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Formative Evaluation of Emergency Department Clinical Decision Support for Agitation Symptoms: A Study Protocol

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ABSTRACT

Introduction

The burden of mental health related visits to emergency departments (EDs) is growing, and agitation episodes are prevalent with such visits. Best practice guidance from experts recommends early assessment of at-risk populations and pre-emptive intervention using de-escalation techniques to prevent agitation. Time pressure, fluctuating work demands, and other systems-related factors pose challenges to efficient decision-making and adoption of best practice recommendations during an unfolding behavioral crisis. As such, we propose to design, develop, and evaluate a computerized clinical decision support (CDS) system, "Early Detection and Treatment to Reduce Events with Agitation Tool," (**ED-TREAT)**. We aim to identify patients at risk of agitation and guide ED clinicians through appropriate risk assessment and timely interventions to prevent agitation with a goal of minimizing restraint use and improving patient experience and outcomes.

Methods and Analysis

This will be a formative evaluation of the health-record embedded CDS tool through three phases of iterative development and refinement. We will first (1) apply user-centered qualitative methods such as contextual inquiry and focus groups to assess needs of key stakeholders (ED physicians, nurses, technicians, and patients with lived experience of restraints and behavioral crises) to identify essential user requirements, (2) usability testing with "think-aloud" and simulation sessions, and (3) field testing in the clinical environment. Next, we will conduct a pilot randomized controlled trial at two sites within our health system to evaluate feasibility, fidelity, and bedside acceptability of the intervention prototype.

Ethics and Dissemination

Ethical approval by the Yale University Human Investigation Committee was obtained in 2021 (HIC# 2000030893 and 2000030906). All participants will provide informed verbal consent prior to being enrolled in the study. Results will be disseminated through publications in open-access, peer-reviewed journals, via scientific presentations, or through direct email notifications. The pilot trial was registered on clinicaltrials.gov (NCT04959279).

ARTICLE SUMMARY

Strengths and Limitations of this Study

- This is one of the first studies to develop and evaluate a clinical decision support (CDS) system to facilitate management of agitation in an acute care setting.
- Our tool will include pragmatic strategies to implement best practice recommendations for risk assessment and timely de-escalation techniques in agitation management *prior* to definitive psychiatric treatment.
- The CDS design process will follow an iterative, user-centered approach with feedback from end-users at every step to refine and develop an electronic health record-embedded, fully functional prototype.
- Our risk assessment data, qualitative design, and pilot trial will arise from the same geo-political area and health system, which may limit generalizability.

INTRODUCTION

Behavioral health related visits to emergency departments (EDs) are growing.[1-3] Agitation, defined as excessive psychomotor activity leading to aggressive and violent behavior,[4] is a frequent symptom of such visits. An estimated 1.7 million agitation episodes occur annually in EDs across the United States alone.[5,6] When an individual becomes agitated, they may cause harm to themselves, hospital staff, and property.[7-9] Rapid management of agitation is imperative and use of physical restraint may be necessary to facilitate patient assessment and prevent injury.[5] Although physical restraints are routinely used in the ED,[10,11] they are associated with up to 37% risk of injury in patients, including blunt chest trauma, asphyxiation, respiratory depression, to sudden death.[12-17] To address these challenges, the American Association for Emergency Psychiatry sponsored Project BETA (Best Practices in Evaluation and Treatment of Agitation).[18] Project BETA was a pioneer effort to create a comprehensive list of five sets of best practices for preventing and managing agitation through multidisciplinary consensus panels. Key strategies within Project BETA included use of structured risk assessment[4] to help clinicians screen patients at risk of developing agitation and pre-emptive intervention using behavioral techniques,[19] environmental modification,[20] and consensual use of medication therapy[18] to obviate use of restraints.

Despite these established best practice recommendations, multiple systems level barriers challenge their practical implementation.[21-23] Care delivery in the ED occurs in a uniquely complex environment. Clinical decisions are made under time pressure, using limited information, and amidst multiple and frequent interruptions and other unpredictable factors due to the dynamic course of acute, undifferentiated conditions.[24] As burden on the emergency care system rises in the U.S.,[25-28] these systems-level challenges are particularly relevant for patients at risk for agitation, as behavioral and de-escalation techniques require investment in time and effort to build a strong rapport and trusting therapeutic relationship with the patient. Given that clinicians may have difficulty accurately identifying patients at risk for agitation and access to expert psychiatric evaluation in such settings may be limited,[29-32] there is a significant mismatch between resources available and application of those resources to individuals who would most benefit from early risk assessment and intervention. A recent prospective study observing 100 at-risk patients in the ED found that over 60% of individuals develop agitation more than 30 minutes into their visit,[33-35] presenting opportunities to prevent agitation earlier in the course.

Clinical decision support (CDS) tools can help address systems-based challenges, facilitate risk assessment, and guide clinicians to use best practices strategies recommended by Project BETA in the

ED. CDS tools show increasing promise in the emergency setting to help clinical staff identify high-risk patients and provide more efficient and higher quality of care,[36] including individuals requiring use of high-cost imaging[37] and older adults.[38-41] A CDS system encompasses any on-screen tool designed to improve healthcare delivery by enhancing medical decisions with targeted clinical knowledge, patient data, and other health-related information.[42] Use of a CDS tool to assist in assessment and management of potentially agitated patients may be an effective strategy in the ED.[40,43,44]

Rationale and Aims of Study

This study is one of the first that aims to prevent agitation and improve outcomes for ED patients with agitation. We will achieve this by (**Figure 1**):

1. Designing and developing an EHR-embedded, user-centered, CDS system, "Early Detection and Treatment to Reduce Events with Agitation Tool" (**ED-TREAT)**, using a contextual design approach to obtain input from key stakeholders and iterative user-centered design process; and

2. Conducting a pilot study to evaluate the feasibility, fidelity, and bedside acceptability of ED-TREAT. ED-TREAT aims to help ED staff and clinicians to identify patients at high-risk for developing agitation, guide them through appropriate risk assessment and efficient decision-making to implement best practice recommendations to prevent development of agitation, and minimize use of restraints.

We hypothesize that, with the use of ED-TREAT, ED staff will be able to identify at-risk individuals, conduct appropriate risk-assessment, implement interventions to minimize use of restraints and improve patient experience and outcomes related to agitation management in the ED. If this study is successful, a planned subsequent clinical effectiveness trial will compare effectiveness of ED-TREAT to usual care across multiple ED sites in the future. The long-term goal of this CDS tool is to increase fidelity with best practice recommendations for prevention of agitation through early use of behavioral techniques prior to onset of agitation.

METHODS AND ANALYSIS

Patient and Public Involvement

We invited patients to help us design, develop, and test the intervention so that it is designed to improve the public good and help individuals with lived experience of mental illness and behavioral crises. In addition, we will solicit patient feedback and guidance on dissemination of study results to participants and the local community through networks at our affiliated community-based organizations that have had sustained engagement with our team for several years to implement a research agenda in agitation care that is patient-centered and recovery-oriented.

Aim 1: Developing and Refining ED-TREAT

With the goal of developing a final prototype that maximizes usability, staff self-efficacy, satisfaction, and patient-centered care, ED-TREAT will be designed, developed, and refined in three phases (P1-P3) (**Figure 2**). During phase 1 **(**P1), we will conduct a needs assessment to collect input from key stakeholders including ED physicians, nurses, patient care technicians, behavioral health experts, informatics experts, and patients with lived experience of being in restraints in the ED. We will combine needs assessment findings with Project BETA recommendations for agitation management in the ED[5] and risk factors for agitation from the literature to design an initial prototype. Next, in phase 2 (P2), we will conduct formative usability testing, which will consist of "think aloud" protocols, a standard usability procedure for CDS design[45], with clinician users and standardized patients in a controlled simulation setting to guide further modifications of the tool in an iterative fashion. Finally, in phase 3 (P3), we will conduct field testing in the ED through observational workflow analyses to identify and address barriers in the real-world clinical environment.

Participant Recruitment

We will design ED-TREAT for use by staff members that work mostly closely with agitated patients in the ED.[7,35,46-48] These consist of ED physicians, nurses, and patient care technicians. We plan to recruit these staff participants via email and biweekly staff meetings. In addition, we will also recruit patients with prior lived experience of being restrained in the ED to solicit their input and ensure that patient-centered practices are considered during the design process. We will recruit these patients from the pool of peer support workers from local community-based recovery organizations via email and presentations at monthly staff meetings. These peer support workers have a history of mental health and substance use disorders and have received training to become employed as patient advocates on community-based

treatment teams. Finally, our design team will interview informatics and behavioral health experts to solicit ideas and relevant CDS design strategies to improve decision-making during agitation management.[49,50]

Phase 1: Needs Assessment and Initial Design of ED-TREAT

We will conduct focus groups and observations starting June 2023 via a contextual inquiry[36] approach. This approach seeks to engage prospective users and participants described above to understand clinical workflow, roles of different members of the patient care team, and thought processes involved in managing a behavioral health crisis in the ED. We will first conduct in-depth qualitative interviews with staff and patient participants using a semi-structured interview guide that will include open-ended questions to cover topics (**Supplemental Table 1)** related to application of Project BETA recommendations in preventing agitation and user-centered design.[37] Each focus group will consist of 2-5 participants from the same stakeholder group and be approximately 60 minutes duration. Sessions will be audio recorded after obtaining participant verbal consent. In addition, members of the design team will conduct observation sessions in the ED to observe ED staff during real-life agitation management events. These sessions will provide information about environmental and systems contexts, interactions amongst members of patient care team during an active agitation episode, logistics of integrating CDS tool into EHR workflow to facilitate clinical decision-making.

After identifying crucial user requirements in P1, we will develop an initial low-fidelity prototype for ED-TREAT. This will occur in collaboration with EHR analysts and informatics experts by incorporating Project BETA recommendations for preventing and managing agitation[5] and potential risk factors for agitation to identify potential at-risk patients in the ED. These risk factors (**Supplemental Table 2)** will be based on existing literature on risk factors for agitation and workplace violence in the healthcare setting[4,42,51] our team's prior work on agitation management in the ED,[48] patient perspectives of ED visits resulting in restraint use,[52] characterization of physical restraint use among adults presenting to the ED with agitation,[11] and attributes and levels of agitation impacting thresholds for restraint use in the ED.[34,35]

Preliminary work by our team has shown that identifying risk factors for agitation and implementing EHR-based interventions for agitation are feasible in the emergency setting.[46] The CDS will extract patient specific data on variables of interest from existing patient chart data via EPIC's Cogito analytics performance suite.[53] Based on current expert recommendations from Project BETA[46], we anticipate that

ED-TREAT will likely stratify patients into three risk groups (**Table 1**) and recommend increasing levels of resource utilization and pre-emptive management as the risk level increases based on best practices for preventing agitation from Project BETA. Depending on results from the needs assessment, ED-TREAT's recommendations may include automated order sets for medication therapy, staff instructions and communication orders, and templated clinical documentation. Our team will collaborate with EHR analysts to create an initial interactive prototype within the EHR testing environment, "Epic Playground", a non-production, functional, simulated EHR replica used for developing and validating new workflows. We anticipate that our final product will be an EHR-integrated web application through a dedicated graphical Application Programming Interface.[54]

Table 1: Sample elements of initial ED-TREAT prototype

Risk Level	Project BETA[5] guidelines	Recommended tasks
Negligible	(1) Medical evaluation & triage[13]	• Medical history & physical exam • Early vital signs and fingerstick glucose • Address psychosocial needs & establish rapport • Standardize assessment to avoid structural biases/inequities
Mild to moderate	(2) Psychiatric evaluation & risk assessment[55] (3) Psychopharmacology[18]	Tasks in negligible risk level PLUS: • Measure Behavioral Activity Rating Scale (BARS)[56] • Offer voluntary oral medication (with allergies cross-checked)
High	(4) Environmental modification (avoidance of restraint & seclusion)[20] (5) Verbal de-escalation[19]	Tasks in mild to moderate risk level PLUS: • Alert clinician early (from triage/nursing assessment) • Pre-emptive verbal de-escalation (ten domains) • Move to quiet, low activity/volume area

Phase 2: Usability Testing of ED-TREAT

Heuristic Evaluation

We will first perform heuristic evaluation[57] of CDS interface usability before testing with clinician participants. This will consist of an expert team of three evaluators with experience in emergency medicine as well as CDS design who will navigate through different aspects of the CDS and judge the compliance and usability of the tool in agitation management triangulated between their expertise and usability standards. Each evaluator will inspect the interface and assess the guidelines and recommendations provided by the CDS for various levels of agitation. After individual assessment is completed, we will debrief as a group and aggregate the results of each evaluator to examine deficiencies

in the prototype design. After addressing concerns and refining the prototype CDS tool, we will conduct further usability testing with clinicians in simulated training protocols.

"Think Aloud" Protocol

Next, our team will perform one-on-one "think aloud" protocol[45] sessions with clinician users in a quiet office at the EHR training classroom. We will ask participants to perform designated tasks with ED-TREAT using mock patient charts in Epic Playground and "think aloud" how they would use ED-TREAT to test whether the user understands and is using the CDS as intended. We will develop a facilitator guide that focuses on domains related to usability of the prototype and design of the CDS interface (**Supplemental Table 3**). We will video-record each usability testing session, incorporating user screen captures and field notes[58] taken during the session. At the end of the session, each participant will complete the System Usability Scale[59] to measure perceived usability of and satisfaction with a health informatics tool. The System Usability Scale is a widely used and effective survey composed of ten statements assessed on a 5-point Likert scale, with inter-item correlations of 0.69-0.75 and a reliability coefficient α of 0.91.[60] Each session is expected to take 30 minutes.

Simulation Sessions

Additionally, we will observe the clinical team in a simulation session with a live actor or mannequin simulating being an agitated patient. Participants will be briefed on how the CDS tool works and will be encouraged to use it at various points in the care process. We will similarly video-record each session and distribute the System Usability Scale to gather participant feedback. We will make iterative refinements to the prototype until the team reaches consensus that it has reached a threshold level of usability.

Phase 3: Field Testing of ED-TREAT

We will recruit staff participants working in the ED for field testing of the ED-TREAT prototype through observational workflow analysis of ED visits with mild-moderate or high risk of agitation (**Table 1**). We will develop an observational guide based on sample topics of usability testing (**Supplemental Table 3**) that will detail both the workflow of managing an at-risk patient and barriers to adopting ED-TREAT in the clinical environment. Field notes will detail events, actions, and their time and duration,[58] while maintaining an open-ended format to describe and follow variations or workarounds in workflow. Either

the PI or a trained research associate will complete the observations as an unobtrusive non-participant observer through a patient's visit from ED arrival to patient disposition, similar to procedures we developed for prior observations of agitation.[34,35] We will enter field notes using a portable electronic tablet into a word document for free text and a spreadsheet for data elements.

Data Analysis

In P1 (design and development), our team will use the iterative and phased approach of building an affinity diagram, a commonly used organizational tool that allows large numbers of ideas stemming from brainstorming and qualitative data to be sorted into groups, based on their natural relationships, for review and analysis.[61,62] Following completion of each focus group and contextual inquiry session, we will conduct an interpretation session to review the user-provided key notes from the inquiry session and capture them as affinity notes.[63] To help identify common issues, work patterns, and needs, we will arrange the affinity notes into hierarchical categories ("must-have," "good to have", and "nice to have") based on common themes in the data to create an affinity diagram.[63] Building of the affinity diagram will occur online using Miro software (RealtimeBoard, Inc, San Francisco, CA, United States).[64] We will mock up a low fidelity prototype of ED-TREAT based on current best practices and iteratively refine it based on user data from P1.

For P2 (usability testing) and P3 (field testing), field notes will be analyzed using a deductive coding method to conduct directed content analysis[65] based on predetermined usability requirements and recommended tasks from ED-TREAT (**Supplemental Table 3**).[66] We will use Dedoose (SocioCultural Research Consultants, Manhattan Beach, CA, United States),[67] a collaborative and cloud-based qualitative software package, for thematic analysis and data organization of transcripts. Codes identifying suboptimal or deficient performance of the prototype will uncover critical system factors impacting adoption and usability that need optimization and adjustment. Two trained reviewers will perform independent coding and we will calculate inter-rater reliability assessments with kappa scores. For the System Usability Scale,[59] participants' scores from each question of are added together and then multiplied by 2.5 to convert the original scores to continuous data from 0-100. Scores will be described using mean and standard deviation and >85 will be indicative of excellent usability.[68] We will use the results generated from this analysis process at each round of revisions to make appropriate adjustments to the ED-TREAT prototype in close collaboration with the EHR analyst team until we derive a final deliverable prototype that will be ready for the pilot trial.

Sample Size

We will use purposive sampling[69] to ensure the full spectrum of perspectives for clinicians who will engage with ED-TREAT and peer support workers who have had experience as patients in the ED. We will conduct data collection until reaching thematic saturation,[70] when new concepts no longer emerge from iterative analysis of the data.[71] For initial design (P1), we anticipate that this will occur after five to six focus groups with six participants (staff and patients) in each focus group.[72] As enrollment of 10-12 subjects can identify up to 90% of usability problems,[73] we will perform usability testing (P2) for approximately five participants in each round of refinement and expect about three rounds of refinement (15 participants total) as per our prior published work.[74] For field testing (P3), we plan to observe eight patient encounters to detect any usability problems when deployed in the ED.

Aim 2: Pilot Trial and Feasibility Testing for ED-TREAT

We will conduct a pilot randomized control trial for ED-TREAT to compare the intervention to usual care. This will allow us to evaluate acceptability of the intervention to its end-users (ED staff), fidelity of its intended outcomes to identify at-risk individuals and prevent agitation, feasibility of randomization, ease of subject enrollment, and measurement of other outcomes of interest. This will be a mixed methods study, wherein we will quantitatively measure usability and efficiency of clinical decision-making via the System Usability Scale[59] and specific patient outcomes, as well as qualitatively assess the effect of ED-TREAT on clinical workflow and patient care. In addition, this pilot trial will (1) test the integrity of the study protocol in preparation for a future comparative effectiveness clinical trial, (2) evaluate randomization protocols, (3) estimate rates of recruitment and retention of trial subjects, and (4) estimate effect size for sample size calculation in the subsequent trial.[75] Pilot trials[76] are not designed to test the efficacy of the intervention, but will help establish acceptability and feasibility in preparation for a future multicenter RCT. We hypothesize that it will be feasible to implement the tool, measure identified outcomes, be acceptable to its end-users, and work as intended.

Study Setting, Participants, and Randomization

We will conduct the pilot trial at two adult ED campuses that belong to a large regional healthcare system in the Northeast United States, with a planned trial start date in the Fall of 2024. Prior to initiation of the

pilot trial, all emergency physicians, ED nurses, and ED patient care technicians at both campuses will receive an email introduction and a link to a brief training regarding the use of ED-TREAT. Eligibility criteria for patients and recruitment will include ability to provide verbal consent for the study and a score of "4" (quiet and awake; normal level of activity) or less on the Behavioral Activity Rating Scale (BARS),[56] an accepted seven-point scale to assess levels of agitation in acute care settings. We will first perform screening for eligibility via an ED-TREAT administrative interface that performs risk assessment for each ED patient on arrival. A research associate will then approach eligible patients and their designated clinician team members for enrollment after confirming ability to consent and assessing patient BARS scores as close to the beginning of the visit as feasible. Study procedures, risks/benefits of participating, and the purpose of ED-TREAT will be described, and verbal consent will be obtained for patients and staff participants. Since we plan to enroll patients prior to onset of agitation, we anticipate that most patients should be able to engage in decisions and provide verbal consent. Our prior work found that >70% of ED patients with subsequent agitation arrived with a normal mental status and BARS scores ≤ 4.[34,35] We will perform 2:1 randomization at the patient level and also recruit a higher proportion of high-risk patients in each arm, as a primary aim of the pilot trial is to test the acceptability of ED-TREAT and we anticipate that our intervention will recommend more tasks for high-risk patients. Randomization will occur using sequentially numbered, opaque, sealed envelopes that will only be opened by the research team member after enrollment of each patient. In the intervention group, ED-TREAT will automatically launch as part of the clinical team's workflow in the EHR after randomization. We anticipate that critical steps in ED-TREAT will occur at four stages of a visit (**Figure 3)**: (1) at initial arrival with automated risk stratification using pre-determined criteria set during the CDS design process; (2) at triage assessment; (3) at initial nurse interaction; and (4) at initial clinician interaction. In the control group, ED-TREAT will notify the research team regarding the patient's risk group but will not launch for the clinical team's interfaces.

Data collection

Our anticipated data collection strategy is summarized in **Table 2**. In addition to visit characteristics (system factors, relevant clinical data) collected through the EHR during the visit, we will collect acceptability and fidelity measures, feasibility assessment, and potential outcomes of interest for each visit.

Acceptability & fidelity. For all clinicians caring for patients in the intervention group, we will administer the System Usability Scale (SUS)[59] either in person at the end of the ED visit or within 72 hours by email. In addition, we will perform observation workflow analyses as described earlier using a task checklist to determine if clinicians were using ED-TREAT as intended, and if any barriers or unintended consequences occurred because of the intervention. We will perform brief, semi-structured interviews with patients either at the end of a visit or within one week after disposition to evaluate the impact of ED-TREAT on their experiences.

Feasibility. To assess the feasibility of a comparative effectiveness trial, we will evaluate the following at three-month intervals: 1) available number of potential subjects (# of eligible patient visits), 2) subject identification (% of eligible patients/staff approached), 3) enrollment (% of patients/staff with consent to enroll), and 4) retention (% of visits with completed outcome measures). We will also conduct brief, semi-structured interviews with staff participants to evaluate their experiences with ED-TREAT and effect on clinical workflow.

Outcome measures. The anticipated primary outcome of the comparative effectiveness trial will be the presence of a physical restraint order during the ED visit (> 30 minutes after arrival). Additional secondary outcomes include the presence of an intramuscular chemical sedative order, highest level of agitation on the Behavioral Activity Rating Scale (BARS)[56] during visit, disposition, and length of stay.

Table 2. Anticipated data collection for ED-TREAT pilot trial

Measure	Tool or strategy	Timing of measurement
Visit characteristics		
System factors	EHR (e.g., staff traits, National ED Overcrowding Scale)[77]	During & end of visit
Clinical data	EHR/ED-TREAT (e.g., risk category; see also Table 2)	During & end of visit
Acceptability, fidelity		
Clinician acceptability of ED-TREAT	System Usability Scale[59] (satisfied, useful)	End of visit
Fidelity of ED-TREAT	Observational workflow checklist (perform as intended)	During visit
Effect on patient experience	Qualitative interviews with patients	End of visit or <72h after visit
Potential bias or differential treatment	Implicit Association Test (for clinicians), patient interviews	End of visit or <72h after visit
Feasibility		
Available subjects	# of eligible visits	Every 3 months
Subject identification	% eligible visits approached	Every 3 months
Enrollment	% visits with consent to enroll from patient/clinical staff	Every 3 months
Retention	% visits with completed measures	Every 3 months
Effect on clinical workflow	Qualitative interviews with clinicians	Every 3 months
Outcomes		

Physical restraint order	EHR	During & end of visit
Intramuscular chemical sedative order	EHR	During & end of visit
Level of agitation	Behavioral Activity Rating Scale (BARS)[56]	Highest level during visit
Disposition	EHR	End of visit
Length of stay	EHR	End of visit

Sample size and Data Analysis

As this pilot trial is not designed to test the efficacy of ED-TREAT, a power calculation is not appropriate.[75] To determine the sample size for this pilot randomized trial, we will use the outcome of fidelity as measured by the proportion of visits in the intervention arm that are adherent to >80% of the observational workflow checklist. To estimate the proportion achieving this level of fidelity with a reasonable precision (95% CI with a width of +/- 20%), a total of at least 26 eligible subjects will be enrolled in the pilot trial. We will determine ratings from the System Usability Scale[59] and calculate proportions of each clinician group with scores of >85, indicating excellent usability. We will consider ED-TREAT to be acceptable if ≥90% of each clinician group give ratings >85. For feasibility, we will measure the proportion of potentially eligible patient visits with successful enrollment and collection of all outcomes of interest. Based on our group's anecdotal experience with pilot studies, we will consider a comparative effectiveness trial feasible if ≥30% of visits assessed for eligibility are enrolled and ≥90% of all outcome measures are collected. Qualitative data obtained from interviews will be analyzed with Dedoose using the analytic strategy mentioned earlier for iterative refinement of the study protocol in preparation for a comparative effectiveness trial.

ETHICS AND DISSEMINATION

We plan to conduct our study in accordance with the Yale Institutional Review Board (IRB). We have obtained the necessary regulatory and human subjects protection approvals for each aspect or phase of our protocol. As we work with structured EHR patient data, we will maintain de-identification where necessary and keep access to datasets secure. Additionally, all clinicians and patients participating in focus groups, feasibility testing, or the pilot trial will be informed of their rights as subjects. Clinicians will retain the right to retain control of their practice and patients will retain the right to not participate and request termination of participation at any point in the study. All staff, participants, and patients will provide verbal consent prior to involvement with the study and a study exemption determination has been

granted by the Yale IRB for the design and development of ED-TREAT. Our clinical trial has been reviewed and approved (Clinical Trials Registration Number: NCT04959279).

Monitoring for data integrity and safety will be the responsibility of principal investigator (AHW) and the Yale Human Investigation Committee, and a Data Safety Monitoring Board (DSMB). DSMB members will be composed of experts in care disparities and health equity for vulnerable and disadvantaged populations, clinical trials for mental illness and substance use disorders, measurement and risk stratification for disinhibited behaviors, and an expert in statistical analysis of clinical trials in emergency medicine. Twice annually, the DSMB will review the progress of the study and frequency of serious adverse events. All adverse events, as well as any unanticipated problems that arise, will be reported within 48 hours to the Human Investigation Committee. A full report will be provided annually or upon request to the IRB and the sponsor's Program Official. The effect of adverse events on the risk/benefit ratio of the study will be re-evaluated by the investigators with each event, with appropriate adjustments made to the protocol or consent forms if needed. Given the minimal risk of the study and intervention, the investigators do not anticipate the occurrence of any serious adverse events.

Results and outcomes of the study will be disseminated through peer-reviewed journals and presentations at relevant scientific meetings throughout the study timeline. A successful pilot trial will aid in a future full randomized control trial to fully measure the effectiveness of the ED-TREAT CDS tool in agitation management in emergency department settings. At the time of publication of any manuscripts that arise from this research, the de-identified data for that manuscript will be made available to share for scholarly activities. Sharing of the data will require a Data Use Agreement to be established between the requesting and host institutions. Data will be shared through secure file transfer.

AUTHOR CONTRIBUTIONS

AHW, JDD, KAY, SLB, and ERM designed the study protocol and obtained funding. AHW is responsible for the overall logistical and scientific aspects of the study, data collection and analysis, and draft of this manuscript. DS, AK, MB, PO, and IF provided administrative and logistical support for the study. BN, RK, KA, MB, RAT, and TM contributed statistical, scientific, and design expertise in the development and planned scientific activities of the protocol. All authors contributed to critical revisions and gave final approval of the manuscript.

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COMPETING INTERESTS

Dr Wong reported receiving grants from National Institute of Health outside the conduct of the study. Dr. Melnick reported receiving grants and contracts from the National Institute of Health, Agency for Healthcare Research and Quality, American Medical Association, and Centers for Medicare & Medicaid Services outside of this study. Dr. McCall reported receiving grants from the National Institute of Health, Agency for Healthcare Research and Quality, and Google outside of this study. Dr. McCall is a member of the Clinical Diversity Advisory Board at Woebot Health and Advisory Board at RACE Space Inc. Dr. Heckmann reported receiving salary support from the Centers for Medicare & Medicaid Services to develop, implement, and maintain clinical performance outcome measures that are publicly reported, in addition to receiving research support from the U.S. Food and Drug Administration, Centers for Disease Control and Prevention, National Institute of Health, Connecticut Department of Public Health, and from the Community Health Network of Connecticut for her work as a medical consultant.

Figure Legends

Figure 1. Overview and steps for each phase of ED-TREAT design and pilot implementation study.
Figure 2. Overview and steps for Aim 1: ED-TREAT user-centered design and prototype development.
Figure 3. Anticipated clinical steps for the intervention arm of ED-TREAT.

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Figure 1. Overview and steps for the phase of ED-TREAT design and pilot implementation study.

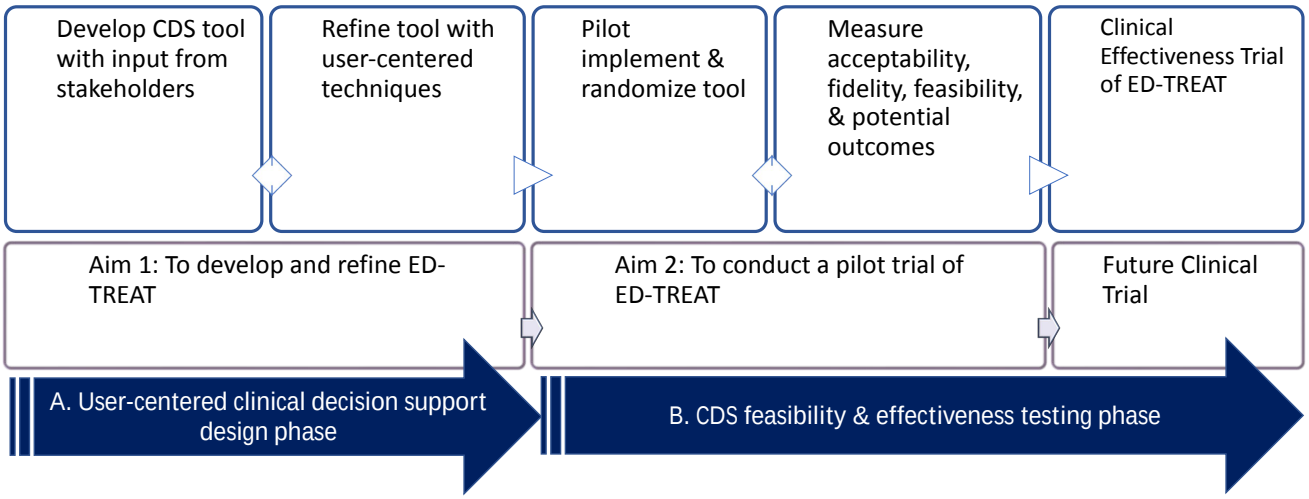


Figure 2. Overview and steps for Aim 1: ED-TREAT user-centered design and prototype development.

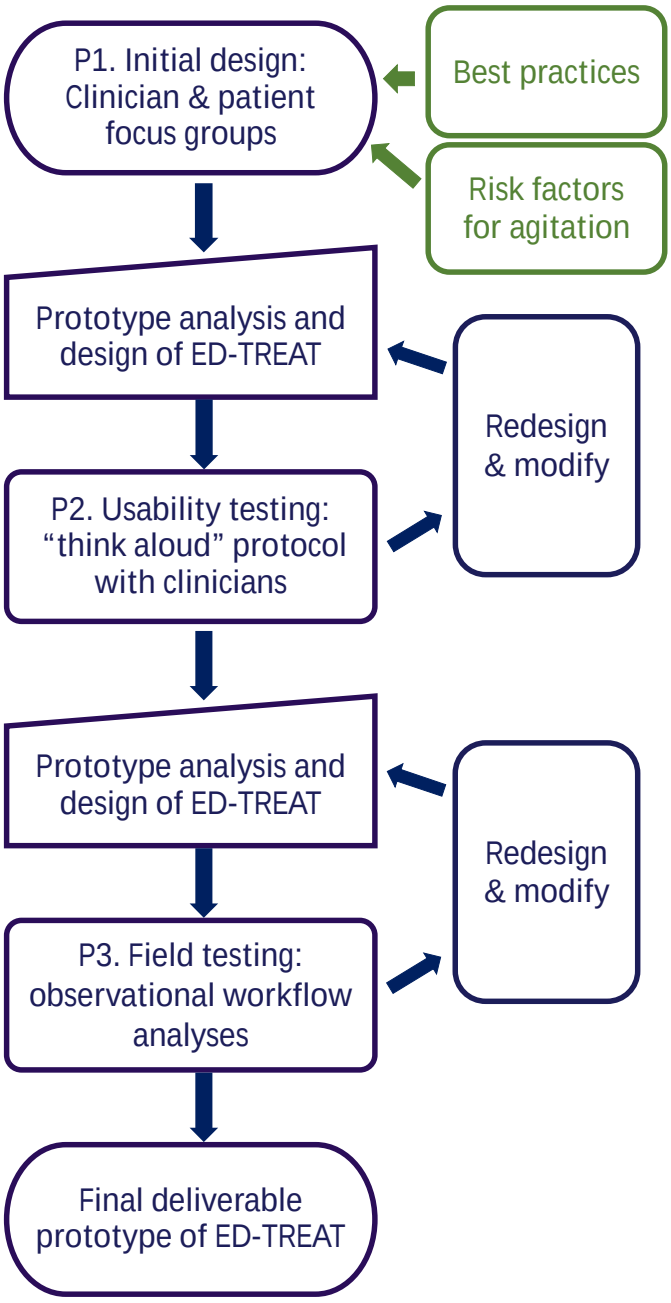
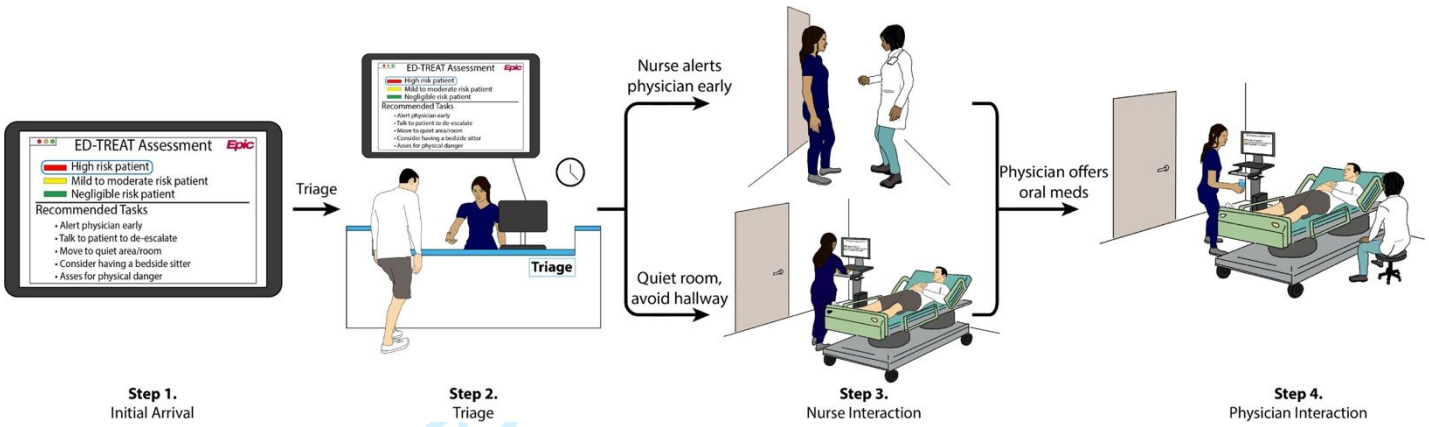


Figure 3. Anticipated clinical steps for the intervention arm of ED-TREAT.



Supplemental Table 1: Sample focus group topics for design and development of ED-TREAT (P1)

Design Domain[51]	Example factors and sample question prompts
User groups	• Timing, benefits & obstacles to using CDS for managing at-risk patients • Attitudes, beliefs, & knowledge regarding treatment of at-risk patients • Potential impact of ED-TREAT on patient experience and needs during visit
Tasks and technology	• Potential formats and interfaces for ED-TREAT prototype • Types of data and information to be included in ED-TREAT • Clinician interface with EHR and clinical duties related to ED-TREAT recommendations
System and organization	• Potential effect of ED-TREAT on management of at-risk patients • Workflow and care coordination amongst team members that can impact ED-TREAT across user types • Facilitators & barriers to implementing best practices for preventing agitation in real-world clinical environment

Supplemental Table 2: Potential risk factors that predict development of agitation in the ED

Domain	Data elements
Patient factors	• Violence history: presence of violence alert, Brøset Violence Checklist (BVC)[54] • History: chief complaint, psychiatric/medical history, alcohol/substance use, # ED visits/year, medications
Clinical data	• Laboratory data: complete blood count, urine toxicology, point-of-care glucose & alcohol, basic metabolic panel • Initial vital signs: heart rate, temperature, systolic/diastolic blood pressures, oxygen saturation, respiratory rate • Restraint characteristics: type/route/dose of chemical sedative(s) used, reasons for & type of physical restraint
Environment	• Physical parameters: initial bed location assignment, hallway spot, time of day of presentation • Staff contact: initial staff contact, staff characteristics & interactions, presence of security officers at arrival into ED
System	• Pre-arrival: mode of transport into ED, presence of law enforcement escort • Outpatient services: mental health visits, assertive community treatment, rehabilitation services

Suppemental Table 3: Sample usability testing topics and observational tasks (field testing)

Usability testing goals and objectives (P2)	Field testing observation task examples (P3)
• Effectiveness: Ability of users to achieve task goals	• Triage assessment and room assignment
• Efficiency: Time/speed to complete tasks within tool	• Initial contact at bedside and assessment
• Satisfaction: Ease of use & acceptability of ED-TREAT	• Potential structural biases and differential treatment plans
• Understandability: Users comprehending what ED-TREAT can do	• History and physical exam, monitoring and re-assessment
• Learnability: Training/time/effort to learn how to use ED-TREAT	• De-escalation and establishing rapport
• Operability: Support of user and overcoming potential problems	• Ordering of medications, laboratory & imaging tests
• Flexibility: Ability to accommodate for different situations/needs	• Patient behaviors, responses, experiences
• Attractiveness: Motivation of user interest to explore/use system	• EHR documentation & interface with ED-TREAT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15-16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15-16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2, 9, 14
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5, 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9, 12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12-14
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12, 14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4-14

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, 10, 11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14-15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14-15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9, 11, 14-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12, 14-15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14-15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Formative evaluation of an emergency department clinical decision support system for agitation symptoms: a study protocol

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Formative evaluation of an emergency department clinical decision support system for agitation symptoms: a study protocol

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ABSTRACT

Introduction

The burden of mental health related visits to emergency departments (EDs) is growing, and agitation episodes are prevalent with such visits. Best practice guidance from experts recommends early assessment of at-risk populations and pre-emptive intervention using de-escalation techniques to prevent agitation. Time pressure, fluctuating work demands, and other systems-related factors pose challenges to efficient decision-making and adoption of best practice recommendations during an unfolding behavioral crisis. As such, we propose to design, develop, and evaluate a computerized clinical decision support (CDS) system, Early Detection and Treatment to Reduce Events with Agitation Tool (ED-TREAT). We aim to identify patients at risk of agitation and guide ED clinicians through appropriate risk assessment and timely interventions to prevent agitation with a goal of minimizing restraint use and improving patient experience and outcomes.

Methods and analysis

This study describes the formative evaluation of the health-record embedded CDS tool. Under Aim 1, the study will collect qualitative data to design and develop ED-TREAT using a contextual design approach and an iterative user-centered design process. Participants will include potential CDS users, i.e., ED physicians, nurses, technicians, as well as patients with lived experience of restraint use for behavioral crisis management during an ED visit. We will use purposive sampling to ensure the full spectrum of perspectives until we reach thematic saturation. Next under Aim 2, the study will conduct a pilot, randomized controlled trial of ED-TREAT at two adult ED sites in a regional health system in the Northeast United States to evaluate the feasibility, fidelity, and bedside acceptability of ED-TREAT. We aim to recruit a total of at least 26 eligible subjects under the pilot trial.

Ethics and dissemination

Ethical approval by the Yale University Human Investigation Committee was obtained in 2021 (HIC# 2000030893 and 2000030906). All participants will provide informed verbal consent prior to being enrolled in the study. Results will be disseminated through publications in open-access, peer-reviewed journals, via scientific presentations, or through direct email notifications.

Study registration

The pilot trial is registered on ClinicalTrials.gov, NCT04959279.

ARTICLE SUMMARY

Strengths and limitations of this study

- With limited prior evidence on real-life implementation of best practice recommendations to prevent development of agitation symptoms in an acute care setting, this study aims to identify patient and user-centered strategies to develop a clinical decision support (CDS) system that facilitates management of agitation in an acute care setting.
- Our tool will include pragmatic strategies to implement best practice recommendations for risk assessment and timely de-escalation techniques in agitation management *prior* to definitive psychiatric treatment.
- The CDS design process will follow an iterative, user-centered approach with feedback from end-users at every step to refine and develop an electronic health record-embedded, fully functional prototype.
- Our risk assessment data, qualitative design, and pilot trial will arise from the same geo-political area and health system, which may limit generalizability.

INTRODUCTION

Behavioral health related visits to emergency departments (EDs) are growing.[1-3] Agitation, defined as excessive psychomotor activity leading to aggressive and violent behavior,[4] is a frequent symptom of such visits. An estimated 1.7 million agitation episodes occur annually in EDs across the United States alone.[5,6] When an individual becomes agitated, they may cause harm to themselves, hospital staff, and property.[7-9] Rapid management of agitation is imperative and use of physical restraint may be necessary to facilitate patient assessment and prevent injury.[5] Although physical restraints are routinely used in the ED,[10,11] they are associated with up to 37% risk of injury in patients, including blunt chest trauma, asphyxiation, respiratory depression, to sudden death.[12-17] To address these challenges, the American Association for Emergency Psychiatry sponsored Project BETA (Best Practices in Evaluation and Treatment of Agitation).[18] Project BETA was a pioneer effort to create a comprehensive list of five sets of best practices for preventing and managing agitation through multidisciplinary consensus panels. Key strategies within Project BETA included use of structured risk assessment[4] to help clinicians screen patients at risk of developing agitation and pre-emptive intervention using behavioral techniques,[19] environmental modification,[20] and consensual use of medication therapy[18] to obviate use of restraints.

Despite these established best practice recommendations, multiple systems level barriers challenge their practical implementation.[21-23] Care delivery in the ED occurs in a uniquely complex environment. Clinical decisions are made under time pressure, using limited information, and amidst multiple and frequent interruptions and other unpredictable factors due to the dynamic course of acute, undifferentiated conditions.[24] As burden on the emergency care system rises in the U.S.,[25-28] these systems-level challenges are particularly relevant for patients at risk for agitation, as behavioral and de-escalation techniques require investment in time and effort to build a strong rapport and trusting therapeutic relationship with the patient. Given that clinicians may have difficulty accurately identifying patients at risk for agitation and access to expert psychiatric evaluation in such settings may be limited,[29-32] there is a significant mismatch between resources available and application of those resources to individuals who would most benefit from early risk assessment and intervention. A recent prospective study observing 100 at-risk patients in the ED found that over 60% of individuals develop agitation more than 30 minutes into their visit,[33-35] presenting opportunities to prevent agitation earlier in the course.

Clinical decision support (CDS) tools can help address systems-based challenges, facilitate risk assessment, and guide clinicians to use best practices strategies recommended by Project BETA in the

ED. CDS tools show increasing promise in the emergency setting to help clinical staff identify high-risk patients and provide more efficient and higher quality of care,[36] including individuals requiring use of high-cost imaging[37] and older adults.[38-41] A CDS system encompasses any on-screen tool designed to improve healthcare delivery by enhancing medical decisions with targeted clinical knowledge, patient data, and other health-related information.[42] Use of a CDS tool to assist in assessment and management of potentially agitated patients may be an effective strategy in the ED.[40,43,44]

Rationale and aims

This study is one of the first that aims to prevent agitation and improve outcomes for ED patients with agitation. We will achieve this by (**Figure 1**):

1. Designing and developing an EHR-embedded, user-centered, CDS system, Early Detection and Treatment to Reduce Events with Agitation Tool (ED-TREAT), using a contextual design approach to obtain input from key stakeholders and iterative user-centered design process; and

2. Conducting a pilot study to evaluate the feasibility, fidelity, and bedside acceptability of ED-TREAT. ED-TREAT aims to help ED staff and clinicians to identify patients at high-risk for developing agitation, guide them through appropriate risk assessment and efficient decision-making to implement best practice recommendations to prevent development of agitation, and minimize use of restraints.

We hypothesize that, with the use of ED-TREAT, ED staff will be able to identify at-risk individuals, conduct appropriate risk-assessment, implement interventions to minimize use of restraints and improve patient experience and outcomes related to agitation management in the ED. If this study is successful, a planned subsequent clinical effectiveness trial will compare effectiveness of ED-TREAT to usual care across multiple ED sites in the future. The long-term goal of this CDS tool is to increase fidelity with best practice recommendations for prevention of agitation through early use of behavioral techniques prior to onset of agitation.

METHODS AND ANALYSIS

Patient and public involvement

We invited patients to help us design, develop, and test the intervention so that it is designed to improve the public good and help individuals with lived experience of mental illness and behavioral crises. In addition, we will solicit patient feedback and guidance on dissemination of study results to participants and the local community through networks at our affiliated community-based organizations that have had sustained engagement with our team for several years to implement a research agenda in agitation care that is patient-centered and recovery-oriented.

Aim 1: Developing and refining ED-TREAT

With the goal of developing a final prototype that maximizes usability, staff self-efficacy, satisfaction, and patient-centered care, ED-TREAT will be designed, developed, and refined in three phases (P1-P3) (**Figure 2**). During phase 1 **(**P1), we will conduct a needs assessment to collect input from key stakeholders including ED physicians, nurses, patient care technicians, behavioral health experts, informatics experts, and patients with lived experience of being in restraints in the ED. We will combine needs assessment findings with Project BETA recommendations for agitation management in the ED[5] and risk factors for agitation from the literature to design an initial prototype. Next, in phase 2 (P2), we will conduct formative usability testing, which will consist of "think aloud" protocols, a standard usability procedure for CDS design[45], with clinician users and standardized patients in a controlled simulation setting to guide further modifications of the tool in an iterative fashion. Finally, in phase 3 (P3), we will conduct field testing in the ED through observational workflow analyses to identify and address barriers in the real-world clinical environment.

Participant recruitment

We will design ED-TREAT for use by staff members that work mostly closely with agitated patients in the ED.[7,35,46-48] These consist of ED physicians, nurses, and patient care technicians. We plan to recruit these staff participants via email and biweekly staff meetings. In addition, we will also recruit patients with prior lived experience of being restrained in the ED to solicit their input and ensure that patient-centered practices are considered during the design process. We will recruit these patients from the pool of peer support workers from local community-based recovery organizations via email and presentations at monthly staff meetings. These peer support workers have a history of mental health and substance use disorders and have received training to become employed as patient advocates on community-based treatment teams. Finally, our design team will interview informatics and behavioral health experts to solicit ideas and relevant CDS design strategies to improve decision-making during agitation management.[49,50]

Phase 1: Needs assessment and initial design of ED-TREAT

We will conduct focus groups and observations starting June 2023 via a contextual inquiry[36] approach. This approach seeks to engage prospective users and participants described above to understand clinical workflow, roles of different members of the patient care team, and thought processes involved in managing a behavioral health crisis in the ED. We will first conduct in-depth qualitative interviews with staff and patient participants using a semi-structured interview guide that will include open-ended questions to cover topics (**Supplemental Table 1)** related to application of Project BETA recommendations in preventing agitation and user-centered design.[37] Each focus group will consist of 2-5 participants from the same stakeholder group and be approximately 60 minutes duration. Sessions will be audio recorded after obtaining participant verbal consent **(S1).** In addition, members of the design team will conduct observation sessions in the ED to observe ED staff during real-life agitation management events. These sessions will provide information about environmental and systems contexts, interactions amongst members of patient care team during an active agitation episode, logistics of integrating CDS tool into EHR workflow to facilitate clinical decision-making.

After identifying crucial user requirements in P1, we will develop an initial low-fidelity prototype for ED-TREAT. This will occur in collaboration with EHR analysts and informatics experts by incorporating Project BETA recommendations for preventing and managing agitation[5] and potential risk factors for agitation to identify potential at-risk patients in the ED. These risk factors (**Supplemental Table 2)** will be based on existing literature on risk factors for agitation and workplace violence in the healthcare setting[4,42,51] our team's prior work on agitation management in the ED,[48] patient perspectives of ED visits resulting in restraint use,[52] characterization of physical restraint use among adults presenting to the ED with agitation,[11] and attributes and levels of agitation impacting thresholds for restraint use in the ED.[34,35]

Preliminary work by our team has shown that identifying risk factors for agitation and implementing EHR-based interventions for agitation are feasible in the emergency setting.[46] The CDS will extract patient specific data on variables of interest from existing patient chart data via EPIC's Cogito analytics performance suite.[53] Based on current expert recommendations from Project BETA[46], we anticipate that ED-TREAT will likely stratify patients into three risk groups (**Table 1**) and recommend increasing levels of resource utilization and pre-emptive management as the risk level increases based on best practices for preventing agitation from Project BETA. Depending on results from the needs assessment,

ED-TREAT's recommendations may include automated order sets for medication therapy, staff instructions and communication orders, and templated clinical documentation. Our team will collaborate with EHR analysts to create an initial interactive prototype within the EHR testing environment, "Epic Playground", a non-production, functional, simulated EHR replica used for developing and validating new workflows. We anticipate that our final product will be an EHR-integrated web application through a dedicated graphical Application Programming Interface.[54]

Table 1. Sample elements of initial ED-TREAT prototype

Risk Level	Project BETA[5] guidelines	Recommended tasks
Negligible	(1) Medical evaluation & triage[13]	• Medical history & physical exam • Early vital signs and fingerstick glucose • Address psychosocial needs & establish rapport • Standardize assessment to avoid structural biases/inequities
Mild to moderate	(2) Psychiatric evaluation & risk assessment[55] (3) Psychopharmacology[18]	Tasks in negligible risk level PLUS: • Measure Behavioral Activity Rating Scale (BARS)[56] • Offer voluntary oral medication (with allergies cross-checked)
High	(4) Environmental modification (avoidance of restraint & seclusion)[20] (5) Verbal de-escalation[19]	Tasks in mild to moderate risk level PLUS: • Alert clinician early (from triage/nursing assessment) • Pre-emptive verbal de-escalation (ten domains) • Move to quiet, low activity/volume area

Phase 2: Usability testing of ED-TREAT

Heuristic evaluation

We will first perform heuristic evaluation[57] of CDS interface usability before testing with clinician participants. This will consist of an expert team of three evaluators with experience in emergency medicine as well as CDS design who will navigate through different aspects of the CDS and judge the compliance and usability of the tool in agitation management triangulated between their expertise and usability standards. Each evaluator will inspect the interface and assess the guidelines and recommendations provided by the CDS for various levels of agitation. After individual assessment is completed, we will debrief as a group and aggregate the results of each evaluator to examine deficiencies in the prototype design. After addressing concerns and refining the prototype CDS tool, we will conduct further usability testing with clinicians in simulated training protocols.

"Think Aloud" Protocol

Next, our team will perform one-on-one "think aloud" protocol[45] sessions with clinician users in a quiet office at the EHR training classroom. We will ask participants to perform designated tasks with ED-

TREAT using mock patient charts in Epic Playground and "think aloud" how they would use ED-TREAT to test whether the user understands and is using the CDS as intended. We will develop a facilitator guide that focuses on domains related to usability of the prototype and design of the CDS interface (**Supplemental Table 3**). We will video-record each usability testing session, incorporating user screen captures and field notes[58] taken during the session. At the end of the session, each participant will complete the System Usability Scale[59] to measure perceived usability of and satisfaction with a health informatics tool. The System Usability Scale is a widely used and effective survey composed of ten statements assessed on a 5-point Likert scale, with inter-item correlations of 0.69-0.75 and a reliability coefficient α of 0.91.[60] Each session is expected to take 30 minutes.

Simulation sessions

Additionally, we will observe the clinical team in a simulation session with a live actor or mannequin simulating being an agitated patient. Participants will be briefed on how the CDS tool works and will be encouraged to use it at various points in the care process. We will similarly video-record each session and distribute the System Usability Scale to gather participant feedback. We will make iterative refinements to the prototype until the team reaches consensus that it has reached a threshold level of usability.

Phase 3: Field testing of ED-TREAT

We will recruit staff participants working in the ED for field testing of the ED-TREAT prototype through observational workflow analysis of ED visits with mild-moderate or high risk of agitation (**Table 1**). We will develop an observational guide based on sample topics of usability testing (**Supplemental Table 3**) that will detail both the workflow of managing an at-risk patient and barriers to adopting ED-TREAT in the clinical environment. Field notes will detail events, actions, and their time and duration,[58] while maintaining an open-ended format to describe and follow variations or workarounds in workflow. Either the PI or a trained research associate will complete the observations as an unobtrusive non-participant observer through a patient's visit from ED arrival to patient disposition, similar to procedures we developed for prior observations of agitation.[34,35] We will enter field notes using a portable electronic tablet into a word document for free text and a spreadsheet for data elements.

Data analysis

In P1 (design and development), our team will use the iterative and phased approach of building an affinity diagram, a commonly used organizational tool that allows large numbers of ideas stemming from brainstorming and qualitative data to be sorted into groups, based on their natural relationships, for review

and analysis.[61,62] Following completion of each focus group and contextual inquiry session, we will conduct an interpretation session to review the user-provided key notes from the inquiry session and capture them as affinity notes.[63] To help identify common issues, work patterns, and needs, we will arrange the affinity notes into hierarchical categories ("must-have," "good to have", and "nice to have") based on common themes in the data to create an affinity diagram.[63] Building of the affinity diagram will occur online using Miro software (RealtimeBoard, Inc, San Francisco, CA, United States).[64] We will mock up a low fidelity prototype of ED-TREAT based on current best practices and iteratively refine it based on user data from P1.

For P2 (usability testing) and P3 (field testing), field notes will be analyzed using a deductive coding method to conduct directed content analysis[65] based on predetermined usability requirements and recommended tasks from ED-TREAT (**Supplemental Table 3**).[66] We will use Dedoose (SocioCultural Research Consultants, Manhattan Beach, CA, United States),[67] a collaborative and cloud-based qualitative software package, for thematic analysis and data organization of transcripts. Codes identifying suboptimal or deficient performance of the prototype will uncover critical system factors impacting adoption and usability that need optimization and adjustment. Two trained reviewers will perform independent coding and we will calculate inter-rater reliability assessments with kappa scores. For the System Usability Scale,[59] participants' scores from each question of are added together and then multiplied by 2.5 to convert the original scores to continuous data from 0-100. Scores will be described using mean and standard deviation and >85 will be indicative of excellent usability.[68] We will use the results generated from this analysis process at each round of revisions to make appropriate adjustments to the ED-TREAT prototype in close collaboration with the EHR analyst team until we derive a final deliverable prototype that will be ready for the pilot trial.

Sample size

We will use purposive sampling[69] to ensure the full spectrum of perspectives for clinicians who will engage with ED-TREAT and peer support workers who have had experience as patients in the ED. We will conduct data collection until reaching thematic saturation,[70] when new concepts no longer emerge from iterative analysis of the data.[71] For initial design (P1), we anticipate that this will occur after five to six focus groups with six participants (staff and patients) in each focus group.[72] As enrollment of 10-12 subjects can identify up to 90% of usability problems,[73] we will perform usability testing (P2) for approximately five participants in each round of refinement and expect about three rounds of refinement

(15 participants total) as per our prior published work.[74] For field testing (P3), we plan to observe eight patient encounters to detect any usability problems when deployed in the ED.

Aim 2: Pilot trial and feasibility testing

We will conduct a pilot randomized control trial for ED-TREAT to compare the intervention to usual care. This will allow us to evaluate acceptability of the intervention to its end-users (ED staff), fidelity of its intended outcomes to identify at-risk individuals and prevent agitation, feasibility of randomization, ease of subject enrollment, and measurement of other outcomes of interest. This will be a mixed methods study, wherein we will quantitatively measure usability and efficiency of clinical decision-making via the System Usability Scale[59] and specific patient outcomes, as well as qualitatively assess the effect of ED-TREAT on clinical workflow and patient care. In addition, this pilot trial will (1) test the integrity of the study protocol in preparation for a future comparative effectiveness clinical trial, (2) evaluate randomization protocols, (3) estimate rates of recruitment and retention of trial subjects, and (4) estimate effect size for sample size calculation in the subsequent trial.[75] Pilot trials[76] are not designed to test the efficacy of the intervention, but will help establish acceptability and feasibility in preparation for a future multicenter RCT. We hypothesize that it will be feasible to implement the tool, measure identified outcomes, be acceptable to its end-users, and work as intended.

Study setting, participants, and randomization

We will conduct the pilot trial at two adult ED campuses that belong to a large regional healthcare system in the Northeast United States, with a planned trial start date in the Fall of 2024. Prior to initiation of the pilot trial, all emergency physicians, ED nurses, and ED patient care technicians at both campuses will receive an email introduction and a link to a brief training regarding the use of ED-TREAT. Eligibility criteria for patients and recruitment will include ability to provide verbal consent for the study and a score of “4” (quiet and awake; normal level of activity) or less on the Behavioral Activity Rating Scale (BARS),[56] an accepted seven-point scale to assess levels of agitation in acute care settings. We will first perform screening for eligibility via an ED-TREAT administrative interface that performs risk assessment for each ED patient on arrival. Inclusion criteria for ED patients include adult (age≥18) patients, presenting to the ED during the pilot trial period, deemed to have a mild-moderate or high risk of agitation as determined by ED-TREAT, do not require physical restraint orders within <30 minutes of arrival, with a score of "4" (quiet and awake; normal level of activity) on the Behavioral Activity Rating Scale, have comfort with conversational English, and able to provide verbal consent. Exclusion Criteria include presence of a restraint order <30 minutes of arrival and presence of a non-violent physical

restraint order where indications are not due to agitation (e.g., for protecting intubation or life-preserving equipment). A research associate will then approach eligible patients and their designated clinician team members for enrollment after confirming ability to consent and assessing patient BARS scores as close to the beginning of the visit as feasible. Study procedures, risks/benefits of participating, and the purpose of ED-TREAT will be described, and verbal consent will be obtained for patients and staff participants. Since we plan to enroll patients prior to onset of agitation, we anticipate that most patients should be able to engage in decisions and provide verbal consent. Our prior work found that >70% of ED patients with subsequent agitation arrived with a normal mental status and BARS scores ≤ 4.[34,35] We will perform 2:1 randomization at the patient level and also recruit a higher proportion of high-risk patients in each arm, as a primary aim of the pilot trial is to test the acceptability of ED-TREAT and we anticipate that our intervention will recommend more tasks for high-risk patients. Randomization will occur using sequentially numbered, opaque, sealed envelopes that will only be opened by the research team member after enrollment of each patient. In the intervention group, ED-TREAT will automatically launch as part of the clinical team's workflow in the EHR after randomization. We anticipate that critical steps in ED-TREAT will occur at four stages of a visit (**Figure 3**): (1) at initial arrival with automated risk stratification using pre-determined criteria set during the CDS design process; (2) at triage assessment; (3) at initial nurse interaction; and (4) at initial clinician interaction. In the control group, ED-TREAT will notify the research team regarding the patient's risk group but will not launch for the clinical team's interfaces.

Data collection

Our anticipated data collection strategy is summarized in **Table 2**. In addition to visit characteristics (system factors, relevant clinical data) collected through the EHR during the visit, we will collect acceptability and fidelity measures, feasibility assessment, and potential outcomes of interest for each visit.

Acceptability & fidelity

For all clinicians caring for patients in the intervention group, we will administer the System Usability Scale (SUS)[59] either in person at the end of the ED visit or within 72 hours by email. In addition, we will perform observation workflow analyses as described earlier using a task checklist to determine if clinicians were using ED-TREAT as intended, and if any barriers or unintended consequences occurred because of the intervention. We will perform brief, semi-structured interviews with patients either at the

end of a visit or within one week after disposition to evaluate the impact of ED-TREAT on their experiences.

Feasibility

To assess the feasibility of a comparative effectiveness trial, we will evaluate the following at three-month intervals: 1) available number of potential subjects (# of eligible patient visits), 2) subject identification (% of eligible patients/staff approached), 3) enrollment (% of patients/staff with consent to enroll), and 4) retention (% of visits with completed outcome measures). We will also conduct brief, semi-structured interviews with staff participants to evaluate their experiences with ED-TREAT and effect on clinical workflow.

Outcome measures

The anticipated primary outcome of the comparative effectiveness trial will be the presence of a physical restraint order during the ED visit (> 30 minutes after arrival). Additional secondary outcomes include the presence of an intramuscular chemical sedative order, highest level of agitation on the Behavioral Activity Rating Scale (BARS)[56] during visit, disposition, and length of stay.

Table 2. Anticipated data collection for ED-TREAT pilot trial

Measure	Tool or strategy	Timing of measurement
Visit characteristics		
System factors	EHR (e.g., staff traits, National ED Overcrowding Scale)[77]	During & end of visit
Clinical data	EHR/ED-TREAT (e.g., risk category)	During & end of visit
Acceptability, fidelity		
Clinician acceptability of ED-TREAT	System Usability Scale[59] (satisfied, useful)	End of visit
Fidelity of ED-TREAT	Observational workflow checklist (perform as intended)	During visit
Effect on patient experience	Qualitative interviews with patients	End of visit or <72h after visit
Potential bias or differential treatment	Implicit Association Test (for clinicians), patient interviews	End of visit or <72h after visit
Feasibility		
Available subjects	# of eligible visits	Every 3 months
Subject identification	% eligible visits approached	Every 3 months
Enrollment	% visits with consent to enroll from patient/clinical staff	Every 3 months
Retention	% visits with completed measures	Every 3 months
Effect on clinical workflow	Qualitative interviews with clinicians	Every 3 months
Outcomes		
Physical restraint order	EHR	During & end of visit
Intramuscular chemical sedative order	EHR	During & end of visit
Level of agitation	Behavioral Activity Rating Scale (BARS)[56]	Highest level during visit
Disposition	EHR	End of visit

Length of stay	EHR	End of visit

Sample size and data analysis

As this pilot trial is not designed to test the efficacy of ED-TREAT, a power calculation is not appropriate.[75] To determine the sample size for this pilot randomized trial, we will use the outcome of fidelity as measured by the proportion of visits in the intervention arm that are adherent to >80% of the observational workflow checklist. To estimate the proportion achieving this level of fidelity with a reasonable precision (95% CI with a width of +/- 20%), a total of at least 26 eligible subjects will be enrolled in the pilot trial. We will determine ratings from the System Usability Scale[59] and calculate proportions of each clinician group with scores of >85, indicating excellent usability. We will consider ED-TREAT to be acceptable if ≥90% of each clinician group give ratings >85. For feasibility, we will measure the proportion of potentially eligible patient visits with successful enrollment and collection of all outcomes of interest. Based on our group's anecdotal experience with pilot studies, we will consider a comparative effectiveness trial feasible if ≥30% of visits assessed for eligibility are enrolled and ≥90% of all outcome measures are collected. Qualitative data obtained from interviews will be analyzed with Dedoose using the analytic strategy mentioned earlier for iterative refinement of the study protocol in preparation for a comparative effectiveness trial.

ETHICS AND DISSEMINATION

We plan to conduct our study in accordance with the Yale Institutional Review Board (IRB). We have obtained the necessary regulatory and human subjects protection approvals for each aspect or phase of our protocol. Ethical approval by the Yale University Human Investigation Committee was obtained in 2021 (HIC# 2000030893 and 2000030906). After careful review, Yale IRB has approved Aim 1 of this study to be eligible for exempt of full IRB review under 45 CFR 46.104(d)(4), since any information collected by the investigator will be in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects. Aim 2 of the study has been approved as a full protocol for a clinical trial and is undergoing annual continuing review. As we work with structured EHR patient data, we will maintain de-identification where necessary and keep access to datasets secure. Additionally, all clinicians and patients participating in focus groups, feasibility testing, or the pilot trial will be informed of their rights as subjects. Clinicians will retain the right to retain control of their practice and patients will retain the right to not participate and request termination of participation at any point in the study. All staff, participants, and patients will provide verbal consent prior to involvement

with the study. Sample consent forms for patients and staff are included as **Supplement Materials**. The pilot trial is registered at ClinicalTrials.gov (Clinical Trials Registration Number: NCT04959279).

Monitoring for data integrity and safety will be the responsibility of principal investigator (AHW) and the Yale Human Investigation Committee, and a Data Safety Monitoring Board (DSMB). DSMB members will be composed of experts in care disparities and health equity for vulnerable and disadvantaged populations, clinical trials for mental illness and substance use disorders, measurement and risk stratification for disinhibited behaviors, and an expert in statistical analysis of clinical trials in emergency medicine. Twice annually, the DSMB will review the progress of the study and frequency of serious adverse events. All adverse events, as well as any unanticipated problems that arise, will be reported within 48 hours to the Human Investigation Committee. A full report will be provided annually or upon request to the IRB and the sponsor's Program Official. The effect of adverse events on the risk/benefit ratio of the study will be re-evaluated by the investigators with each event, with appropriate adjustments made to the protocol or consent forms if needed. Given the minimal risk of the study and intervention, the investigators do not anticipate the occurrence of any serious adverse events.

Results and outcomes of the study will be disseminated through peer-reviewed journals and presentations at relevant scientific meetings throughout the study timeline. A successful pilot trial will aid in a future full randomized control trial to fully measure the effectiveness of the ED-TREAT CDS tool in agitation management in emergency department settings. At the time of publication of any manuscripts that arise from this research, the de-identified data for that manuscript will be made available to share for scholarly activities. Sharing of the data will require a Data Use Agreement to be established between the requesting and host institutions. Data will be shared through secure file transfer.

CONTRIBUTORS

AHW, JDD, KAY, SLB, and ERM designed the study protocol and obtained funding. AHW is responsible for the overall logistical and scientific aspects of the study, data collection and analysis, and draft of this manuscript. DS, AK, MB, PO, and IF provided administrative and logistical support for the study. BN, RK, KA, MB, RAT, and TM contributed statistical, scientific, and design expertise in the development and planned scientific activities of the protocol. All authors contributed to critical revisions and gave final approval of the manuscript.

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COMPETING INTERESTS

Dr Wong reported receiving grants from National Institute of Health outside the conduct of the study. Dr. Melnick reported receiving grants and contracts from the National Institute of Health, Agency for Healthcare Research and Quality, American Medical Association, and Centers for Medicare & Medicaid Services outside of this study. Dr. McCall reported receiving grants from the National Institute of Health, Agency for Healthcare Research and Quality, and Google outside of this study. Dr. McCall is a member of the Clinical Diversity Advisory Board at Woebot Health and Advisory Board at RACE Space Inc. Dr. Heckmann reported receiving salary support from the Centers for Medicare & Medicaid Services to develop, implement, and maintain clinical performance outcome measures that are publicly reported, in addition to receiving research support from the U.S. Food and Drug Administration, Centers for Disease Control and Prevention, National Institute of Health, Connecticut Department of Public Health, and from the Community Health Network of Connecticut for her work as a medical consultant. All other authors declare no competing interests.

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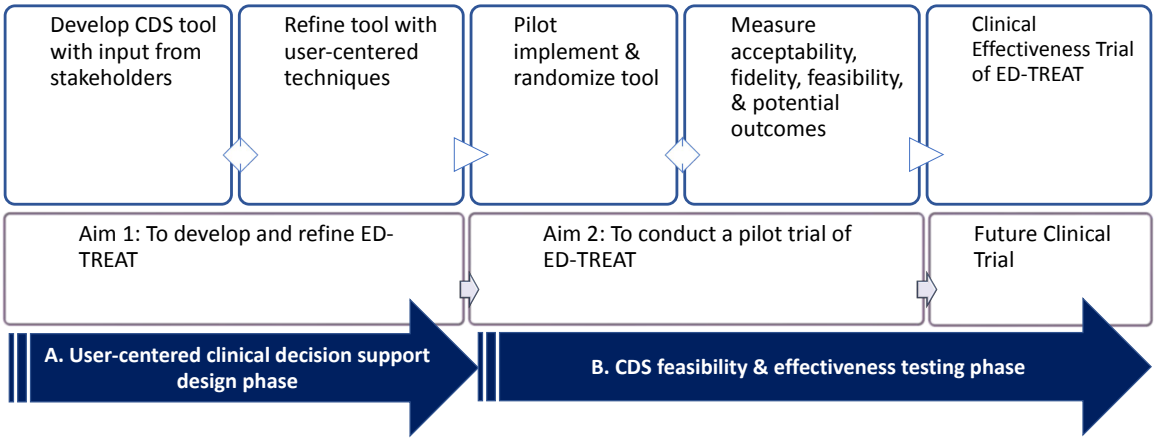
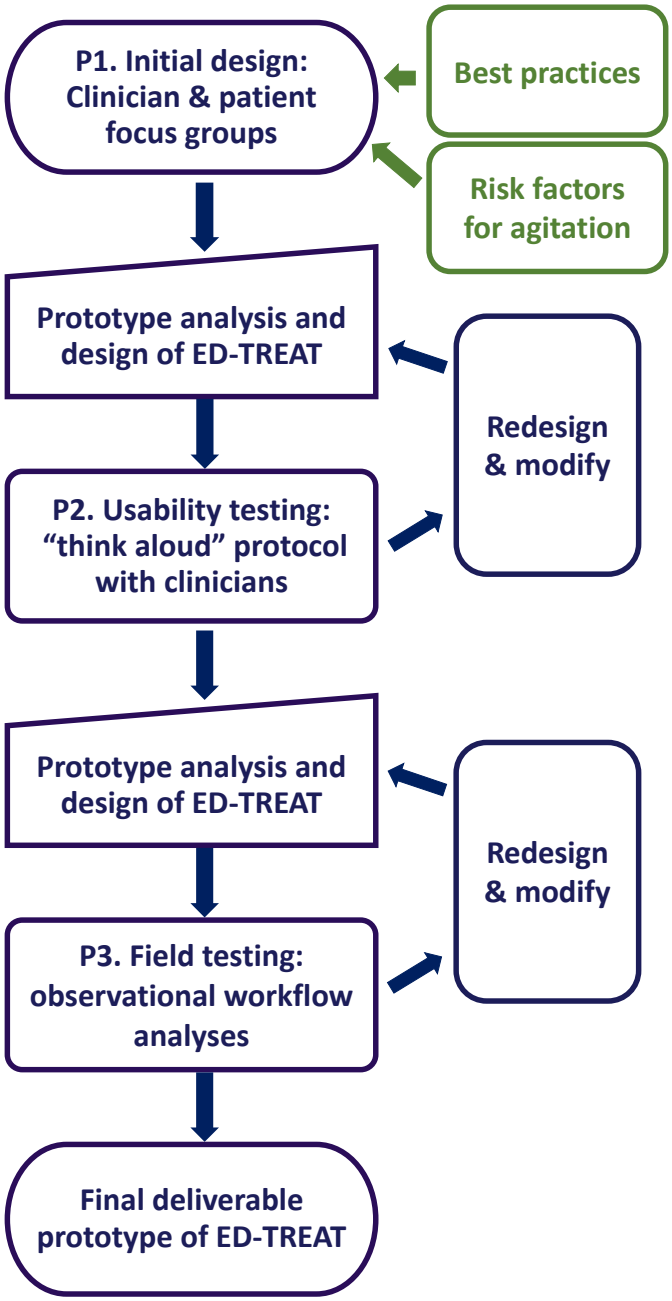
Figure titles

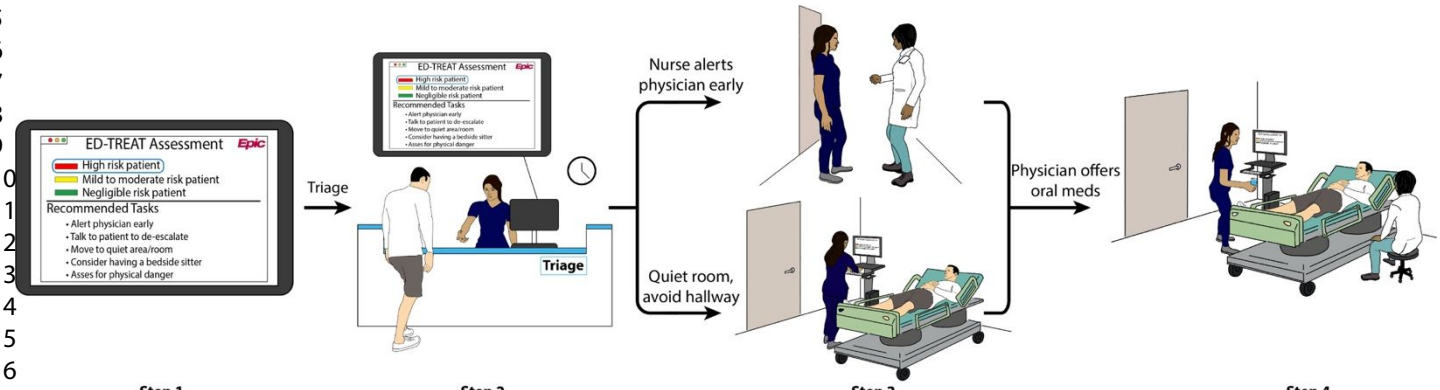
Figure 1. Overview and steps for each phase of ED-TREAT design and pilot implementation study

Figure 2. Overview and steps for Aim 1: ED-TREAT user-centered design and prototype development

Figure 3. Anticipated clinical steps for the intervention arm of ED-TREAT




P1. Initial design: Clinician & patient focus groups
Best practices
Risk factors for agitation
Prototype analysis and design of ED-TREAT
Redesign & modify
P2. Usability testing: "think aloud" protocol with clinicians
Prototype analysis and design of ED-TREAT
Redesign & modify
P3. Field testing: observational workflow analyses
Final deliverable prototype of ED-TREAT



Step 1. Initial Arrival

Step 2. Triage

Step 3. Nurse Interaction

Step 4. Physician Interaction

Supplemental Table 1: Sample focus group topics for design and development of ED-TREAT (P1)	
Design Domain[51]	**Example factors and sample question prompts**
User groups	• Timing, benefits & obstacles to using CDS for managing at-risk patients • Attitudes, beliefs, & knowledge regarding treatment of at-risk patients • Potential impact of ED-TREAT on patient experience and needs during visit
Tasks and technology	• Potential formats and interfaces for ED-TREAT prototype • Types of data and information to be included in ED-TREAT • Clinician interface with EHR and clinical duties related to ED-TREAT recommendations
System and organization	• Potential effect of ED-TREAT on management of at-risk patients • Workflow and care coordination amongst team members that can impact ED-TREAT across user types • Facilitators & barriers to implementing best practices for preventing agitation in real-world clinical environment

Supplemental Table 2: Potential risk factors that predict development of agitation in the ED	
Domain	**Data elements**
Patient factors	• Violence history: presence of violence alert, Brøset Violence Checklist (BVC)[54] • History: chief complaint, psychiatric/medical history, alcohol/substance use, # ED visits/year, medications
Clinical data	• Laboratory data: complete blood count, urine toxicology, point-of-care glucose & alcohol, basic metabolic panel • Initial vital signs: heart rate, temperature, systolic/diastolic blood pressures, oxygen saturation, respiratory rate • Restraint characteristics: type/route/dose of chemical sedative(s) used, reasons for & type of physical restraint
Environment	• Physical parameters: initial bed location assignment, hallway spot, time of day of presentation • Staff contact: initial staff contact, staff characteristics & interactions, presence of security officers at arrival into ED
System	• Pre-arrival: mode of transport into ED, presence of law enforcement escort • Outpatient services: mental health visits, assertive community treatment, rehabilitation services

Suppemental Table 3: Sample usability testing topics and observational tasks (field testing)	
Usability testing goals and objectives (P2)	**Field testing observation task examples (P3)**
• Effectiveness: Ability of users to achieve task goals • Efficiency: Time/speed to complete tasks within tool • Satisfaction: Ease of use & acceptability of ED-TREAT • Understandability: Users comprehending what ED-TREAT can do • Learnability: Training/time/effort to learn how to use ED-TREAT • Operability: Support of user and overcoming potential problems • Flexibility: Ability to accommodate for different situations/needs • Attractiveness: Motivation of user interest to explore/use system	• Triage assessment and room assignment • Initial contact at bedside and assessment • Potential structural biases and differential treatment plans • History and physical exam, monitoring and re-assessment • De-escalation and establishing rapport • Ordering of medications, laboratory & imaging tests • Patient behaviors, responses, experiences • EHR documentation & interface with ED-TREAT

YALE UNIVERSITY
YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL

Verbal Consent for Participation in a Research Study

Title: Early Detection and Treatment to Reduce Events with Agitation Tool (ED-TREAT) Tool Development

Principal Investigator:
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Introduction

You are being asked to join a research study. The following information will explain the purpose of the study, what you will be asked to do, and the potential risks and benefits. You should ask questions before deciding whether you wish to participate, or at any time during the course of the study. You will be asked to provide verbal consent to participate at the end of this process.

Purpose

The purpose of this study is to develop and refine the Early Detection and Treatment to Reduce Events with Agitation Tool (ED-TREAT) by engaging patients in the process. ED-TREAT will be a clinical decision support tool in the electronic health record to help clinicians at the point of initial encounter in preventing agitation and aggressive behavior during a visit to the emergency department. We wish to receive input from patients directly for development and refinement of ED-TREAT during initial design of ED-TREAT.

You are being asked to participate because you work as a peer support worker and/or have been physically restrained as a patient in the emergency department (ED).

Procedures

As part of this study, we will ask you to participate in a 60 to 90-minute online or in-person focus group where we will discuss your experience with agitation events, how a decision tool to detect agitation can impact/improve management of agitation, and what design for a clinical decision tool would best help prevention of agitation and/or your experience in the ED.

Possible Risks

There are minimal risks to you for participation in this study. To protect your anonymity you will be assigned a study number and subsequently will be identified only through this number. Only research investigators will have access to the data. Electronic data will be maintained in password-protected files or on a password-protected online serve that only the PI and research assistant may access. All data will be maintained securely for three years after the conclusion of the study, at which time it will be permanently destroyed.

We are counting the numbers of participants, but assure you that your answers will be anonymized before they are analyzed by the research team. Your contributions will be secured and protected throughout the study and will remain confidential to everyone including the research team.

Voluntary Participation

Participation in this study is completely voluntary. Your email response will count as verbal consent to participate. However, you are free to decline to participate, to end participation at any time for any reason, or to refuse to answer any individual question at any time. You may withdraw from the study at any time without negative consequences. Your responses and decision to participate or withdraw from participation will not affect your relationship with Yale School of Medicine, Yale-New Haven Health, or any affiliated locations of employment or healthcare delivery. You will only be asked to participate for one phase of the study and will not be required or asked again to join another phase of the study.

Questions

If you have any further questions about this study or the focus group questions, you may contact the investigator, Dr. Ambrose Wong, MD, MSEd, at (203) 737-2489 or at ambrose.wong@yale.edu. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15-16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15-16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2, 9, 14
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5, 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9, 12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12-14
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12, 14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4-14

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, 10, 11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14-15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14-15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9, 11, 14-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12, 14-15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14-15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.