ClinicalTrials.gov Study Protocol and Statistical Analysis Plan

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Project Title: Pilot Study of Targeted Normoxia in Critically Ill Trauma Patients

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Principal Investigator: **Adit Ginde, MD, MPH**

Version Date: 09/16/2019 **Version 2**

I. Hypotheses and Specific Aims:

Supplemental oxygen is fundamental in caring for critically ill trauma patients to enhance cellular energy production, optimize recovery, and maximize survival. While the avoidance of hypoxia is vital, the current clinical practice of excessive oxygenation in military and civilian settings is common, is unnecessary, and may even be harmful. Specifically, excessive oxygen supplementation promotes hyperoxic organ injury through pro-inflammatory reactive oxygen species and ischemic vasoconstriction. Indeed, hyperoxia has been shown to increase mortality in critically ill patients.

We convened a panel of 31 national and local experts in trauma surgery, critical care, and emergency medicine to define optimal oxygenation targets in critically ill trauma patients. The strong consensus was to target normoxia at an oxygen saturation (SpO2) range of 90-96% and arterial oxygen (PaO2) range of 60-100 mmHg. In addition, we performed a retrospective study of critically ill trauma patients at University of Colorado Hospital and found that hyperoxia (SpO2 >96%) was present in the context of supplemental oxygen for more than half of the hospitalization. This identifies a discordance between current practice and expert consensus. The primary reason for this is convenience, as physician, nursing, and respiratory therapy leaders at University of Colorado Hospital all agree that targeting normoxia is optimal for patient care. Indeed, a similar normoxia strategy is already written into local clinical protocols (see attachment), yet is not well followed. Therefore, clinical leaders from Emergency Medicine, Trauma Surgery, Neurosurgery, and Critical Care at University of Colorado Hospital are increasing educational efforts to improve adherence to the established clinical guidelines for oxygenation in critically ill trauma patients.

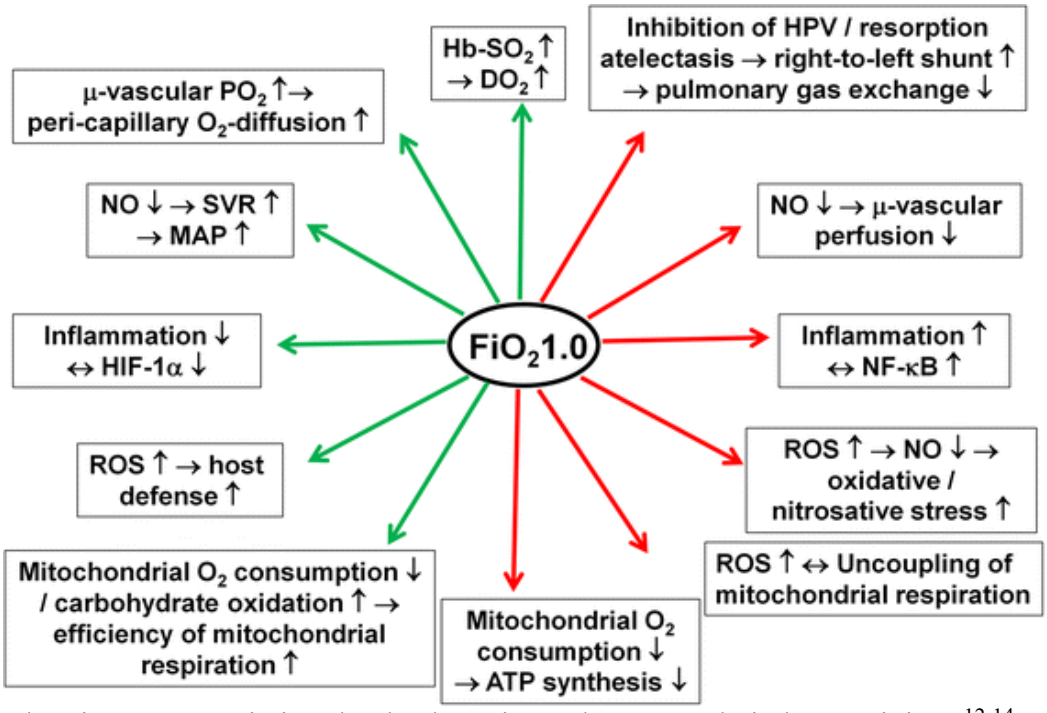
Specific Aim:
We will conduct an observational pre/post study to evaluate the impact of these efforts to optimize oxygen delivery and oxygenation in critically ill trauma patients.

Hypotheses:
We hypothesize that the clinical efforts to improve adherence to oxygen guidelines will:

a) improve the proportion of time spent with target normoxia thresholds (oxygen saturation [SpO2] 90-96%) by
b) reducing utilization of unnecessary supplementation oxygen
c) without a substantive increase in hypoxic episodes or an adverse impact on clinical outcomes.

II. Background and Significance:
Oxygen therapy has undisputed importance in the care of critically ill medical and trauma patients to treat and prevent morbidity associated with hypoxia.[1,2] However, generous supplemental oxygen is routine, and often results in hyperoxia.[3-6] While there is no known benefit of excessive oxygenation, common clinical perception has been that this practice is safe and creates a margin of safety against hypoxia.[7-9] However, evidence indicates that hyperoxia can also harmful. Here we summarize the rationale and relevance of the proposed research to avoid but hypoxia and hyperoxia and target normoxia.

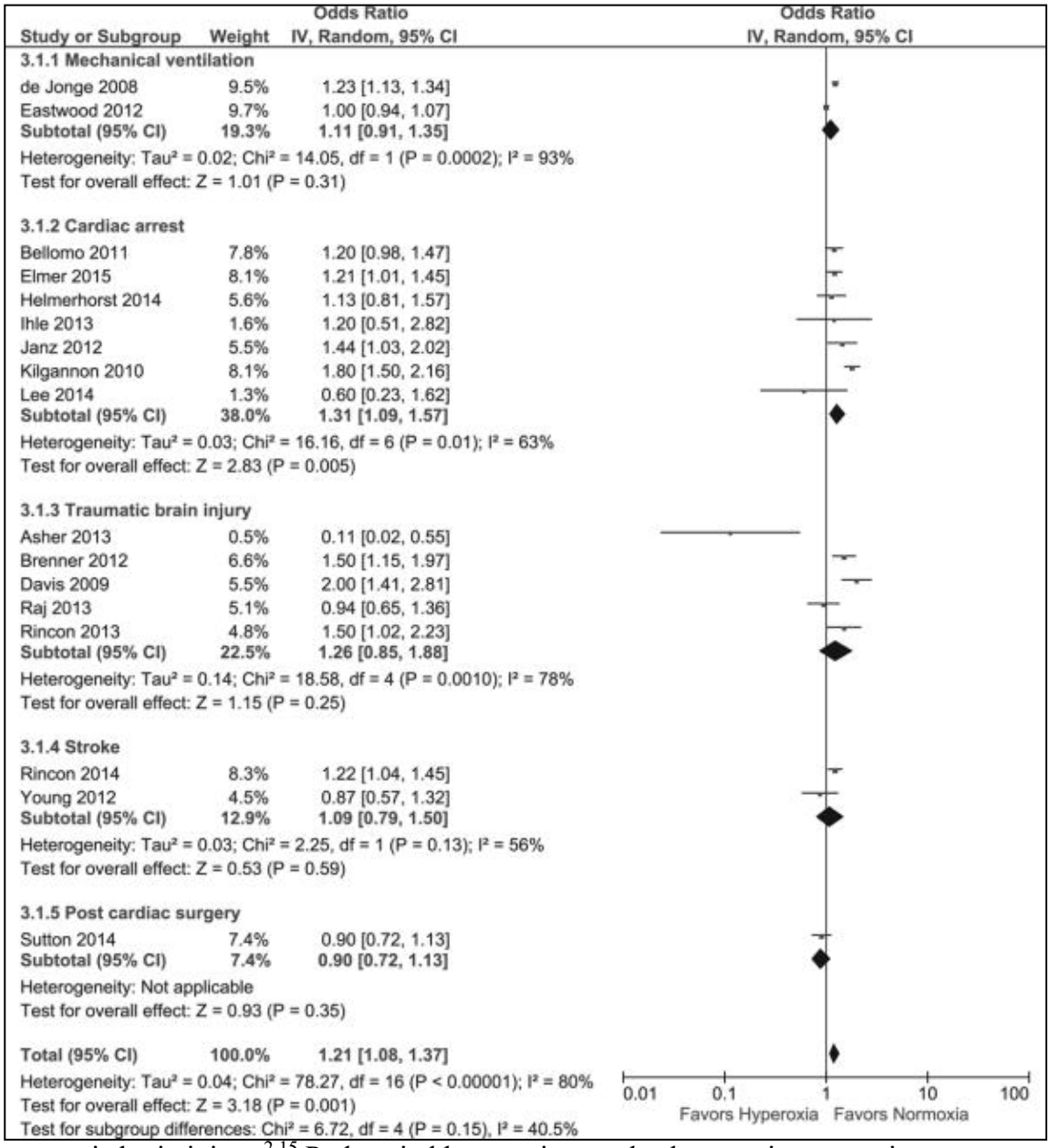
Pre-clinical and observational data support the concept of targeted normoxia. There is a U-shaped relationship between oxygenation and mortality in critically ill patients, with both ends of the spectrum—hypoxia and hyperoxia—independently associated with higher mortality.[10,11] Laboratory evidence has long demonstrated toxicity associated with hyperoxia through mitochondrial production of pro-inflammatory reactive oxygen species and



ischemic vasoconstriction that leads to tissue damage and vital organ injury.[12-14] **Figure 1** summarizes the underlying cellular mechanisms for balance between the beneficial and harmful effects of oxygen therapy.

Figure 1. Beneficial (*green arrows*) and deleterious (*red arrows*) effects of oxygen therapy during circulatory shock. ***Adapted from Asfar P et al. Intensive Care Med 2015;41:1118.***

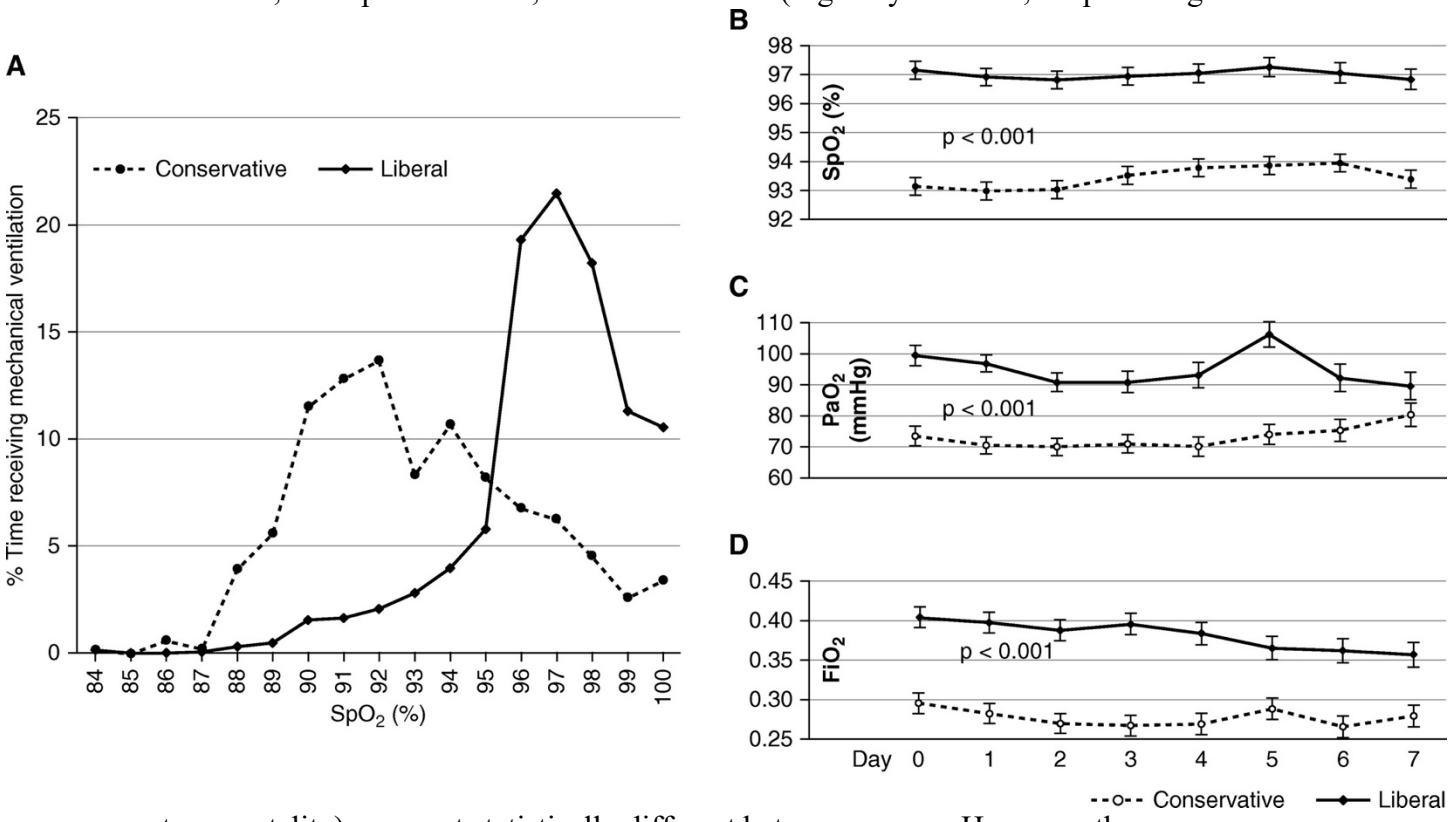
Numerous observational cohort studies have demonstrated an association between hyperoxia and higher mortality broadly in intensive care unit patients and in specific subpopulations, such as cardiac arrest, myocardial infarction, ischemic stroke, and



traumatic brain injury.[2,15] Prehospital hyperoxia can also have an important impact on clinical outcomes.[16] In a recent meta-analysis, hyperoxia (compared to normoxia) was associated with a 21% higher odds of mortality across a broad range of critical illness, even after adjusting for baseline characteristics and illness severity (**Figure 2**).[15]

Figure 2. Adjusted associations between arterial hyperoxia and hospital mortality overall and by subsets of critical illness.[15]

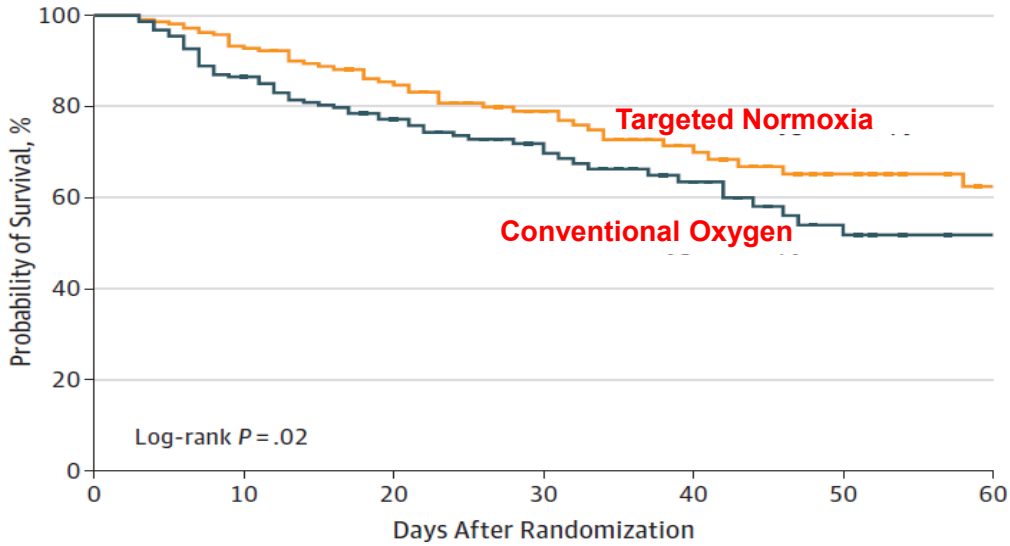
Clinical trial evidence also supports the safety and potential efficacy of targeted normoxia. Panwar et al. recently published the first randomized controlled trial to compare different oxygen targets in critically ill patients, comparing a target oxygen saturation (SpO_2) 88-92% ("conservative") vs. ≥96% ("liberal"/conventional).[18] In this multicenter pilot trial (4 intensive care units [ICU] in Australia/New Zealand; n=103), targeted normoxia (conservative group) safely reduced the amount of supplemental oxygen administered (mean FiO_2 >10% lower in the conservative group during the first 7 days**;** **Figure 3**) and duration of time in the hyperoxic range (4% conservative vs 22% liberal) without an increase in time spent with SpO_2 <88% (0.3% conservative vs 1% liberal). In this small, underpowered trial, clinical outcomes (organ dysfunction, hospital length of



stay, mortality) were not statistically different between groups. However, there were promising signals for targeted normoxia reducing 90 day mortality (adjusted hazard ratio 0.77 [95%CI, 0.40-1.50]), especially in the pre-specified subgroup with acute lung injury (adjusted hazard ratio 0.49 [95%CI, 0.20-1.17]).

<u>Figure 3</u>. Percentage of time spent at each SpO_2 level (A) and treatment separation for SpO_2 (B), PaO_2 (C), and FiO_2 (D) targeted normoxia (conservative oxygen) and relative hyperoxia (liberal oxygen) arms in Panwar trial.[18]

Girardis et al. similarly compared a targeted normoxia strategy (arterial oxygen pressure [PaO_2] 70-100 mmHg or SpO_2 94-98%) to a conventional (relative hyperoxic) strategy (PaO_2 ≥150 mmHg or SpO_2 ≥97%) in a single Italian ICU (n=434).[10] The targeted normoxia group had substantially lower ICU mortality (11.6% vs. 20.2% in the conventional group; p=0.02; **Figure 4**) and a lower incidence of hospital mortality (24.2%



vs

33.9%; p=0.03), shock (3.7% vs. 10.6%; p=0.006), and duration of mechanical ventilation (mechanical ventilation free hours 72 vs. 48; p=0.02). Collectively, these two trials provide strong rationale for the feasibility, safety, and potential efficacy for a targeted normoxia strategy in critically ill trauma patients.

Figure 4. Probability of survival through day 60 for the targeted normoxia and conventional (relative hyperoxia) arms in the Girardis trial.[10]

Additional clinical trial evidence in other populations suggests that targeting either hypoxia or hyperoxia may be harmful. In three high-profile randomized trials of pre-term infants, permissive hypoxia (SpO_2 85-89%) was associated with a higher mortality and disability.[19-21] The applicability of these trials to critically injured adults is unknown; however, we propose a normoxia, rather than permissive hypoxia, strategy. Similarly, five trials of clinical trials have demonstrated worse clinical outcomes of hyperoxia in non-critical trauma,[22] abdominal surgery,[23] myocardial infarction,[24] septic shock (NCT01722422), and ischemic stroke (NCT00414726) patients. Therefore, the prehospital, emergency, and critical care communities now recommend careful titration to ***normoxia*** to avoid hypoxia and preserve tissue oxygenation while preventing iatrogenic hyperoxia.[25,26]

Implementation of targeted normoxia is desirable, safe, and feasible. Prehospital, emergency, trauma, and critical care physicians now firmly believe that avoidance of hypoxia and hyperoxia are both important and that oxygen titration should be practiced in critically ill patients.[27,28] Several implementation studies demonstrate that oxygen titration based on non-invasive oxygen saturation can be safely protocolized to achieve normoxia,[25,26,29] and markedly reduce consumption of supplementary oxygen.[4,18] Accordingly, targeted normoxia is now widely accepted as standard care in emergency departments and ICUs.[12-14] For example, ARDS Network oxygenation targets (SpO_2 88-95%) has been widely accepted for patients with and without ARDS.[30] Yet, widespread use of excessive oxygenation persists in routine care in the prehospital setting, emergency departments, and ICUs with over 75% of patients exposed to prolonged periods of hyperoxia.[12,31]

III. Preliminary Studies/Progress Report:

We conducted a Delphi consensus process enlisting panel of 31 national and local experts in trauma surgery, critical care and emergency medicine.

We asked the expert panel to rate how strongly they agreed or disagreed with specific SpO2 low thresholds, SpO2 high thresholds, PaO2 low thresholds and PaO2 high thresholds. Based off our analysis of the data, we were able to identify what the majority of experts felt were appropriate oxygenation thresholds. Initial votes are summarized in Figures 4-7 below.

Figure 4: Agreement with Lower SpO2 Thresholds in Delphi Stage 2

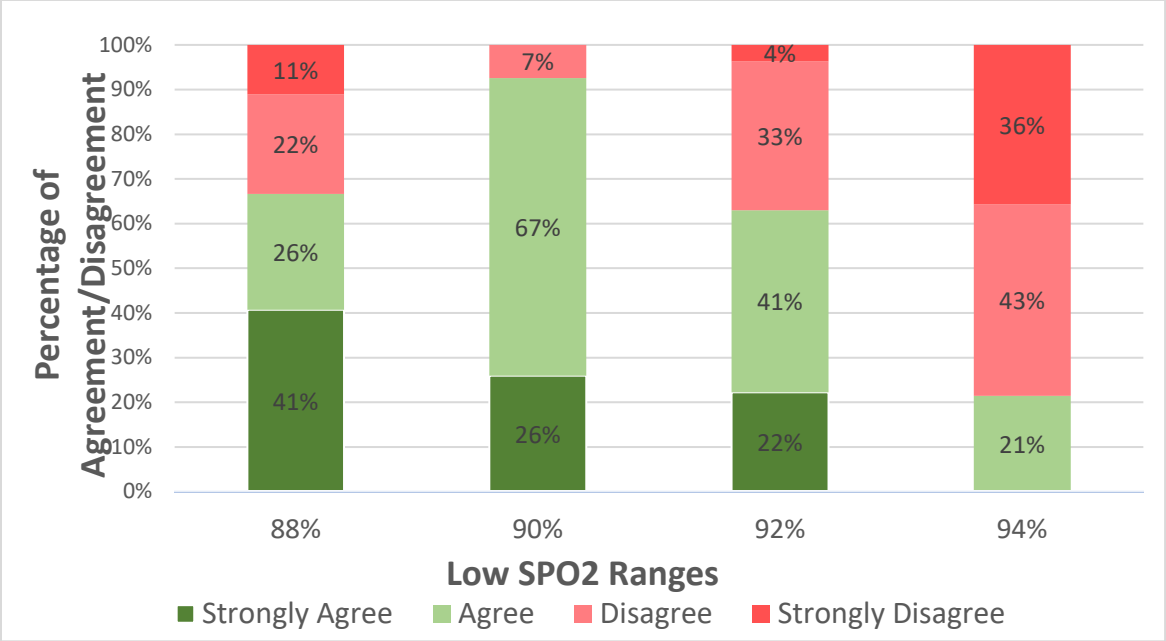


Figure 5: Agreement with Higher SpO2 Thresholds in Delphi Stage 2

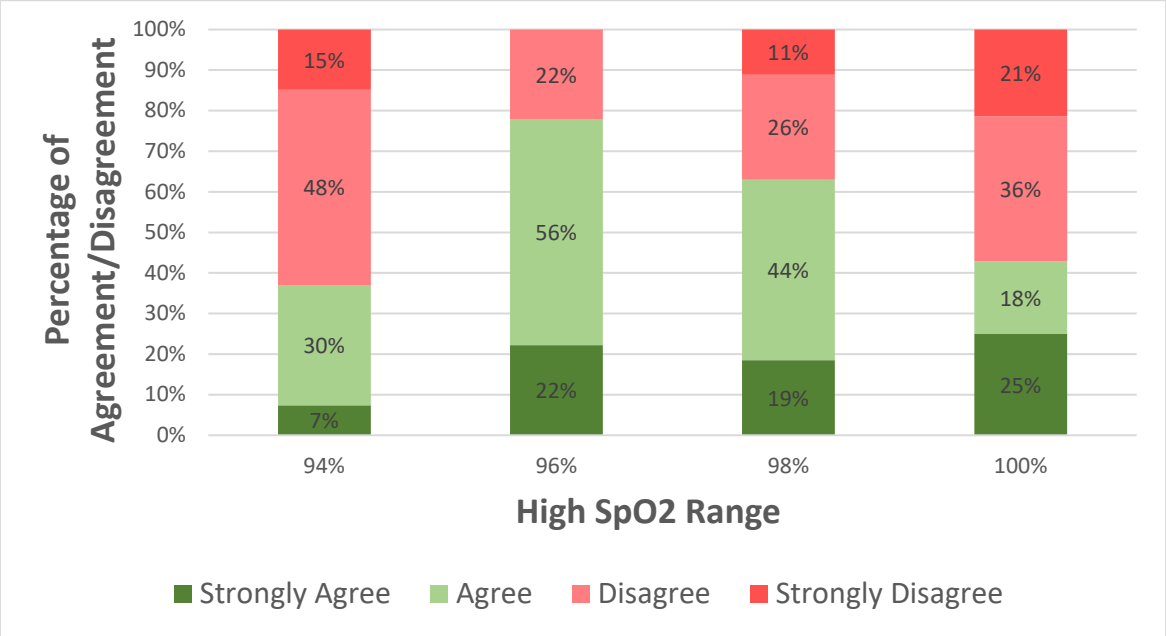


Figure 6: Agreement with Lower PaO2 Thresholds in Delphi Stage 2

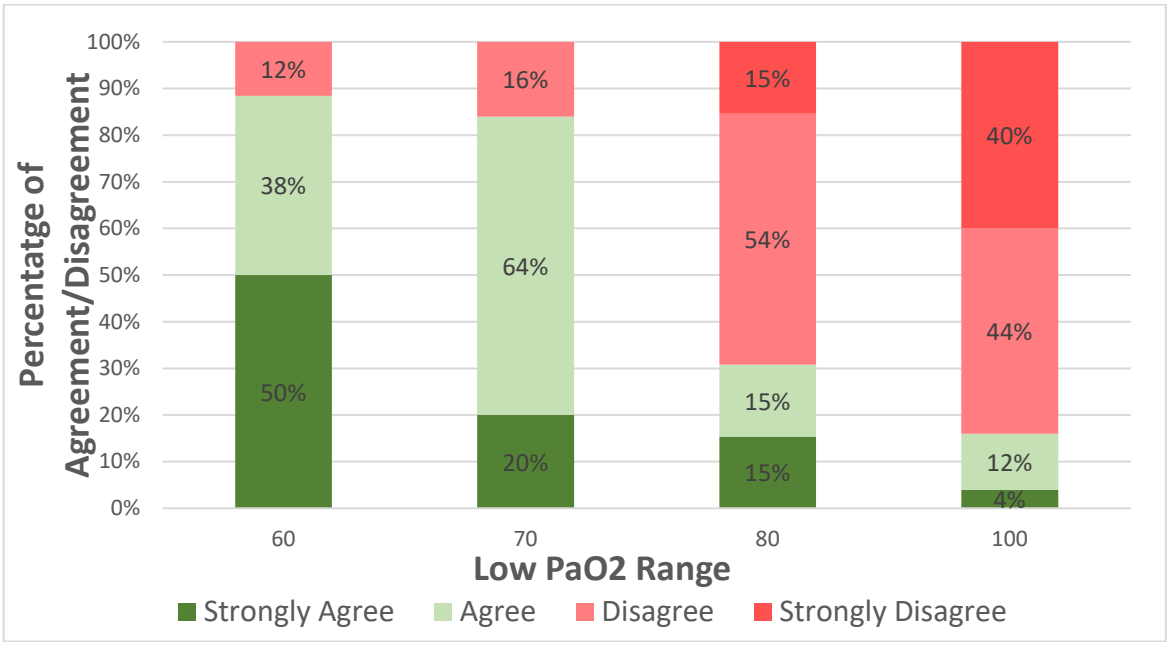
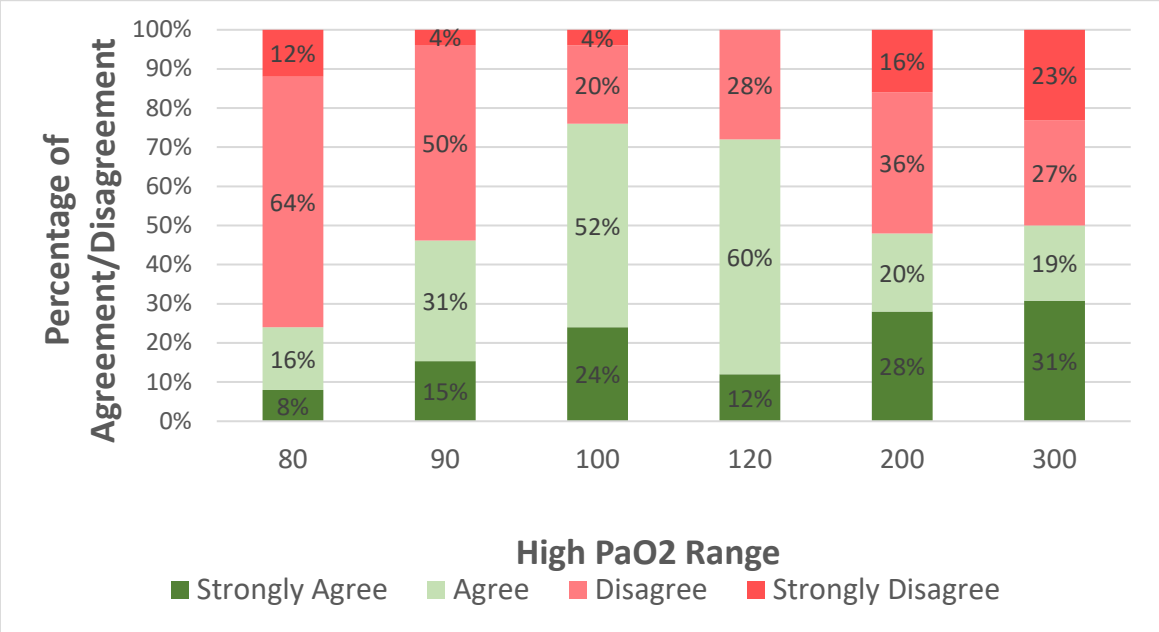


Figure 7: Agreement with Higher PaO2 Thresholds in Delphi Stage 2



For these data, we proposed an SpO2 range of 90-96%, PaO2 range of 60-100 mmHg. In the Final Delphi Stage, we asked our expert panel for a final yes/no vote on these thresholds to confirm final consensus on oxygenation in critically ill trauma patients. Voting was as follows, which confirmed our final target ranges (>80% agreement was pre-defined as consensus):

- Low SpO2 threshold = 90%
  - 89% agreement
- High SpO2 threshold = 96%
  - 89% agreement
- Low PaO2 threshold = 60 mmHg
  - 96% agreement
- High PaO2 threshold = 100 mmHg
  - 89% agreement

These thresholds are concordant with existing clinical guidelines at University of Colorado Hospital, and the data from the expert consensus process has provided additional motivation for clinical leadership to improve their adherence to guidelines. In an observational study design, we will evaluate the impact of clinical efforts to improve guideline adherence.

III. Research Methods

A. Outcome Measure(s):

For the primary feasibility outcome, we will assess oxygenation, as measured by SpO2 and PaO2, relative to amount of supplementation oxygen during the first 7 days. For ventilated

patients, supplemental include fraction of inspired oxygen (FiO_2), positive end expiratory pressure, ventilator mode, mean airway pressure, and tidal volume. With this information we can calculation both P/F ratio and oxygenation index. For non-ventilated patients, we will collect volume and route of supplemental oxygen. These data will be used to longitudinally calculate the observed oxygenation compared to the defined oxygenation targets (SpO2 90-96% and PaO2 60-100 mmHg). In addition, we will calculate the duration of hyperoxia time (SpO2 >96% or PaO2 >100 mmHg, unless no supplemental oxygen is delivered), and number/duration of hypoxia episodes (SpO2 <88% or PaO2<60 mmHg, unless FiO2 is 100%).

Although this pilot study will be underpowered for clinical outcomes, we will measure in-hospital mortality, ventilator-free days, duration of supplemental oxygen, acute organ injury (as measured by daily Sequential Organ Failure Assessment [SOFA] scores over 7 days), intensive care unit length of stay, hospital length of stay, and hospital disposition (facility vs. home).

B. Description of Population to be Enrolled and C. Study Design and Research Methods

We will conduct a pilot study to inform a future larger scale implementation study across multiple trauma centers to test the clinical effectiveness of the targeted normoxia strategy. In the proposed pilot study, we will test and optimize feasibility and potential for effectiveness.

Study Design and Setting: This study will be an observational before-after study conducted at the University of Colorado Hospital.

Participants: We will compare oxygenation and outcomes trauma patients admitted to the ICU during the 6 months after the clinical implementation to similar patients during the same 6 months in the prior year (to adjust for seasonal effects) and the immediate preceding 6 month period (to minimize potential for secular trends).

The clinical implementation of normoxia guidelines is part of standard care and therefore there is no specific research intervention. While the research team will help the clinical leadership with education of clinical staff, the research team will have no interactions with patients or surrogates. Patient care will occur per treating clinicians, including decisions on when to adhere and not to adhere to the guidelines on normoxia. The research procedures will be observational, retrospective data collection. We will collect data on patients with acute injury that are admitted from the emergency department to the surgical-trauma or neurosurgical intensive care units.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

The risks of this research are related to retrospective data collection and interviews as below.

<u>Identifiers</u>

Human subjects will be identified based on the unique hospital encounter number that is specific to the exact hospitalization for an individual patient. Additional identifiers will be temporarily collected (medical record number and date of birth) to ensure proper matching for electronic data collection and to facilitate manual chart review when needed. These identifiers will be removed from the dataset as soon as the database is cleaned and closed for analysis (thereby creating a completely de-identified dataset thereafter).

Confidentiality

Privacy and confidential of human subjects and study data are of utmost importance. We will collect, manage, and store protected health information data using a REDCap database developed for this study, in collaboration with the Colorado Clinical and Translational Sciences Institute. Data will be collected using Health Data Compass and verified by manual chart review. REDCap is a secure and encrypted web application designed to support data capture for research studies, providing user-friendly, web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes University of Colorado Denver and was initiated at Vanderbilt University. The database is hosted at the University of Colorado Denver Development and Informatics Service Center, which will be used as a central location for data processing and management. REDCap is considered more secure than applications such as Survey Monkey and programs such as Microsoft Excel or Access; therefore, it is the preferred data collection, management, and storage modality preferred by our Colorado Multiple Institutional Review Board.

Identifiers will be destroyed as soon as no longer required, typically after data cleaning is complete and database is closed for analysis. IRB-approved study investigators and coordinators will have access to study data; because this study is sponsored by the Department of Defense, we will make allowances for United States Army Medical Research and Material Command (USAMRMC) to be eligible to review study records if needed. We do not anticipate collecting sensitive information (purposefully or inadvertently); however, state and federal regulations will be followed relating to mandatory reporting requirements and study staff are trained appropriately.

Disposition of data

Electronic data will be stored on University servers or on password-protected/encrypted computers that are behind the University firewall. We do not anticipate any hard copy data, but should be generated, they will be secured in a locked file cabinet in a locked office. Data will be stored for as long as IRB and DOD regulations recommend, whichever is longer (typically 5 years). A limited de-identified dataset will be archived long-term for future use by the local investigators and the general research community. The proposed research does not interface with the FDA, and thus, there are no special requirements relating to disposition of data.

E. Potential Scientific Problems:

The biggest challenge to the research will be the extent to which guideline adherence is improved during the study period.

There can also be challenges with electronic data collection with Health Data Compass. However, we have worked closely with Compass in the preparatory work (COMIRB #17-1359), and also will supplement electronic data collection with manual chart review as needed.

F. Data Analysis Plan:

We will model continuous SpO_2 and PaO_2 data separately and a third model where both are combined. The SpO_2 model will have the most field relevance but incorporating the PaO_2 data will be useful in applying results to the hospital setting in future implementation trials. Specific attention will be paid to the defined normoxia target range, as well as short-term episodes of hypoxia or hyperoxia. Oxygenation and oxygen supplementation data will be analyzed descriptively.

Clinical outcomes will be analyzed descriptively to compare the pre- and post-periods. We will also adjust for a limited number of covariates (eg, injury severity) to reduce risk of confounding. However, we fully recognize that the primary purpose of this pilot intervention is feasibility and safety, and so clinical outcomes will be underpowered.

G. Summarize Knowledge to be Gained:

The proposed pilot study will help us to understand the feasibility, barriers, and facilitators for improving oxygenation practices in critically ill trauma patients. The results will provide valuable preliminary data for planning a large multicenter implementation trial to evaluation the impact of this intervention on clinical outcomes and safety. These data collectively will provide actionable data to improve care of critically injured civilians and military service members.

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