HIC#2000025000

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL (2020)

Protocol Title: *R*isk *EV*aluation *A*nd its Impact on Clinic*AL* Decision Making and Outcomes in *H*eart *F*ailure at Yale: The REVeAL-HF Trial (www.reveal-hf.com)

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Version Date: 3/23/20

Clinicaltrials.gov Registration #: NCT03845660

SECTION I: RESEARCH PLAN

Statement of Purpose: Heart failure is the major cause of mortality and morbidity in the United States and Western Europe and prognosis in individual patients is highly variable.[1] Quantifying a patient's survival prospects based on their overall risk profile has the potential to help identify those patients in need of more intensive monitoring and help target appropriate populations for therapies. In fact, several comprehensive risk scores in patients with heart failure are currently available of both reduced and preserved ejection fraction but their applicability to contemporary heart failure populations is unknown.[2,3] Additionally, the impact of knowing a patient's prognostic information on treatment decisions in heart failure has never been studied.[2,4-6] In fact, guidelines do not recommend using risk assessments to decide on therapeutic decision making in heart failure due to a lack of data for this strategy.

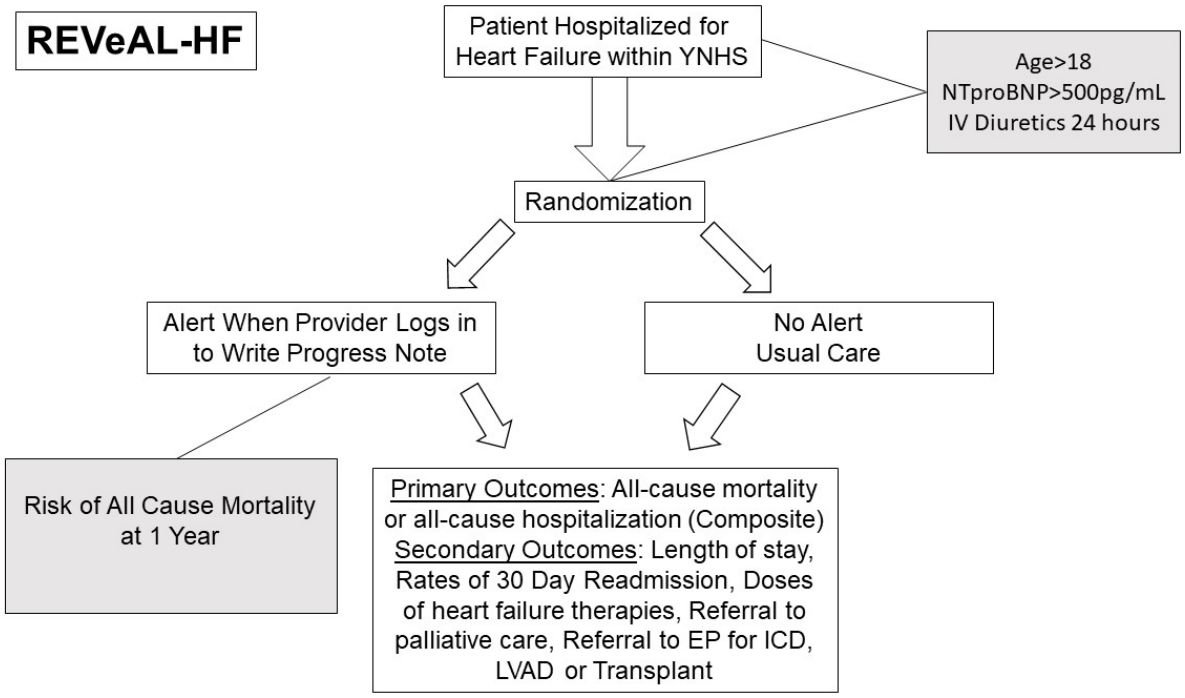
We therefore propose a randomized controlled trial of an electronic alert system that informs practitioners about their patients risk of 1-year predicted mortality using data from the electronic health record (EHR) in the inpatient setting.[7] The primary outcome for the trial will be a composite of all-cause mortality and 30-day risk of heart failure rehospitalization. The secondary outcomes will be length of stay, discharge doses of heart failure therapies, palliative care referral, referral for advanced therapies like transplant or mechanical circulatory support, referral to electrophysiology, and change in weight during hospitalization (aggressiveness of diuresis). We will enroll into the trial across 4 major teaching hospitals that comprise the Yale New Haven Health System: Yale New Haven Hospital, Hospital of Saint Raphael, Bridgeport Hospital, and Greenwich Hospital.

Probable Duration of Project: Approximately 4000 unique patients with a diagnosis of heart failure are seen annually at the proposed sites, with a planned enrollment of 3124 patient which will start soon after IRB approval, we estimate, conservatively, that the study will take 5 years to complete.

APPROVED BY THE YALE UNIVERSITY IRB 3/24/2020

Background: Heart failure is a complex and heterogenous disease with mortality and morbidity that equals more cancers.[8] Numerous studies have examined the ability to improve prognostication from heart failure, ranging from basic statistical methodologies to machine learning, with impressive improvements in both predictive indices. However, no study to date has examined, in a randomized fashion, the impact of providing prognostic information on provider behavior and downstream clinical outcomes. It is for this reason that we plan to perform the REVeAL-HF Trial within the Yale New Haven Health System (www.reveal-hf.com).

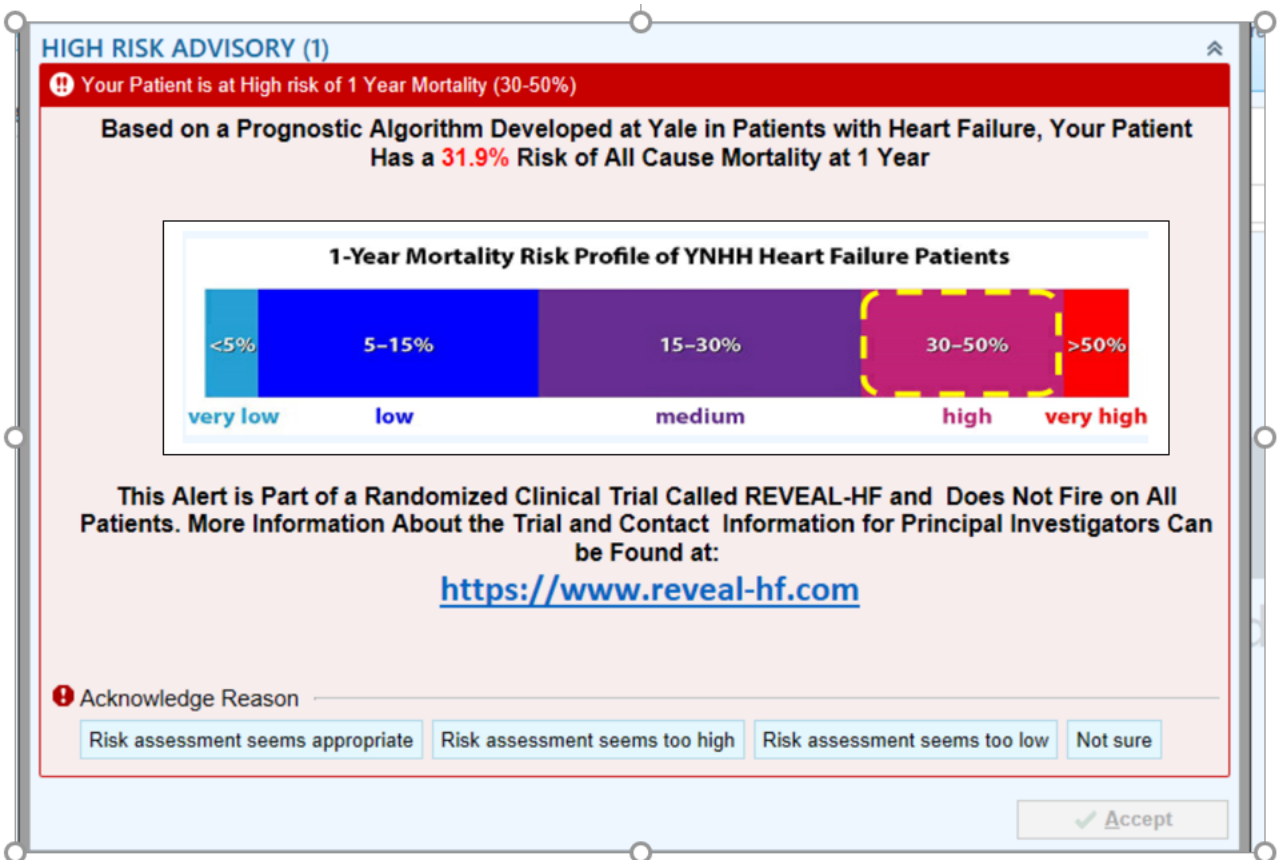
Research Plan: We plan to conduct a randomized, single-blind intervention trial that is testing the clinical impact of providing prognostic information to the provider on heart failure outcomes in the inpatient settings. Our hypothesis is that electronic alerting about prognostic information on heart failure patients will lead to reductions in all-cause mortality and 30-day HF hospitalizations via improved use of therapies. The following is the study flow diagram:



Due to the nature of this research, subjects will be recruited when electronically identified. The inclusion criteria will be all adults ≥18 years who have an NTproBNP levels of >500 pg/mL and received intravenous diuretics within 24 hours of admission within the YNHS. Identification of subjects will be performed within the EPIC system, using a best-practice alert build developed by JDAT. The build will focus on patients admitted to 4 teaching hospitals that comprise the YNHS with a diagnosis of heart failure.

As this is an intervention assessing the influence of an alert system on provider behaviors surrounding heart failure prognosis, we cannot inform patients of their participation in the study at the time of enrollment, as this would contaminate the randomized exposure. Patients randomized to the intervention will have an alert of their prognosis based on the best available prognostic model for 1-year mortality generated with information from their electronic health

record, which will consist of a "pop-up" when the provider accesses a patient record to enter an order. Providers will also have access to a link to best available guideline recommended information regarding treatment of heart failure via a website link (www.reveal-hf.com). Providers who will receive an alert include physicians, physician assistants (PA's), nurse practitioners (NP's), advanced practice registered nurses (APRN's), fellows, physicians, and residents. Any of the above type of providers will receive the alert only when the chart is open to enter a progress note.



Endpoints: The co-primary endpoints of the study will be all-cause mortality during hospitalization and at 1 year as well as rates of 30 days readmission. The secondary endpoints will be: length of stay, discharge doses of heart failure therapies, palliative care referral, referral for advanced heart failure therapies, referral to electrophysiology, and change in weight during hospitalization (aggressiveness of diuresis).

Engaging Providers: While the unit of randomization is the patient, clinicians may also be considered subjects of this research. We will engage in pre-trial and periodic outreach to all clinicians who may be exposed to this study, informing them of the nature of the study, the fact that it is a randomized trial, and that alerts do not fire for all patients with heart failure. We will additionally inform them that limited data is being collected regarding provider behavior. However, we will also make it clear that data subject to clinician will not be linked to individual clinicians. All such data will only be analyzed in aggregate.

Method for Assigning Subjects to Intervention: Subjects will be randomized via simple randomization in concealed allocation to either the intervention or the control arm via the Epic electronic medical record; there will be no human intervention regarding the randomization process.

Prior and Concomitant Therapy: All therapies are permissible within this protocol.

Blinding of Intervention: Subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. Also, there are no guideline-based specific recommendations based on a risk score assessment, or any other prognostic assessment for that matter. All investigators will be blinded to treatment assignment until the end of the trial period. Care providers will, obviously, not be blinded to the intervention as they are receiving the alert. We will engage in both pre-trial and periodic teaching and discussion with all care providers (administered through short presentations at divisional conferences) to inform clinicians about the nature of the study, the fact that prognosis alerts do not fire for all patients with heart failure and to discuss specific factors that are being measured.

Intervention Duration: The prognosis alert will be displayed to the relevant provider whenever the chart is opened to enter an order. If the provider dismisses the alert, it will continue to "pop-up" on each subsequent opening of the patient's medical record. The alert will stop firing for the provider under the following conditions.

- The provider asks to no longer see the alert
- The patient is transferred to the hospice service
- The patient is discharged from the hospital

Randomization: Randomization will occur the moment the patient meets the inclusion criteria by the electronic monitoring system within the EPIC best practice alert framework as developed by JDAT. Beyond the primary intervention, no further tests or procedures will be performed on subjects in this trial. Randomization is achieved within the Epic EHR system using an internal randomization method. Randomization occurs within the Epic system using a random number rule that is incorporated in the alert. This ensures that, upon meeting criteria, each patient is immediately and randomly assigned to an arm. Logic checks within the alerts ensure that once a patient is assigned to an arm, they remain on that arm for the remainder of their hospital stay.

Genetic Testing **N/A** ☒ No biological material will be collected on patients.

1. **Subject Population:** We will aim to recruit approximately 4000 patients who are admitted with a diagnosis of heart failure at 4 teaching hospitals within the YNHS.

2. **Subject classification:** N/A

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons

☐ Decisionally Impaired and/or fetuses ☐ Employees ☐Pregnant women

☐Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

No ☒

Inclusion/Exclusion Criteria:

- Age >18
- NTproBNP levels of >500pg/mL within 24 hours of admission
- Intravenous diuretics within 24 hours of admission

How will eligibility be determined, and by whom? Randomization will occur the moment the patient meets the inclusion criteria (see above) by the electronic monitoring system within the EPIC best practice alert framework as developed by JDAT.

Protection of Human Subjects: This Human Subjects Research meets the definition Non-Exempt Human Subjects Research. Here we outline our plan to protect human subjects based on the current iteration of our proposed research.

Modifications Made in Response to Findings from the Electronic Alerts for the recently completed Acute Kidney Injury Amelioration (ELAIA-1) trial: The recently completed ELAIA-1 trial was *negative*. Alerts about acute kidney injury (AKI) did not reduce progression, dialysis initiation or death rates among hospitalized patients with AKI. However, there was a small signal for harm at *one* non-teaching hospital (Lawrence and Memorial Hospital). *Despite* heart failure being an *entirely* different disease state and the intervention being tested in REVAL-HF being *non-prescriptive*, we are making the following modifications to the study out of an abundance of caution. *These have been made in partnership with the leadership at both Yale School of Medicine/Yale Center for Clinical Investigation (YCCI) and Yale New Haven Hospital: Drs. Brian Smith (YCCI), Teisha Johnson (YCCI), Allen Hsiao (YNHS), and Nitu Kashyap (YNHS) who believe that studies of decision support tools continue to pose minimal risk to patients.* The changes are as follows:

- We will restrict the study only to *teaching* hospitals within the YNHS: Yale New Haven, Greenwich, Bridgeport, Saint Raphael
- Our Data Safety Monitoring committee will perform an interim analysis of the data at 50% enrollment

Human subjects' involvement, characteristics and design: The studies outlined in this proposal depend on the enrollment of hospitalized individuals with heart failure. No vulnerable populations are being specifically targeted. We are limiting enrollment to individuals above age 18 years as the etiology and practices surrounding heart failure in pediatrics populations differ significantly from those in adults. All data is transmitted in encrypted and secure fashion, stored on servers with "triple-lock" certification, and is available only to members of the study team, IRB, and any state or federal agencies with auditing power.

Sources of Materials: No biological materials will be obtained or stored as part of these studies. Only data, as collected during routine medical care will be obtained. Data includes medical record elements such as demographics, medication usage and dosing, laboratory values, and administrative codes. All data will be stored in the absence of PHI, though we will retain a linking dataset to be able to re-link individual data to actual patients for future studies (for example, studies examining longer term outcomes of patients, which may require linking to national datasets). Access to individually identifiable information will be limited to the executive committee of the study, and only then via a linking file as aforementioned. All data used for analysis and dissemination to other investigators will be de-identified.

Potential risks: The risks to subjects in these trials is minimal, as the studies randomize them to usual care versus an alert that simply synthesizes data that is already present in the medical record.

Over or under treatment: If alerts affect physician behavior, then patients randomized to an alert arm may be more or less likely to undergo certain tests or interventions. These interventions fall within the standard-of-care and may benefit patients, but it is also possible that additional interventions may not benefit patients and could incur additional costs. However, this is what we are testing as part of this pragmatic trial.

Alert Fatigue: We have modified the protocol in response to findings from the AKI-Alert study at Yale. The following are the interventions we have made:

A. Alert is both sensitive and specific to heart failure by including NTproBNP and IV diuretics as inclusion criteria
B. Alert only fires when clinician enters chart to place order. This prevents clinicians who are peripheral to the patients care from getting alert and focusing on alerts during a more reflective time in the workflow.

Even with these changes, it is possible that alert fatigue might result. While a potential risk, this is also a major motivation of this line of research, as only via randomized trials can truly effective alerts be discovered. Should no effect be found in these studies, alerts will not be continued at the institution.

Adequacy of Protection Against Risks: The study is being conducted under a waiver of informed consent. This research is minimal risk, as outlined above, and cannot be practicably performed in the absence of a waiver of informed consent as it would terminally contaminate the study. There is no infringement of rights or welfare of patients, as the alert has no direct effect on the patient, short of via the actions of their providers. Data abstracted from the medical record will be de-identified, as described in the confidentiality section above. Another defense against these risks is the alert language itself. Each alert calls attention to the fact that alerts are not issued for all patients with heart failure.

Potential benefits of the proposed research to the subjects and others: Subjects in this study may benefit from their provider being given information about their prognosis. Regardless of the outcome for participants, the results of these studies may lead to significant societal benefit, as even a negative study would lead to less enthusiastic adoption of ineffective

alerting. The risk/benefit ratio, given the minimal risk to study subjects, is more than acceptable in this series of studies.

Data and Safety Monitoring Plan:

- *What is the investigator's assessment of the overall risk level for subjects participating in this study?* We believe that this poses minimal risk to the patients

- *If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?* No children will be involved.

Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

i. **Minimal risk**
ii. Greater than minimal

The principal investigators (PI) is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency regularly. During the review process the PIs will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The PIs or the Institutional Review Board (IRB) has the authority to stop or suspend the study or require modifications.

Despite this being a minimal risk study, we reviewed results of the AKI-Alert study that was recently completed that showed a small signal of harm at a *non-teaching* hospital within the YNHS. We realize that heart failure is an entirely different disease state and the intervention being tested in REVAL-HF being non-prescriptive. Out of an abundance of caution, we decided to include an independent DSMB that will review the study results 50% enrollment. These have been made in partnership with the leadership at both Yale School of Medicine/Yale Center for Clinical Investigation (YCCI) and Yale New Haven Hospital: Drs. Brian Smith (YCCI), Teisha Johnson (YCCI), Allen Hsaio (YNHS), and Nitu Kashyap (YNHS) who believe that studies of decision support tools continue to pose minimal risk to patients. Of note, we are also restricting the study only to teaching hospitals within the YNHS: Yale New Haven, Greenwich, Bridgeport, Saint Raphael.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings and via email as they are reviewed by the principal investigator.

d. For multi-site studies for which the Yale PI serves as the lead investigator: **this is a single-center study**
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

Statistical Considerations

Sample Size Determination: The composite outcome of 30-day heart failure hospitalization and 1-year mortality occurs in approximately 30% of HF patients. A reduction in this proportion to 25% in the intervention arm would be considered clinically meaningful. To that end, a sample size of 1562 in each arm achieves 90% power to detect a difference this large at a two-sided alpha of 0.05 as calculated using the Cochran-Mantel-Haenszel test. This gives a total population of 3124 individuals hospitalized with heart failure in order to test our primary hypothesis.

Primary Analysis: The primary analysis will utilize the intention to treat principle. The proportion of patients experiencing the primary outcome in the intervention and control groups will be compared by the Cochran-Mantel-Haenszel test. Statistical significance will be based on a *P* value of <0.048.

Interim Analysis: We plan to have one interim analysis when 50% of the patients have been enrolled. The interim analysis will allow us to alter the sample size or stop the trial earlier for ethical considerations, unexpected adverse events, or high efficacy. Earlier stopping will be considered for the reason of safety and efficacy. The trial will stop for declaring efficacy if the effect size is large. We will use the O'Brien and Fleming stopping rule to stop the trial earlier if the *P* value is 0.005 for efficacy. Alerting harm will also be assessed using the primary outcome, with a stopping threshold at a *P* value of 0.005. Following is the breakdown regarding enrollment at each hospital:

Hospital	Beds	%	Patients to enroll	Total Patients
Bridgeport Hospital	383	17.98	562	3124
Greenwich Hospital	206	9.67	302	
St. Ray's	511	23.99	749	
YNHH	1030	48.36	1511	
Total	2130		3124	

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

C. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: 4000 participants

b. If this is a multi-site study, give the total number of subjects targeted across all sites: NA

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	

*** Requests for medical records should be made through JDAT as described at** http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

Describe how potential subjects will be identified: Patients will be identified based on the following inclusion/exclusion criteria:

- Age >18
- NTproBNP levels of >500pg/mL within 24 hours of admission
- Intravenous diuretics within 24 hours of admission
- We will exclude patients who have opted out of research

Describe how potential subjects are contacted. While the unit of randomization is the patient, clinicians may be considered subjects of this research. We will engage in pre-trial and periodic outreach to all clinicians who may be exposed to this study, informing them of the nature of the study, the fact that it is a randomized trial, and that alerts do not fire for all

patients with heart failure. We will additionally inform them that limited data is being collected regarding provider behavior. However, we will also make it clear that data subject to clinician will not be linked to individual clinicians. All such data will only be analyzed in aggregate.

Who is recruiting potential subjects? This will be done electronically via the electronic health record. Patients will be identified if they are admitted to the hospital and meet the inclusion and exclusion criteria stated above.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☒Yes, some of the subjects

☐No

If yes, describe the nature of this relationship. Some members of the research team might have previously treated a subject. We do not foresee this impacting the care of any patient.

5. Request for waiver of HIPAA authorization: We are requesting HIPAA Waiver
Choose one:

☒ For entire study

☐ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. **Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data**: Subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. *Also, there are no guideline-based specific recommendations based on a risk score assessment, or any other prognostic assessment for that matter.* All investigators will be blinded to treatment assignment until the end of the trial period. Care providers will, obviously, not be blinded to the intervention as they are receiving the alert. We will engage in both pre-trial and periodic teaching and discussion with all care providers (administered through short presentations at divisional conferences) to inform clinicians about the nature of the study, the fact that prognosis alerts do not fire for all patients with heart failure and to discuss specific factors that are being measured. The following letter will be sent to providers who will take care of heart failure patients:

"Dear Provider,

We are conducting a pragmatic clinical trial via the electronic health record (EHR) that examines the impact of an electronic alert system that informs practitioners about their heart failure patients' risk of mortality on therapeutic decision making [HIC#2000025000]. The subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. Care providers will not be blinded to the intervention as they are receiving the alert. They have the option to ignore the alert and request that it not fire again. Any data collected will not be linked to individual clinicians and will only be analyzed in aggregate.

Please feel free to contact me with any questions or concerns.

With Warmest Regards,

Tariq Ahmad MD MPH
Cell phone: 203-843-1667
Email: tariq.ahmad@yale.edu"

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: The study is being conducted under a waiver of informed consent. This research is minimal risk, as outlined above, and cannot be practicably performed in the absence of a waiver of informed consent (as patients randomized to the usual care arm would be required not to reveal their HF diagnosis to their providers). There is no infringement of rights or welfare of patients, as the alert has no direct effect on the patient, short of via the actions of their providers. Data abstracted from the medical record will be de-identified, as described in the confidentiality section above. Another defense against these risks is the alert language itself. Each alert calls attention to the fact that alerts are not issued for all patients with heart failure.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. Also, there are no guideline-based specific recommendations based on a risk score assessment, or any other prognostic assessment for that matter. All investigators will be blinded to treatment assignment until the end of the trial period. Care

providers will, obviously, not be blinded to the intervention as they are receiving the alert. We will engage in both pre-trial and periodic teaching and discussion with all care providers (administered through short presentations at divisional conferences) to inform clinicians about the nature of the study, the fact that prognosis alerts do not fire for all patients with heart failure and to discuss specific factors that are being measured.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** N/A (see above).

8. **Non-English-Speaking Subjects:** Since the focus of this study is provider behavior, the language status of the subject would not matter.

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐**Not Requesting any consent waivers**

☒**Requesting a waiver of signed consent:**

☐ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☒ **Entire Study (**Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? **YES ☐ NO ☐**
- Does a breach of confidentiality constitute the principal risk to subjects? **YES ☐ NO ☐**

OR

- Does the research pose greater than minimal risk? **YES ☐ NO☒**
- Does the research include any activities that would require signed consent in a non-research context? **YES ☐ NO ☒**

☒ **Requesting a waiver of consent:**

☐ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☒ **Entire Study**

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ **Yes** ***If you answered yes, stop. A waiver cannot be granted.***
  ☒ **No**
- Will the waiver adversely affect subjects' rights and welfare? **YES ☐ NO☒**
- **Why would the research be impracticable to conduct without the waiver?** The research proposed is of minimal risk to subjects. No procedures or tests are being performed. No additional studies are being requested. The sole intervention is an electronic alert that will be sent to relevant members of the subjects' clinical care team. The risk of the alert itself is minimal. Subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled. Also, there are no guideline-based specific recommendations based on a risk score assessment, or any other prognostic assessment for that matter. All investigators will be blinded to treatment assignment until the end of the trial period. Care providers will, obviously, not be blinded to the intervention as they are receiving the alert. We will engage in both pre-trial and periodic teaching and discussion with all care providers (administered through short presentations at divisional conferences) to inform clinicians about the nature of the study, the fact that prognosis alerts do not fire for all patients with heart failure and to discuss specific factors that are being measured.
- **Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?** We expect that there will be considerable academic output that results from these efforts. This will be shared with the providers who participated in the study and any publication that result will be made available to the general public.

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. **What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?** Age, gender, date of birth and several categories of health information (provider encounters, notes,

comorbidity, medication lists, problem lists, family history, allergies, laboratory findings, procedures, immunizations, vital signs, and medical record numbers) and relevant clinical outcomes will be collected on subjects. This data will be deidentified. Individual provider data will not be collected.

2. **How will the research data be collected, recorded and stored?** This data will initially be transferred to The Program of Applied Translational Research (PATR) to a data analyst associated with this project for cleaning. All YNHS patient data will then be shared using Yale ITS managed file transfer. This platform is a web-based application used to share data packages over the internet through a secure channel. When being shared, the data will be encrypted using https secure protocol. Access to this data will only by available to study personnel who are a part of the study team.

3. **How will the digital data be stored?** ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☐Desktop Computer ☐Other

4. **What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?** All data used at Yale will be transferred over secure channels and encrypted during sending. Data will be stored on 3-lock compliant servers within Yale or on secure, Yale-issued IronKey devices. Only study personnel directly involved in data analysis with a need to access PHI will have access to these data.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. **What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.** Data will be maintained on secure, encrypted servers at the Program of Applied Translational Research (PATR) after completion of the research study for a minimum of 5 years after publication of our findings in a peer-reviewed journal (in such case as there is a need to return to the original data source to validate a finding or respond to a question).

6. **If appropriate, has a Certificate of Confidentiality been obtained?**
   Since the data obtained are from broad health characteristics from personal health records that do not target any particular sensitive research areas, a CoC has not been obtained.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Subjects in this study may benefit from their provider being given information about their prognosis. Regardless of the outcome for participants, the results of these studies may lead to significant societal benefit, as even a negative study would lead to

less enthusiastic adoption of ineffective alerting. The risk/benefit ratio, given the minimal risk to study subjects, is more than acceptable in this series of studies.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** The provider can dismiss the alert if they choose.

2. **Payments for Participation (Economic Considerations):** There will be no monetary compensation.

3. **Costs for Participation (Economic Considerations):** None.

4. **In Case of Injury:** Not applicable.

IMPORTANT REMINDERS

Will this study have a billable service? **No**☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes** ☐

If Yes, please answer questions a through c and note instructions below.
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes** ☐
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? ☐ **No** ☐
c. Will a novel approach using existing equipment be applied? **No** ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

References:

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2. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J.* 2013;34(19):1404-1413.
3. Peterson PN, Rumsfeld JS, Liang L, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes.* 2010;3(1):25-32.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013.
5. Allen LA, Matlock DD, Shetterly SM, et al. Use of Risk Models to Predict Death in the Next Year Among Individual Ambulatory Patients With Heart Failure. *JAMA Cardiol.* 2017;2(4):435-441.
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7. Yancy CW, Januzzi JL, Jr., Allen LA, et al. 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol.* 2018;71(2):201-230.
8. Ahmad T, Desai N, Wilson F, et al. Clinical Implications of Cluster Analysis-Based Classification of Acute Decompensated Heart Failure and Correlation with Bedside Hemodynamic Profiles. *PLoS One.* 2016;11(2):e0145881.
9. Wilson FP, Greenberg JH. Acute Kidney Injury in Real Time: Prediction, Alerts, and Clinical Decision Support. *Nephron.* 2018;140(2):116-119.