Study Protocol and Statistical Analysis Plan

Protocol for: *Real-time Machine Learning Alerts to Prevent Escalation of Care: A Pragmatic Clinical Trial*

NCT Number: NCT04026555

Document Date: 07/28/2022

This supplement contains the following items:

1. Original protocol, which is also the final protocol. No changes to the protocol occurred during the trial.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

Subject: APPROVAL OF RESEARCH GCO 19-0729
Date: Tuesday, June 18, 2019 at 8:13:13 AM Eastern Daylight Time
From: Richmond, Megan
To: Levin, Matthew
CC: Zhao, Shan (MSH), Kia, Arash
Attachments: image001.jpg

Mount Sinai

Icahn School of Medicine at Mount Sinai
Mount Sinai Beth Israel
Mount Sinai Brooklyn
The Mount Sinai Hospital
Mount Sinai Queens
New York Eye and Ear Infirmary
of Mount Sinai
Mount Sinai St. Luke's
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APPROVAL OF RESEARCH

Date: 6/18/2019

To: **Matthew Levin, (matthew.levin@mssm.edu)**

On **6/17/2019**, an Institutional Review Board of the Mount Sinai School of Medicine, in accordance with Mount Sinai's Federal Wide Assurances (FWA#00005656, FWA#00005651) to the Department of Health and Human Services approved the following human subject research from **6/17/2019** until **6/3/2020** inclusive:

Type of Review:	**Initial Request for Approval**
Project Title:	**ReSCUE-ME**
Investigator:	**Matthew Levin (Dept: AN - Anesthesiology)**
Project Information:	**HS#: 19-00318** **GCO#1: 19-0729(0001) ISMMS**
Sites:	**Mount Sinai**
IND or IDE (if any):	**No INDs;No IDEs;**
Submission Details (if any):	**None**

Between **4/17/2020** and **4/22/2020**, or within 30 days prior to study close, whichever is earlier, you are to submit a completed FORM HRP-212: Continuing/Final Review Progress Report and required attachments, in order to request continuing IRB approval or study closure. If IRB continuing

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Initial Application
IRB-19-01700
Matthew Levin

Table of Contents

1. Summary - Title

Protocol Title

ReSCUE-ME

Principal Investigator Matthew Levin

When the application is complete, it will be sent to the PI for submission

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Primary Department Anesthesiology

When the application is complete, it will be sent to the PI for submission

Application Initiated By Shan Zhao

Lay Summary

The escalation of care for patients in a hospitalized setting between nurse practitioner managed services, teaching services, step-down units, and intensive care units is critical for appropriate care for any patient. Often such "triggers" for escalation are initiated based on the nursing evaluation of the patient, followed by physician history and physical exam, then augmented based on laboratory values. These "triggers" can enhance the care of patients without increasing the workload of responder teams. One of the goals in hospital medicine is the earlier identification of patients that require an escalation of care. We have developed a model through a retrospective analysis of the historical data from the Mount Sinai Data Warehouse (MSDW), which can provide machine learning based triggers for escalation of care (Approved by: IRB-18-00581). This model is called "Medical Early Warning Score ++" (MEWS ++). This IRB seeks to prospectively validate the developed model through a pragmatic clinical trial of using these alerts to trigger an evaluation for appropriateness of escalation of care on two general inpatients wards, one medical and one surgical. These alerts will not change the standard of care. They will simply suggest to the care team that the patient should be further evaluated without specifying a subsequent specific course of action. In other words, these alerts in themselves does not designate any change to the care provider's clinical standard of care. We estimate (see "Narrative" section for details) that this study would require the evaluation of ~ 18380 bed movements and approximately 30 months to complete, based on the rate of escalation of care and rate of bed movements in the selected units (9W, 9E, 10W, 10E).

IF Number IF2411760

2. Summary - Setup

Funding Has Been Requested / Obtained	No
Application Type	Request to Rely on Mount Sinai IRB
Research Involves	Prospective Study ONLY
Consenting Participants	No
Humanitarian Use Device (HUD) Used Exclusively in the Course of Medical Practice	No
Use of an Investigational Device to Evaluate Its Safety or Effectiveness	No
Banking Specimens for Future Research	No
Cancer Related Research that Requires Approval from the Protocol Review and Monitoring Committee (PRMC).	No

Is this Cancer Related Research? Cancer Related Research is defined as research that has cancer endpoints or has a cancer population as part of or all of its targeted population. This includes protocols studying patients with cancer or those at risk for cancer.

Clinical Trial Yes

**** A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).***
**** Used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.***

Drugs / Biologics No

**** Drugs / Biologics That Are Not a Part of Standard Practice***
**** Controlled Substances***
**** Drugs / Biologics Supplied by the Research Sponsor or Purchased with Study Funds***

Ionizing Radiation for imaging or therapy, including X-Ray, Fluoroscopy, CT, Nuclear Medicine, PET andor Radiation Therapy:

*** Purely for standard of care:**	No
*** In frequency or intensity that exceeds what is necessary for standard of care:**	No

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Hazardous Materials No

**** Recombinant DNA***
**** Viral Vectors***
**** Plasmids***
**** Bacterial Artificial Chromosomes***

**** Toxic Chemicals, Potentially Toxic Medications, Carcinogens***
**** Autologous Cell Lines***

Request Use of Clinical Research Unit Resources No

3. Summary - Background

Objectives

Mount Sinai Hospital has developed a Rapid Response Team (RRT) system designed to give general floor care providers additional support for patients who may be requiring a higher level of care. This system enables both nurses and physicians to notify the RRT and have a critical care team evaluate the patients. During the period of 03/01/2018 to 09/17/2018, Mount Sinai Hospital floor units on 10W and 10E units made 357 rapid response team (RRT) calls with only 58 leading to an actual increase in the level of care (true positive rate ~ 16%). Similarly, the Electronic Health Record (EHR) generated 839 sepsis Best Practice Alerts (BPAs) yet only five led to escalations in care (true positive rate ~ 0.5%). The results above would imply that over 168 evaluations need to be made to identify a single case where the patient required an escalation in care. The goal of ReSCUE-ME is to evaluate prospective model performance and identify the best spot which we can incorporate MEWS++ into RRT and Primary providers workflow. The primary endpoint is rate of escalation of care on 10W and 10E during the study period.

Background

In a prior study, our group has demonstrated that a machine learning model (MEWS++) significantly outperformed a standard, manually calculated MEWS score on a large retrospective cohort of hospitalized patients. To develop this model, we used a data set (Approved by: IRB-18-00581) of 96,645 patients with 157,984 hospital encounters and 244,343 bed movements. We found that MEWS++ was superior to the standard MEWS model with a sensitivity of 81.6% vs. 44.6%, specificity of 75.5% vs. 64.5%, and area under the receiver operating curve of 0.85 vs. 0.71. Encouraged by this prior result, we are seeking to evaluate our model in a prospective study.

A silent pilot of the ReSCUE-ME alerts has been running on 10E and 10W since Feb 2019. We have been continuously monitoring the alert performance via a real-time web-based dashboard. The results are summarized below:

- Median # of alerts to primary team, per floor, per day: 8
- Median # of alerts to RRT, per floor, per day: 4
- Sensitivity 0.76, Specificity 0.68, AUC 0.77
- Accuracy 0.69, Precision 0.3, F1 Score 0.43

This performance compares very favorably to the performance seen in the retrospective historical cohort used to develop the MEWS++ model:

- Sensitivity 0.82, Specificity 0.76, AUC 0.85
- Accuracy 0.76, Precision 0.12, F1 Score 0.19"

Primary and Secondary Study Endpoints

Primary Endpoints:

- Composite of the Rate of escalation of care (from floor to Stepdown, Telemetry, ICU) and rate of RRT initiated therapy (including but not limited to blood pressure support, respiratory care support, anti-biotic augmentation, invasive monitoring) in the selected units (10E and 10W)

Secondary Endpoints:

- Blood pressure support utilization (e.g., initiation of vasopressor medication, administration of fluid bolus)
- Respiratory care support utilization (e.g., nasal cannula to high flow)
- Accuracy of predicting care escalation from the floor to ICU, step-down, and Telemetry
- Cardiac arrest/mortality rate in 10E and 10W compared with two control units (9W and 9E)
- Evaluate the average calls per day and average calls per patient when compared to historical and matched general medical-surgical floor units (9W and 9E)
- Evaluate through a survey format of nursing and physician care providers the utility of MEWS++ scoring in determining whether or not an RRT call should be placed. This survey will be administered at the beginning and end of the enrollment period through an online REDCap form hosted within our institution (or comparable system). The survey will be administered by one of the co-investigators within the study.

Protocol Was Already Approved by the Icahn School of Medicine at Mount Sinai (ISMMS) Institutional Review Board (IRB) Under a Different Principal Investigator	No

Protocol Was Previously Submitted to an External(non-ISMMS) IRB No

4. Research Personnel

Name/Department	Role/Status	Contact	Access	Signature Authority	Phone	Email
Matthew Levin / Anesthesiology	PI / Faculty	Yes	SIGNAUTH			
Shan Zhao / Pharmacology and Systems Therapeutics	Co-Investigator /	Yes	EDIT		310-751-4604	
Rohit Gupta / Surgery	Co-Investigator /		EDIT			
Jennifer Wang / Surgery	Co-Investigator /		READONLY			
Robert Freeman / Office of Clinical Research	Co-Investigator /		READONLY			
Roopa Kohli-Seth / Surgery	Co-Investigator /		EDIT		(212) 241-8867	
Sanam Ahmed / Surgery	Co-Investigator /		READONLY		212-241-8867	
Mirhadi Arash Kia / IT Department	Co-Investigator /	Yes	EDIT			
Prem Timsina / IT Department	Project Director /		READONLY			
Surafel Tsega / Anesthesiology	Co-Investigator /		READONLY			
Benjamin Kummer / Neurology	Co-Investigator /		READONLY			
Michael Kitz / Anesthesiology	Co-Investigator /		READONLY			

5. Sites

Site Name	The Mount Sinai Hospital
Other External Site Name	
Contact Details	
Approved	
Approval Document	
Funded By Mount Sinai	
Other IRB	

6. Subjects - Enrollment

Site Name	The Mount Sinai Hospital
Subjects To Be Enrolled	
18680	
Total Number of Subjects to be Enrolled Across All Listed Sites Above (Auto Populated)	18680

7. Subjects - Setting and Resources

Setting of Human Research Other

Specify Other Setting of Human Research

Hospital Units on 10W, 10E, 9W, 9E.

Total Number of Subjects Needed To Complete Study 18680

Feasibility of Meeting Recruitment Goals

Our initial observation shows the rate of escalation ~ 10% for the selected units (10W and 10E). The estimated sample size is ~ 934 escalations of care which we expect to observe by including ~9340 bed movements. The estimated bed movements per day in the selected units is ~ 10 which makes the expected pilot days ~ 934 days (~ 2.5 yrs.). We anticipate an equal number of escalations for 9W and 9E, which will not receiving any MEWS++ alerts.#

Facilities To Be Used for Conducting Research

Hospital Units on 9W, 9E, 10W, 10E

Multi-Center Study No

Community-Based Participant Research Study No

PI must attest to the following.

**** Process is adequately described to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.***

8. Subjects - Populations

Inclusion Criteria

All patients age 18 or greater who were admitted to a general care unit on 9W, 9E, 10W, 10E.

Exclusion Criteria

Any admitted patient who has a "Do Not Resuscitate (DNR)" and/or a "Do Not Intubate (DNI)" order in the EHR, any patient made "level of care" by RRT as documented in REDCap.

Enrollment Restrictions Based Upon Gender, Pregnancy, Childbearing Potential, or Race	No
Age Range(s)	18 to 64 Years, 65 Years and Over
Targeted Population(s)	Adults - Patients

Other Aspects that Could Increase Subjects Vulnerability

Prisoners and non-laboring pregnant women will be included if they are admitted to 10E/W or 9E/W. This will be rare but possible. Incapacitated patients will be provided the study information sheet within their paper chart and included unless their health care proxy/legally authorized representative chooses to opt them out of the study. If they were to regain consciousness and capacity, then they would have the ability to withdraw from the study."

Safeguards to protect Subjects rights and welfare

All key personnel have been HIPAA trained. All data will be encrypted and stored on secure servers within the hospital data center, with access restricted based on involvement in the project. Patients will also be offered multiple methods of withdrawing participation consent from the study, which includes by phone, email, website, and nursing care.

9. Subjects - Participation

Duration of an Individual Subjects Participation in the Study

During the entirety of their care on 9W, 9E, 10W, 10E

Duration Anticipated to Enroll All Study Subjects

We anticipate, given the current volume of bed movements, that it will take 30 months to complete enrollment.

Estimated Date for the Investigators to Complete This Study Within 3-5 years

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Procedures for Subjects to Request Withdrawal

Subjects may also withdraw from permission for the use and disclosure of any of your protected information for research and can do so by contacting the unit business associate "BA", by email to arash.kia@mssm.edu or by calling to (646) 605-4916 with the information specified in "Waiver Information Sheet" (Appendix 1).

Procedures for Investigator to Withdraw Subjects

The Principal Investigator may stop subject involvement in this research study at any time without subject consent. This may be because the research study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in their best interest, or for any other reason.

"Not participate" or "withdraw" means the alerting will be suppressed/turned off for the patient, their data will not be collected, and no alerts will be sent. Any data or alerts prior to withdrawal will be retained. This information has been added to the consent.

Participants Will Be Recruited Yes

Recruitment Method(s) Clinical Practice

How Participants Will Be Identified

All patients admitted to 10E, 10W, 9E, and 9W

Who Will Initially Approach Potential Participants Clinic Personnel

How Research Will Be Introduced to Participants

Description of the study protocol will be given to participants upon admission to the floor. We will instruct the Business Associate and nursing team members to specifically call to attention to the provided information sheet when a patient is admitted to the unit. We will also post prominent printed notices describing the study throughout the unit (e.g. on the walls near the nursing desk, on any bulletin boards designed for patient communication, etc). Furthermore, if a patient does trigger an alert, the RRT staff will be instructed to notify the patient of the information sheet. Finally, upon discharge, the information sheet would be provided again to the patient as part of their check-out. As such, there exists at least 3 touch points for the patient to discuss the study with a care provider.

How Participants Will Be Screened

Automated screening by the software that generates alerts.

10. Subjects - Risk and Benefits

Risks to Subjects

The MEWS++ alerts will serve to notify the care team of a potential deterioration in a patient's clinical condition. What the provider may choose to do with the MEWS++ alert is left completely to their discretion and we do not propose any determination of care by the MEWS++ alert. As a result, there will be no alteration in the standard of care. All therapeutic interventions will be at the discretion of the care providers and the expected risk of monitoring for select individuals within the interventional cohort should be minimal. The potential risk of breach of confidentiality or loss of protected healthcare information (PHI), will be unlikely as all data will be password protected and any patient identifiers will be encrypted; furthermore, all data gathering will be done on Mount Sinai internal network computers and devices.#

We do not change any workflow for the primary team and RRT. We just increase awareness in the clinicians' mind that a patient may be in danger of deterioration. The primary intervention by the Primary team is simply to increase the frequency of vitalsigns measurement. This will not be associated with any risk or patient safety concerns. We will not remove any of current notifications being received by RRT we will just add one more notification to the current workflow.

One possible risk is alert fatigue. The primary cause of alert fatigue for the RRT team is currently the "Sepsis BPA" generated by Epic, not clinician generated alerts or the alerts that will be generated by this study. The alerting protocol attached to the application was carefully designed to minimize the number of additional alerts. Based on our modeling we anticipate 5 additional alerts to RRT per additional 12-hour shift. This is confirmed by the silent pilot. This was extensively discussed with both nursing and RRT leadership who agreed that the burden of this additional alerting is tolerable. The Sepsis BPA's generate far more alert fatigue. They are being modified to fire less frequently, as part of a non-IRB approved PI/QI changes being made directly by the CMO's office and Epic implementation team, independent of this protocol.

In order to minimize alert fatigue from our alerts, we will be continuously trending the alert burden of the study via the web dashboard and other custom analytic tools. In addition, care provider participants will be polled for their degree of alert fatigue. A review committee will be formed to assess the need to adjust the degree of alerting.

Currently the RRT team and floor nurses are overburdened by Sepsis BPA alerts. Our alerts are more sensitive and more specific and are carefully calibrated to fire less often based on both the retrospective data used to develop the alert and our silent pilot. c. Since the number of alerts is fairly low (5 alerts per 12 hours per floor) and the refractory period can be adjusted automatically based on the clinicians' judgment (see below), we don't believe we will encourage "over testing".

It should be noted that over testing is often a result of inability to ignore results of alerts without perceived medicolegal ramification. By the very fact that our alert is investigational, it would not produce similar concerns.

Inducing a false sense of security is perhaps unavoidable with the introduction of any new monitoring modality. During our education sessions with providers, it will be stressed that MEWS++ is an investigational alert and it should not override clinical judgement. We will have two further mechanisms for soliciting clinician feedback and ensuring a false sense of security is not imbued in the staff. First, we will be in close communication with nursing and RRT leadership throughout the pilot, via check-in meetings initially weekly, and then monthly or as needed throughout the study. Second, the RRT team logs details of every RRT visit to a REDCap database. These data are automatically integrated into our analysis pipeline. We match alerts to RRT calls as part of our performance monitoring. If a deterioration occurs that is missed by our algorithm but seen by RRT, will be able to analyze and understand what factors may have contributed to the miss, and if alert fatigue or a false sense of security contributed to the miss.

Description of Procedures Taken to Lessen the Probability or Magnitude of Risks

No additional data will be gathered beyond that of the standard of care for patients, thus limiting risks of the additional information. The research personnel table lists all personnel who may obtain viewing privileges to the collected data.

Provisions for Research Related Harm / Injury

There is no risk of research related to harm or injury as no therapeutic intervention is made based on the results from this study's evaluation. All participant will receive standard of care interventions.

Expected Direct Benefit to Subjects

As a direct benefit from enrolling in this study, we expect the subjects will be more closely monitored for deterioration in clinical condition and will receive more immediate escalation in care when compared to both historical and matched until controls.

Benefit to Society

We hope that the proposed technology will prove to have a highly sensitive and specificity for predicting individuals who are at risk of clinical deterioration and may require a higher/more intensive level of care. If this does prove to be true, this would be a significant advance to the field of medicine. It would help to reduce death within an inpatient hospital setting.

Provisions to Protect the Privacy Interests of Subjects

By only allowing only members of the investigational team to access PHI we protect subjects' privacy. All study personnel has completed HIPAA training, which ensures the utmost care is used to handle PHI.

Economic Impact on Subjects

There is no economic burden on the patient.

11. Procedures - Narrative

Description of the Study Design

Patients admitted to 10W and 10E meeting the inclusion and exclusion criteria will undergo a modified RRT evaluation protocol as detailed in Appendix 4: Process Flow. In brief, the patient will be evaluated based on our retrospectively validated machine learning algorithm (MEWS++) designed to improve identification of patients who may need care escalation. Patients on 9W and 9E will be followed but no alerts, interventions or changes from standard of care will be pursued. The study is designed to evaluate the equivalence in the proportion of escalations between the standard of care RRT protocol and our proposed ReSCUE-ME protocol. Patients admitted to 9W and 9E will not undergo any additional monitoring and thus will serve as controls.

Further details of the alerting system are listed below.

a. Notifications can be suppressed or re-enabled on a per-patient basis. This is a core feature as it is needed to fulfill the opt-out process that we documented in our application's appendices.

b. Currently there are several automated alerts sent to Vocera. These include ventilator and telemetry alarms, e.g. an alarm if the ECG monitor detects asystole. There is also a simple rules-based Epic BPA for hyperkalemia that sends an alert to the Vocera if a patient's potassium level is high. There is an administrative policy on alarm management that covers these existing alerts - Clinical Alarm Management GPP-242 – link to policy below: http://policies.mountsinai.org/web/general-policies-and-procedures/policies/-/policy-management/viewPolicy/565852/.

c.The maximum number of alerts within the default 8-hour refractory window has been set to 3 in order to minimize alert fatigue. The entire process was carefully modeled in cooperation with a senior operations manager from the hospital process improvement team, with input from the nurse managers on 10E/W and the RRT leadership. The refractory period can also be customized to be shorter based on RRT preference and clinical judgement. The RRT attending simply sends a text message back to the system via Cureator indicating the desired refractory period. Thus, for a very sick patient the refractory period could be set as short as 2 hours.

d. All Nurses on 10E/W will receive in-service training prior to go-live. This is being coordinated with the nurse managers of 10E/W. Members of the research team will be in attendance.

e. Nurses and any other clinician/staff will always be able to call a Stroke Code/Team 7000 at any time.

f. "MEWS++ will run in addition to the current Sepsis BPA. MEWS++ is tuned for deterioration in general, not specifically sepsis. Both MEWS++ and the Sepsis BPA may fire for the same patient at the same time, or within a short interval. If a patient gets a MEWS++ alert and turns out to be Septic, they can be put on the Sepsis Pathway in Epic."

Description of Procedures Being Performed

For each patient, real-time data from the EHR (Epic), the admitting system (Cerner ADT), the ECG (MUSE), and laboratory information systems (SCC) will be used by ReSCUE-ME to produce a MEWS++ score (between 0 to 1) predicting the likelihood that the patient will require escalation of care within the next 6 hours. Upon the patient being admitted to the unit, the patient will be evaluated based on any update in the EMR. If the prediction score exceeds 0.64, the RRT team will be notified directly. If the score is between 0.55 and 0.64, the nursing team will be notified and increased nursing monitoring will be initiated. Otherwise, the patient will undergo re-evaluation with a 8-hour refractory window. If the patient has met criteria for increased nursing monitoring, a refractory 8-hour refractory window will be applied and if the MEWS++ scoring ever exceeds 0.65, the RRT team will be notified. The notification will be processed through Vocera, Connexal and Cureatr, which are hospital approved secure messaging systems. A detailed process flow diagram is provided in Appendix 4.

Description of the Source Records that Will Be Used to Collect Data About Subjects

For each patient, real-time data from the EHR, the admitting system (Cerner ADT), the ECG (MUSE), and laboratory information systems (SCC) will be ingested by the ReSCUE-ME engine and used to generate a prediction score. Additional information provided by the RRT team on the result of the RRT intervention will be extracted from REDCap. These values as specified in Appendix 3 will be processed through the ReSCUE-ME data streaming engine to generate a MEWS++ score for patients who have not been excluded or withdrawn from the study. If an individual withdraws participation from the study, all data pertaining to this patient's current visit will be removed from

ReSCUE-ME. Clinical documents may also be assessed for the purpose of further clarification of events during the RRT intervention.

Description of Data that Will Be Collected Including Long-Term Follow-Up

The data that will be collected during this study include vitals, electrocardiogram, laboratory data, clinical evaluations, and patient demographics from ADT, Epic, MUSE, and Laboratory Information System. A detailed list is provided in Appendix 3. At this time we do not plan on conducting long-term follow-up upon the discharge of the patient from their current hospital visit.

Research Requires HIV Testing No

12. Procedures - Genetic Testing

Genetic Testing Will Be Performed No

Guidance and Policies > Future Use Data Sharing and Genetic Research

13. Procedures - Details

Surveys or Interviews Yes

Type of Instruments Being Used Created By Research Team

Description of Instruments Created By Research Team

A REDCap survey will be created to understand the impact of the alerts on the RRT team. This clinician survey has not yet been developed. We will not do this piece of the research until the survey has been approved by the IRB and the protocol modified appropriately and also approved.

Audio / Photo / Video Recording No

Deception No

Results of the Study Will Be Shared with Subjects or Others No

14. Procedures - Instruments

Instruments Created By Research Team

Type	REDCap RRT survey
Name	REDCap RRT survey
Upload	REDCap RRT Survey Placeholder.docx

15. Procedures - Compensation

Compensation for Participation No

16. Consent - Waiver of Informed Consent

Requesting Waiver For

At the request of the IRB, the principal investigator developed the following opt out process in cases where patients did not want to participate:
Opt-Out Process for ReSCUE-ME
1. Every patient will receive at least one printed copy of the "Waiver Information Sheet" letter at various entry points into the hospital unit:
a. The 9W, 9E, 10W, and 10E business associate will insert a print out of this waiver into their "welcome packet" (a packet of information given to all patients entering any hospital unit) as part of the current standard operating procedure.
2. We will offer to distribute this letter to every hospitalist through Mount Sinai Medicine Department's Division of Hospital Medicine.
4. The opt-out letter will be in English and Spanish.
Educating Nursing and Physicians about the Opt-Out Process
1. An educational conference will be partially devoted to the subject of introducing the study and explaining the scientific background and methods of the research.
a. Medicine Department's Division of Hospital Medicine
b. The Mount Sinai's Institute for Critical Care Medicine
c. Nursing Teams on the participating units.
2. All members of the hospitalist and rapid response care team (attending, residents, and nursing) will be given a script that will be posted on the departmental intranet to give patients information regarding the study.
3. All members of the hospitalist care team and business associates on the participating units will be given instruction as to the procedure for withdrawing patients from the study.
Instructions for Hospitalist Care Team:
1. If the patient has no questions regarding the ReSCUE-ME Study, then proceed as usual.
2. If the patient has questions regarding the ReSCUE-ME Study that you cannot answer, please page one of the investigators listed on the Clinical Data Science group's intranet link for the study. If you cannot obtain an answer quickly for the patient, offer the patient the option of withdrawing from the research.
3. If the patient spontaneously, or after having had questions answered, wishes to withdraw from the research, the provider should submit a request to the http://cds.mountsinai.org/ReSCUEMe website.

Type of Waiver Waiver of Consent

How the Research Involves No More Than Minimal Risks to Participants

All participant subjects will receive standard of care at all times. The MEWS++ alerts will simply inform the clinicians that a patient may be in danger of clinical deterioration, without providing any suggestions on the best course of care. The most appropriate intervention will be determined by the treating clinician.

How the Waiver / Alteration Will Not Adversely Affect the Rights and Welfare of Participants

There will be no alteration to the standard of therapeutic care in the proposed study in either the interventional or non-interventional group. As a result, we don't anticipate any detrimental changes to the welfare of the patient based on the MEWS++ and MEWS scoring and the potential for increased monitoring. Conversely, we expect that ReSCUE-ME will improve patient welfare by improving care.

Why It Is Not Practical To Conduct this Research Without a Waiver or Alteration of Informed Consent

The number of potential patients that need to have consented means that obtaining consent is neither feasible nor practical as it would lead to an overwhelming burden on staffing resources.

Plans for Providing Participants with Additional Pertinant Information After Participation Where Appropriate

The care providers will be contacted during this enrollment period for any clinically relevant information that may arise during analysis, though acting on such information is at the discretion of the care provider. This contact may be through grand rounds presentations, in-service training, email distribution, or other means.

17. Data - Collection

Health Related Information Will Be Viewed, Recorded, or Generated	Yes

Description of Health Information That Will Be Viewed, Recorded, or Generated

The artificial intelligence algorithm will process and analyze data obtained from the EHR and other systems as previously described. The Data Collection Sheet contains the exact list of variables. The algorithm generates a MEWS++ score that is viewable through the EHR by the care provider team.

Non-Health Related Information Will Be Viewed or Recorded	No
HIV / AIDS Related Information Will Be Viewed or Recorded	No
Data That Will Be Viewed, Recorded, or Generated Contains ANY of the Following Directly Identifiable Information	Yes
Will Be Viewed	Medical Record Number
Will Be Recorded	Medical Record Number
Data Collection Sheet	DataElements.xlsx

A Data Collection Sheet is required if you are either performing a retrospective review, or your study meets the category of exempt 4 research, or your study meets the category of expedited 5 research. Please upload it here.

Data Collection Source(s)	Medical Chart (Paper or Electronic), Data Warehouse

18. Data - HIPAA

Obtaining HIPAA Authorization No

Requesting Waiver or Alteration Waiver

Research Could Be Practicably Conducted Without Access to and Use of Protected Health Information (PHI) No

Explanation Why Research Could Not Be Practicably Conducted Without Access to and Use of PHI

In order for a MEWS++ alert to be of value, the provider needs to know the identity of the patient for whom the alert was generated. Thus the alerting system needs to know the identity of the patient as well.

Explanation Why Research Could Not Be Practicably Conducted Without a Waiver or Alteration of Authorization

It is neither practical nor feasible to consent over 18,000 individual patients. Additional details on why we are requesting a waiver can be found under the "Consent" section of this IRB application.

How PHI Will Be Protected from Improper Use or Disclosure

All PHI will be stored in secure, password protected servers that can only be accessed by authorized members of the study team. All study personnel have completed HIPAA and human subjects research training, which ensures utmost care is used to handle PHI.

PHI Will Be Destroyed at the Earliest Opportunity Consistent with the Research Yes

When and How PHI Will Be Destroyed

Data are stored in accordance with the data retention policy of the manuscript in which the results will be published. This may vary by publication but is generally 7 years. Data will be destroyed by overwriting the disk sectors used to store the data with 0s.

PHI Will Be Shared No

PI must attest to the following.

**** I assure that the protected health information (PHI) will not be disclosed to any other person or entity not listed on this form except where required by law or for the authorized oversight of this research project. If at any time I want to reuse this PHI for other purposes or disclose it to other individuals or entities I will seek approval from the IRB.***

19. Data - Storage

Location Where Data Will Be Stored

Secure servers within the hospital data center.

How will the data be stored? Other

Specify How Data Will Be Stored

All data are will be stored within an encrypted, password protected database. The servers can only be accessed via Secure Shell or HTTP-Secure technology requiring a password or military-strength encryption key. Local system firewalls and operating system security patches are kept up-to-date on an ongoing basis. The access to this data will be reviewed on a quarterly basis and any identified breaches will be reported in accordance with HIPAA compliance. Data will also be encrypted during transit among the components of the real time alerting system.

Research Personnel Responsible for:	Matthew Levin
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Shan Zhao
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Rohit Gupta
Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Jennifer Wang
Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Robert Freeman
Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Roopa Kohli-Seth
Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Sanam Ahmed

Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Mirhadi Arash Kia
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Prem Timsina
Accessing Data	Yes
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Surafel Tsega
Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Benjamin Kummer
Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No
Research Personnel Responsible for:	Michael Kitz
Accessing Data	No
Receipt or Transmission of Data	No
Holding Code That Can Be Linked to Identity of Participants	No

Duration Data Will Be Stored

Data are stored in accordance with the data retention policy of the manuscript in which the results will be published. This may vary by publication but is generally 7 years.

Steps That Will Be Taken to Secure the Data During Storage, Use, and Transmission

Only the designated investigator and co-investigators as listed on this form will have access to patient data used in this study and will be the sole arbiters for receipt and transmission of this data. The data will be password protected on Mount Sinai computers. Data are encrypted both at rest (i.e., when stored in the database) and while in motion (i.e., during transit between various components of the alerting system) using industry standard encryption protocols. Data will only be accessed from within the Mount Sinai network to ensure confidentiality, which is also password protected and physical access restricted. Any presentation will separate the presented material from the associated identifiers. All individuals have completed institutionally approved HIPAA training.

Power Analysis/Data Analysis Plan (Including Any Statistical Procedures)

Sample size calculation

Based on the pilot feasibility study, the current true rate of escalation of care in the selected units is ~ 10%. We expect that MEWS++ will identify at least 50% of the escalations, on average ~ 6 hrs before the expected time of deterioration/escalation. It is estimated that RRT and front-line providers collaboratively will be able to prevent ~ 20% of the predicted escalations. We are specifying a non-inferiority or superiority margin of 5%. As a result, the estimated sample size needing to achieve a type 1 error of 5% and power of 95% is 934. based on the rate of escalation ~ 10%, a total of approximately 9340-bed movements will need to be recruited for this study in the MEWS++ group and a total of 18680-bed movements across both groups. We assumed that there is not a significant

difference in the escalation rate between the selected units (10E and 10W) and control units (9E and 9W). Interim evaluations every 6 month will be conducted and if at any point the model meets statistical significance or major flaws identified, a subsequent report will be submitted.

Statistical Analysis:

#The basics of generating a MEWS++ score, the sources of the data and where the results will be made available to the floor patient care providers is described under "Procedures > Narrative" section of this IRB. Briefly, a random forest model has been trained to generate a prediction score based on 36 clinical variables. This score represents the likelihood of clinical deterioration. For all interim reports, final study outcome report, and publication analysis our research team plans to use an array of parametric and non-parametric statistical approaches to evaluate the significances of the primary and secondary endpoints. These would include, but not limited to binomial proportion tests, students t-tests, Mann-Whitney U test, Fisher's exact test, and ANOVA. Additionally, we plan to examine any potential significant difference in the demographics of the patients admitted to 10W and 10E when compared to 9W and 9E, significant differences will be incorporated into a multi-variant model such as a linear/logistic regression model to further elucidate factors that may have confounded the # of RRT evaluation and escalation events.

20. Data - Safety Monitoring

More Than the Minimum Data Safety Monitoring Will Be Done No

The following minimum requirements apply to all projects, including retrospective reviews of medical records, use of tissue samples, and many minimal risk studies, such as observational and survey research. Because these minimum requirements apply to all studies, a specific written DSMP will not usually be required for projects that do not pose greater than minimal risk to subjects. The MSSM PPHS may alter the required level of monitoring if appropriate.

For all projects, the principal investigator must have a plan to assure that data integrity will be maintained during its collection, storage and analysis. All research projects must adhere to MSSM recommendations on the storage of research data. Loss of data containing identifiable information is reportable to the IRB within 5 business days.

Any problems concerning the consent process and any subject complaints should be monitored by the investigator. Reports of such problems must be made at least annually. The discretion of the protocol director will guide the need to report these problems immediately or more frequently.

The principal investigator is, typically, the monitoring entity for the minimum DSMP. When a principal investigator is not a faculty member, the supervising faculty member must be responsible for the data and safety monitoring aspect of the protocol.

Will the Research Include Data Coordinating Center Activities? No

21. Financial Administration

This information will help the Financial Administration of Clinical Trials Services (FACTS) office determine whether a Medicare Coverage Analysis (MCA) is needed for the research study. If you have any questions while completing this form, please contact the FACTS office at (212) 731-7067 or FACTS@mssm.edu.

Clinical Research Study Category Investigator Initiated

Payment Options:
**** Option 1: No protocol-required services will be billed to patients or third-party payers. Does Not Need MCA***
**** Option 2: Protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Must Have MCA***
**** Option 3: Study is initiated and federally funded by a Government Sponsored Cooperative Group who will only pay for services that are solely conducted for research purposes and other protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Billing Grid Only Required, NO MCA***
**** Option 4: Study involves only data collection and has no protocol-required clinical services. Does Not Need MCA***
**** Option 5: Study is not described in any of the above options. Please describe the study and specify whether External Sponsor (i.e., industry, government, or philanthropic source) and/or patient/third party payer will pay for protocol required services. MCA MAY Be Required***

Payment Option Option 4

No MCA is needed per option selected above.

22. Attachments

Type	Name	Version	Status	Filename	Uploaded Date
Data Collection Sheet	Appendix 3 - DataElements.xlsx	1	New	DataElements.xlsx	03/04/2019
Other - Other IRB Correspondance	Appendix 2a - RESCUE ME Opt-out Request Handling Procedure.docx	1	New	Appendix 2a - RESCUE ME Opt-out Request Handling Procedure.pdf	03/05/2019
Other - Other IRB Correspondance	Appendix 2b - Specification for Opt-out Computer Program.docx	1	New	Appendix 2b - Specification for Opt-out Computer Program.docx	06/11/2019
Other - Other IRB Correspondance	Appendix 4a - Notification Process Primary.pdf	1	New	Appendix 4a - Notification Process Primary.pdf	03/05/2019
Other - Other IRB Correspondance	Appendix 4b - Notification Process RRT.pdf	1	New	Appendix 4b - Notification Process RRT.pdf	03/05/2019
Other - Other IRB Correspondance	Appendix 5 - HRP416 Waiver of Consent Documentation	1	New	Appendix 5 - HRP416 Waiver of Consent Documentation.pdf	04/25/2019
Other - Participant Educational Materials	Appendix 1a - Waiver-Consent Information Sheet-CASES.docx	1	New	Appendix 1a - Waiver-Consent Information Sheet-CASES.docx	06/11/2019
	Appendix 1b - Waiver-Consent Information Sheet-CONTROLS.docx	1	New	Appendix 1b - Waiver-Consent Information Sheet-CONTROLS.docx	06/11/2019
Instruments	REDCap RRT Survey Placeholder.docx	1	New	REDCap RRT Survey Placeholder.docx	06/11/2019

Final Protocol

The final protocol was the same as the original protocol. No changes were made to the protocol during the study period.

Original Statistical Analysis Plan
As submitted to the IRB Mar-June 2019

For all interim reports, final study outcome report, and publication analysis our research team plans to use an array of parametric and non-parametric statistical approaches to evaluate the significances of the primary and secondary endpoints. These would include, but not limited to binomial proportion tests, students t-tests, Mann-Whitney U test, Fisher's exact test, and ANOVA. Additionally, we plan to examine any potential significant difference in the demographics of the patients admitted to 10W and 10E when compared to 9W and 9E, significant differences will be incorporated into a multi-variant model such as a linear/logistic regression model to further elucidate factors that may have confounded the # of RRT evaluation and escalation events.

Final Statistical Analysis Plan
December 2021

Data from the first hospitalization for each patient during the study period were included in the study. The analyses focused on patient level, unit level, and alert level, individually. All variables were summarized using the appropriate descriptive statistics. Continuous variables were presented as mean (standard deviation) or median [interquartile range], as appropriate. Two-sample t test was used to examine differences in means and Kruskal-Wallis test was used to assess differences in median between study arms. Categorical variables were presented as count (percentage). Chi-square test was used for categorical variables associated different study arms.

Patient Level Analysis

Study arm at admission was used to define the treatment group throughout the patient level analysis. The intervention group referred to the patients initially assigned to the MEWS intervention, and the control group referred to the patients initially assigned to the non-MEWS intervention. Propensity score modeling with inverse probability of treatment weight (IPTW) was used to account for differences in baseline characteristics for patients between two treatment groups. To reduce influence from extreme weights, we used stabilized weights, where the weight for a MEWS subject was the proportion of subjects receiving MEWS divided by the subject's propensity score, and the weights for a non-MEWS subject was the proportion of subjects receiving non-MEWS divided by one minus of the respective propensity score. These weights were then incorporated into all subsequent analyses.

IPTW Negative binomial regression models were used to model the count data during the entire hospital stay, including the total number of RRT alerts, escalations, blood pressure support, medical orders, laboratory orders, and all orders. Treatment effect is expressed in terms of the adjusted ratio of the two counts between the intervention group and the control group. IPTW Logistic regression models were used to model the binary outcomes, including death within 30 days after admission, death in hospital, ever being escalated, and whether any medical or laboratory orders were ordered. Treatment effect is expressed in terms of the adjusted odds ratio. IPTW Cox proportional hazard regression analysis was used to assess the association of study arm with hospital length of stay. The hazard ratio is used to describe the relative probability of hospital discharge at a given time. A hazard ratio >1 is associated with a shorter hospital stay. As a confirmatory analysis, we also performed the regular covariates-adjusted regression analysis using the same set of predictors used in the propensity score model.

Alert and Unit Level Analysis

At the alert level, the status of ICU escalation, whether a type of medical order or laboratory order is placed, and the total number of medical orders and laboratory orders following each alert were summarized. The descriptive summary of alert level analysis was also performed for the subset of RRT alerts and primary alerts. Confusion matrices were used to analyze the performance of RRT alert versus none alert and any alert (rrt alert or primary alert) versus none alert, individually, in association with actual escalation and actual escalation to ICU within MEWS arm where all patients received MEWS escalation monitoring and provider alerting. In the floor unit level analysis, escalation status, ICU status, alert levels, and the total number alerts were summarized.

Statistical Analysis Plan Summary of Changes

Primary outcome

Analysis was limited to first hospitalization. For patients who had crossover between intervention and control arms, treatment group was determined by initial study arm from the first unit admission. Inverse probability of treatment weight was chosen as the method to account for differences between treatment arms.

Secondary outcomes

The analysis of the secondary outcomes was modified as follows:

Secondary Outcome Number	Secondary Outcome Description	Modification
3	**Number of participants requiring respiratory support**	This outcome was removed due to too few events. Only 20 respiratory therapy orders were placed across both intervention and control groups.
4	**Number of cardiac arrest episodes**	This outcome was removed due to too few events. There were no episodes of cardiac arrest.
5	**Mortality Rate**	This was further clarified to be combined in-hospital and 30-day mortality.
6	**Notification Frequency**	This outcome was removed. As implemented, the number of alerts generated per patient was capped at 3 per unit admission in both arms.
7	**Number of calls**	This outcome was removed. It was intended to measure the number of calls to RRT initiated by clinicians independent of the alert system. Low data quality in the separate RRT call tracking system made the data unusable.

Ad-hoc outcomes

The following ad-hoc outcomes were added:

1. Likelihood of ICU escalation within 12 and 24 hours
2. Likelihood of earlier hospital discharge