigators who are not part of the consenting process, made up of senior faculty members who are familiar with the protocol and have had prior clinical research experience.

16. WITHDRAWAL OF SUBJECTS

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent*
- *Describe procedures for orderly termination*
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Patients may choose to withdraw from the study at any time. They will be asked to provide a reason for withdrawal if they choose to and will be asked if investigators can follow the electronic health record data over time until the study is completed.

Participants may be withdrawn from the study if deemed appropriate by clinician judgement. Data will be analyzed as intention-to-treat.

17. RISKS TO SUBJECTS

- *Describe any potential risks and discomforts to the subject (physical, psychological, social, legal, or other) and assess their likelihood and seriousness and whether side effects are reversible. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.*
- *Include risks to others , like sexual partners (if appropriate)*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to results*
- *Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.*

Potential risks for the patients in the higher dexamethasone dose group include but are not limited to higher risk of hyperglycemia, delirium and bacterial or fungal infections. Most of these side effects are treatable and reversible. To minimize any potential risks, patients will be monitored for signs or symptoms suggestive of secondary infections, so they can be identified and treated early. Glucose levels will be checked as part of routine medical care to ensure adequate control of hyperglycemia. For patients who develop delirium, use of non-pharmacological and pharmacological interventions will be offered based on clinical judgment. These risks are reasonable in relation to the potential benefits and importance of knowledge that can be obtained with the results of the study. A data and safety monitoring committee will be created to assess for the development of adverse events.

18. RESEARCH RELATED HARM/INJURY

- *Describe the availability of medical or psychological resources that subjects might need as a result of anticipated problems that may be known to be associated with the research.*
- *If the research is greater than minimal risk, explain any medical treatments that are available if research-related injury occurs, who will provide it, what will be provided, and who will pay for it.*

If adverse events occur, they will be handled as per routine clinical care protocols (i.e. treatment of hyperglycemia and infection).

19. POTENTIAL BENEFIT TO SUBJECTS

- *Explain what benefits might be derived from participation in the study, noting in particular the benefit over standard treatment (e.g. a once-a-day administration instead of four times a day, an oral formulation over an IV administration).*
- *Also state if there are no known benefits to subjects, but detail the value of knowledge to be gained*

Benefits to participants include enrollment in a study that will help answer questions regarding the optimal dosage of steroids in COVID-19 patients to help improve clinical outcomes and potentially a mortality benefit.

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

- *Describe the methods used to identify potential research subjects, obtain consent and gather information about subjects to ensure that their privacy is not invaded.*
- *In addition consider privacy protections that may be needed due to communications with subjects (such as phone messages or mail).*

Potential research subjects will be screened via Sunrise. Investigators will review the oxygen saturation and oxygen requirements of patients admitted to the COVID floors and review for eligibility. For patients who are discharged prior to 28 days, a survey will be sent out via email using REDCap to determine primary endpoint and subjective symptoms. Only relevant information will be collected and stored directly into REDCap. For patients without access to email or who do not respond to the survey, a follow up phone call will be made. Only information relevant to the research will be reviewed to ensure patient privacy.

21. COSTS TO SUBJECTS

- *Describe any foreseeable costs that subjects may incur through participation in the research*
- *Indicate whether research procedures will be billed to insurance or paid for by the research study.*

All tests that will be performed are part of routine medical care and will not represent any additional cost to subjects participating in the study.

22. PAYMENT TO SUBJECTS

- *Describe the amount of payment to subjects, in what form payment will be received and the timing of the payments.*

No payments will be made to participants.

23. CONSENT PROCESS

If obtaining consent for this study, describe:

- *Who will be obtaining consent*
- *Where consent will be obtained*
- *Any waiting period available between informing the prospective participant and obtaining consent*
- *Steps that will be taken to assure the participants' understanding*
- *Any tools that will be utilized during the consent process*
- *Information about how the consent will be documented in writing. If using a standard consent form, indicate such.*
- *Procedures for maintaining informed consent.*

Informed consent will be obtained by the investigators of the study who are physicians. As the investigators obtaining consent are physicians, consenting investigators will be able to enter the room to provide in-person consent. Based on FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, consent and HIPAA Authorization will be obtained using an electronic method (via REDCap and phone/iPad), when possible. If an electronic method is unavailable, the signed paper consent form will be collected from the patient room following infection control protocols. The pen used by patient to sign the consent form is thrown away and consent form signed by the patient and investigator with a witness will be placed in a biohazard bag and then in a clean bag. The fully signed consent form will be filed in the patient's research record secured at 410 Lakeville Road with a copy filed in the medical record as appropriate. A copy of the blank consent form will be left to the patient for their records. If it is not possible to collect the consent form due to contamination of document by infectious material, the investigator and witness will sign and date a copy the consent form and provide individual attestation that the patient agreed to participate in the study and signed the informed consent form. When informed consent is to be obtained from a Legally Authorized Representative (LAR) via email, who is not present due to isolation rules:

The investigator will contact the LAR on the phone and confirm the LAR's preferred language. If English is confirmed, an email address will be requested to email an electronic informed consent form will be sent to the LAR via REDCap for review during consent conversation with the investigator. A three way call or video conference with (a) the patient's LAR, (b) a witness, and (c) if desired by LAR, additional participants (e.g., patient's next of kin) will be arranged by the investigator. The consent process will include the following: Each attendee who is on the call or video conference identifies themselves (include name and role/relationship to patient), investigator reviews the consent form with the LAR and answers any questions that occur during the conversation, witness verbally confirms that LAR's questions have been answered, investigator asks the LAR to confirm that the LAR is in agreement with patient's participation in the trial while the witness is listening on the phone or video conference, and LAR verbally confirms that they would like the patient to participate in the trial and LAR signs and dates the consent form on REDCap. Investigator and witness will sign and date the electronic copy of the consent form on REDCap. If an electronic form is not accessible via REDCap, an electronic version of the paper copy will be emailed to the LAR and the investigator will ask LAR to sign and date the LAR's copy of consent form and email back a scanned or photographed copy to be placed in the patient's record along with the paper consent form signed by the investigator and witness.

When informed consent is to be obtained from a Legally Authorized Representative (LAR), who is not present due to isolation rules AND does not have access to email or one does not exist, verbal consent will be obtained as follows:
Investigator obtains verbal confirmation from the LAR indicating agreement to allow the patient's participation and when possible requests the LAR to sign and date a blank piece of paper with a written statement that the LAR agrees to allow the patient to participate in the clinical trial, noting both the Protocol 'NUMBER' and the short clinical trial title or acronym. After signing and dating the newly created document, the LAR sends a photograph of the signed and dated statement by fax, text message, or email to the investigator or will return the document to the investigator by mail. Following the LAR's verbal confirmation that they agree to allow patient's participation in the clinical trial, the investigator will mail a copy of the consent form to the LAR and ask for the LAR to sign and date the consent and send it back by mail for confirmation of signature. Investigator and witness will sign and date a copy of the consent form and each should provide attestation that the LAR is in agreement with the patient's participation in the study.

When informed consent is to be obtained from a Legally Authorized Representative (LAR) with Limited English Proficiency (LEP), who is not present due to isolation rules:
The investigator will contact the LAR on the phone and confirm the LAR's preferred language. The investigator will use interpreter services prior to

continuing the consent conversation. Once a translator is on the call, the investigator will request an email address to email a copy of the informed consent form. A copy of the consent form will be emailed to the LAR for review during consent conversation with the investigator and interpreter. The investigator obtaining consent arranges a three way call or video conference with (a) the patient's LAR, (b) interpreter, (c) a witness, and (d) if desired by LAR, additional participants (e.g., patient's next of kin). The consent process will be as listed above. In addition, LAR verbally confirms that they would like the patient to participate in the trial and LAR signs the translated short form and translated HIPAA authorization. Forms will be scanned and emailed back, or the LAR will take a photograph of the signature page of the LAR's signed and dated consent form and translated HIPAA authorization (if applicable) and forward to the investigator. The photo of the LAR's signed and dated signature pages translated short form and HIPAA authorization will be printed and placed in the patient's record along with the paper English consent form signed by the investigator and witness.

If these options are not feasible, the LAR may send an email response to the investigator indicating agreement to allow patient's participation in the clinical trial (if they cannot email or scan the signed consent form). The Investigator and witness will provide individual attestation that the LAR is in agreement with the patient's participation in the study. In addition, the investigator will send, through certified mail, a copy of the translated short consent form, translated HIPAA authorization and a copy of the English consent form to the LAR and ask for the LAR to sign and date the translated short form and translated HIPAA authorization and send it back by mail for confirmation of signature. The LAR may also provide verbal confirmation indicating agreement to allow patient's participation and request the LAR to sign and date a blank piece of paper with a written statement that the LAR voluntarily agrees to allow the patient to participate in the clinical trial, noting both the Protocol 'NUMBER' and the short clinical trial title or acronym. After signing and dating the newly created document, the LAR sends a photograph of the signed and dated statement by fax, text message, or email to the investigator or will return the document to the investigator by mail. Investigator and witness will sign and date a copy of the English consent form and document the interpreter ID#.

When informed consent is to be obtained from a Legally Authorized Representative (LAR) with Limited English Proficiency (LEP), who is not present due to isolation rules AND does not have access to email or one does not exist, verbal consent will be obtained as follows:

The investigator will contact the LAR on the phone and confirm the LAR's preferred language. Once confirmed and an interpreter is included on the call, inform him/her that a three way call or video conference with (a) a witness, and if desired by the LAR, additional participants (e.g., patient's next of kin) will be conducted to discuss the study. During the consent conversation, investigator will review the consent form with the LAR and any additional participants.

The consent process will include the following: each attendee who is on the call or video conference identifies themselves (include name and role/relationship to patient), investigator reviews the consent form with the LAR and answers any questions asked during the conversation, witness verbally confirms that LAR's questions have been answered, investigator asks the LAR to confirm that the LAR is in agreement with patient's participation in the trial while the witness is listening on the phone or video conference. The investigator obtains verbal confirmation from the LAR indicating agreement to allow the patient's participation and when possible requests the LAR to sign and date a blank piece of paper with a written statement that the LAR agrees to allow the patient to participant in the clinical trial, noting both the Protocol 'NUMBER' and brief clinical trial title or acronym. After signing and dating the newly created document, the LAR sends a photograph of the signed and dated statement by fax, text message, or email to the investigator or returns the document to the investigator by mail at a later date. Following the LAR's verbal confirmation that he/she agrees to allow patient's participation in the clinical trial, the investigator will mail a copy of the consent form, translated short form and translated HIPAA authorization to the LAR and ask for the LAR to sign and date the consent form and HIPAA authorization and send it back by mail for confirmation of signature. Investigator and witness should sign and date a copy of the English consent form and document the interpreter ID#. The investigator and witness should also provide attestation that the LAR is in agreement with the patient's participation in the study

All enrollment notes will include a description of the consent process, interpreter ID# and if applicable, will indicate why the signed document was not retained.

The maximum allowable waiting period between informing the prospective participant and obtaining consent would be 48 hours from administration of the first dose of steroids.

In the state of NY, any participants under the age of 18 are considered children. If your study involves children, additional information should be provided to describe:

- *How parental permission will be obtained*
- *From how many parents will parental permission be obtained*
- *Whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. The process used to determine these individual's authority to consent for the child should be provided*
- *Whether or not assent will be obtained from the child*
- *How will assent be documented*
- *Whether child subjects may be expected to attain legal age to consent to the procedures for research prior to the completion of their participation in the research. If so, describe the process that will be used to obtain their legal*

consent to continue participation in the study. Indicate what will occur if consent is not obtained from the now-adult subjects.

N/A

If the study involves cognitively impaired adults, additional information should be provided to describe:

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*
- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*
  - *list the individuals from who permission will be obtained in order of priority*
  - *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
  - *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
  - *Describe whether assent will be documented and the process to document assent*
  - *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

If a patient is not able to provide consent due to cognitive impairment or clinical condition based on investigators and/or clinician's determination, the designated health care proxy or surrogate decision maker will be contacted for consent.

If the study will enroll non-English speaking subjects:

- *Indicate what language(s) other than English are understood by prospective subjects or representatives*
- *Indicate whether or not consent forms will be translated into a language other than English*
- *Describe the process to ensure that the oral and written information provided to those subjects will be in that language*
- *If non-English speaking subjects will be excluded, provide a justification for doing so*

Interpreter services at each facility will be used during the informed consent.

24. WAIVER OR ALTERATION OF THE CONSENT PROCESS ☒ N/A

Complete this section if you are seeking an alteration or complete waiver of the consent process.

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk to the subject:*
- *Explain why the waiver/ alteration will not adversely affect the rights and welfare of subjects*
- *Explain why it is impracticable to conduct this research if informed consent is required*
- *Explain why it is not possible to conduct this research without using the information or biospecimens in an identifiable form*
- *If appropriate, explain how the subjects will be provided with additional pertinent information after participation. If not appropriate to do so, explain why.*

Complete this section if you are obtaining informed consent but you are requesting a waiver of the documentation of consent (i.e., verbal consent will be obtained). *To proceed with a waiver based on these criteria, each subject must be asked whether they wish to have documentation linking them to this study.* ***Only complete subsection 1 OR subsection 2.***

SUBSECTION 1

- *Explain how the only record linking the subject to the research would be the consent document.*
- *Explain how the principal risk of this study would be the potential harm resulting from a breach in the confidentiality*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

SUBSECTION 2

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk.*
- *Confirm that the research only involves procedure for which consent is not normally required outside the research context.*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

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25. WAIVER OF HIPAA AUTHORIZATION ☒ N/A

Complete this section if you seek to obtain a full waiver of HIPAA authorization to use and/or disclose protected health information.

- *Describe the risks to privacy involved in this study and explain why the study involves no more than minimal risk to privacy:*
- *Describe your plan to protect identifiers from improper use or disclosure and to destroy them at the earliest time.*
- *Indicate why it is not possible to seek subjects' authorization for use or disclosure of PHI.*
- *Indicate why it is not possible to conduct this research without use or disclosure of the PHI.*
- *Indicate if PHI will be disclosed outside NSLIJ Health System, and if so, to whom. Note: PHI disclosed outside NSLIJ Health System, without HIPAA authorization needs to be tracked. Please see guidance at www.nslij.com/irb for information about tracking disclosures.*

Complete this section if you seek to obtain a partial waiver of the patient's authorization for screening/recruitment purposes *(i.e., the researcher does not have access to patient records as s/he is not part of the covered entity)*

Note: Information collected through a partial waiver for recruitment cannot be shared or disclosed to any other person or entity.

- *Describe how data will be collected and used:*
- *Indicate why you need the PHI (e.g.PHI is required to determine eligibility, identifiers are necessary to contact the individual to discuss participation, other)*
- *Indicate why the research cannot practicably be conducted without the partial waiver (e.g. no access to medical records or contact information of the targeted population, no treating clinician to assist in recruitment of the study population, other)*

26. VULNERABLE POPULATIONS:

Indicate whether you will include any of these vulnerable populations. If indicated, submit the appropriate appendix to the IRB for review:

- ☐ *Children or viable neonate*
- ☒ *Cognitively impaired*
- ☐ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- ☐ *Prisoners*
- ☐ *NSLIJ Employees, residents, fellows, etc*
- ☒ *poor/uninsured*
- ☐ *Students*
- ☒ *Minorities*

☒ *Elderly*
☐ *Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

We are going to include vulnerable populations such as elderly patients, cognitively impaired patients, poor/uninsured and minorities as long as they meet eligibility criteria for the study. We will ensure that the recruitment procedures include language translation, the participants are not coerced and that participants or surrogate decision makers understand the consent process and research protocol.

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g. results, new information, unanticipated problems involving risks to subjects or others, or protocol modifications) among sites to protect subjects.

A PHI team was created on Microsoft Teams to allow for communication and information dissemination. It is a PHI teams, therefore, exchange of information (including PHI) would be permissible. Site specific channels were created for each of the sites to allow for communication between investigators at a particular site. The general channel will be used to exchange information between all the sites. All changes to the protocol and important information and unanticipated problems will be discussed on the general channel.

28. REFERENCES/BIBIOGRAPHY

Provide a reasonable list of references directly related to the study. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

1. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. Jul 2020;doi:10.1056/NEJMoa2021436
2. Sterne JAC, Murthy S, Diaz JV, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 10 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023
3. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 10 2020;324(13):1307-1316. doi:10.1001/jama.2020.17021
4. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 03 2020;8(3):267-276. doi:10.1016/S2213-2600(19)30417-5

5. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, Najafizadeh SR, Farhadi E, Jalili N, Esfahani M, Rahimi B, Kazemzadeh H, Mahmoodi Aliabadi M, Ghazanfari T, Sattarian M, Ebrahimi Louyeh H, Raeeskarami SR, Jamalimoghadamsiahkali S, Khajavirad N, Mahmoudi M, Rostamian A. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J. 2020 Dec 24;56(6):2002808. doi: 10.1183/13993003.02808-2020.
6. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol. 2020;72(4):529-556. doi:10.1002/art.41191