Validation and Feasibility of the Coma Recovery Scale-Revised for Accelerated Standardized Assessment (CRSR-FAST): a Brief, Standardized Assessment Instrument to Monitor Recovery of Consciousness in the Intensive Care Unit

ClinicalTrials.Gov: NCT03549572

February 08, 2023

PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Dr. Yelena Bodien

SITE PI
Dr. Brian Edlow

PROTOCOL TITLE
The Coma Recovery Scale-Revised for Accelerated Standardized Assessment (CRSR-FAST): an abbreviated assessment of conscious awareness for patients with disorders of consciousness (DOC)

FUNDING
National Institute on Disability, Independent Living, and Rehabilitation Research, U.S. Department of Health and Human Services

VERSION DATE
02/08/2023

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Specific Aims:
Determine the reliability, validity, sensitivity/specificity and administration time of the CRSR-FAST in the acute care setting.

Hypotheses:

Hypothesis 1: Concurrent validity between CRSR-FAST and CRS-R total scores will be adequate.

Hypothesis 2: Inter-rater reliability of CRSR-FAST-derived diagnostic ratings (conscious v. unconscious) will be adequate.

Hypothesis 3: Test-retest reliability of CRSR-FAST-derived diagnostic ratings (conscious v. unconscious) will be adequate.

Hypothesis 4: Internal consistency between the CRSR-FAST total score and the four subscale scores will be adequate.

Hypothesis 5: The sensitivity of the CRSR-FAST in detecting features of MCS (using the CRS-R as a reference standard) will be adequate.

Hypothesis 6: The average administration time for the CRSR-FAST when administered in the acute care setting will be ≤ 10 minutes.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

The CRS-R[1] is a standardized and validated bedside assessment of conscious awareness. It is used routinely for diagnosis and prognosis of patients with disorders of consciousness (DOC) as well as in research settings. One limitation of the CRS-R is the lengthy administration time required to obtain a total score. Administration time can vary from approximately 15-30 minutes, depending on the patient's level of responsiveness. For this reason, the CRS-R is rarely administered in the acute hospital setting. Less time-consuming scales and metrics are used to assess conscious awareness in the acute hospital/ICU setting, but they lack specificity and sensitivity and have not been validated, increasing the potential for misdiagnosis[2]. In conjunction with the developers of the Neuroscore (an unpublished, abbreviated version of the CRS-R[3]), we have developed the CRSR-FAST and aim to test its validity, inter- and intra- rater reliability. We anticipate that, compared with the CRS-R, the CRSR-FAST will be less time-consuming to administer and score, but will maintain a high level of sensitivity to detecting signs of consciousness in severely brain injured patients.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Study design: prospective, cross-sectional study

Participants: 75 subjects

Inclusion Criteria:

- Age 18 or older
- Fluent in English
- Surrogate available to provide informed consent
- History of severe acquired brain injury
- Sustained a TBI (defined by damage to brain tissue caused by an external mechanical force),
- Be within 3 weeks of injury
- Have a total GCS score <9 within the first 48 hours of injury,

- Be unable to follow simple commands consistently at the time of enrollment

Exclusion Criteria:

- History of developmental, neurologic, or major psychiatric disorder resulting in ongoing functional disability up to the time of the current injury
- Physician orders for comfort measures only

The following clinical factors will necessitate deferral of enrollment until the condition or symptom has resolved:

- Evidence of a reversible medical condition or symptom that is judged to be a safety concern or threat to the validity of the assessment, as deemed by treating physician

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Neurobehavioral Assessment

Patients will be assessed using the CRS-R and the CRSR-FAST. The CRS-R is a standardized neurobehavioral rating scale that consists of 23 items organized into six subscales that address arousal, auditory, visual, motor, oromotor/verbal, and communication systems. Each subscale is organized hierarchically, with lower items representing reflexive behaviors and higher items indicative of cognitively-mediated behaviors. Reliability and validity have been demonstrated in multiple studies[1]. The CRSR-FAST consists of 10 items organized into 4 subscales that address arousal, visual, motor and verbal/oromotor systems. Each subscale is organized hierarchically, with lower items representing reflexive behaviors and higher items indicative of cognitively-mediated behaviors.

An independent member of the study team (i.e., not an examiner) will screen patients at MGH for eligibility through a medical chart review. When a patient meeting the inclusion/exclusion criteria is identified, the study PI and study coordinator will be notified. The study coordinator will work with the patient's clinical team to determine an appropriate time to approach the family for consent. Consent may be conducted remotely or in-person at MGH. Once consent is obtained, the coordinator will work with the family and clinical team to determine an appropriate time to conduct the CRSR-FAST and CRS-R assessment(s). The study will conclude when a sample size of approximately 75 subjects is reached.

The study will be conducted across approximately 4 sessions completed over one or two consecutive days and will be carried out by three independent examiners (A, B, and C). For example:

Examiner A will administer the standard CRS-R and examiners B and C will administer the CRSR-FAST. This will enable calculation of concurrent validity (CRS-R v. CRSR-FAST) as well as inter-rater reliability of the CRSR-FAST (CRSR-FAST Rater A v. CRSR-FAST Rater B). Examiner C will administer the CRSR-FAST twice over a short interval to enable calculation of intra-rater reliability (CRSR-FAST Rater C at Time 1 v. CRSR-FAST Rater C at Time 2).

Examiners may include Yelena Bodien, Joseph Giacino, a dedicated TBI Model Systems research assistant, postdoctoral fellow, and a surgical intensive care unit Fellow.
The test administration order will be pseudo-randomized to prevent order effects and each test administration will be timed.
We will record concomitant medications, dosages and administration times.

Sharing Results with Surrogates and Clinicians
After discussion of the ethical implications of sharing or not sharing the CRS-R and CRSR-FAST with ICU clinicians, family member participants on the TBI Model System Advisory Board, and members of the investigator team with the patient's family and/or clinical team, we have developed the following approach:

-To avoid exposing families to multiple sources of information (i.e., information coming from the clinical team and the research team regarding level of consciousness,) we will not share the CRS-R or the CRSR-FAST data directly with families.
-Upon request, we will make the results of the full version of CRS-R available to the clinical team
-We will provide an option on the consent form allowing the family to opt-out of sharing data with the clinical team
-We will not provide the results of the CRSR-FAST to the clinical team because this is not a validated assessment and the reliability of detecting consciousness is unknown.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

This study does not include treatment or diagnosis.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The CRS-R has been in use for the last 25 years and has amassed a long track record of clinical and research utility. An Administration and Scoring Manual detailing all procedures is used to guide administration and limit adverse events. No reports of harm to patients or subjects arising from CRS-R administration have been reported since its inception.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

To ensure the safety of study subjects, the attending physician will provide medical authorization for participation in the study and identify any potential contraindications. Study procedures will be terminated if there is evidence of extensive distress or discomfort.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

There are no anticipated medical risks associated with the neurobehavioral examinations that will be conducted with the CRSR-FAST and CRS-R.

CRS-R and CRSR-FAST exams sometimes include brief application of noxious stimulation to assess motor responses in the absence of command-following. Discomfort typically lasts approximately 20 seconds and resolves completely. Similar applications of noxious stimulation to elicit localizing or withdrawal behaviors are used routinely in clinical care and are a critical part of assessing brainstem and cortical function.

<u>To protect patient participants against this risk</u>
It is not possible to eliminate the risk of physical discomfort in this study as administration of both scales may requires application of noxious stimulation to assess brain function. Prior to application of noxious stimulation, the examiner will review the medical record and/or speak with the clinical staff to identify any implanted catheters or devices to avoid stimulation at these sites. The examiner will also ensure that there is no local tissue damage at the site of stimulation.

Privacy and Confidentiality

Separating identifying material from data files will protect confidential information and securing both files in locked cabinet files and/or password protected electronic files. Surrogates will be informed that the Partners Institutional Review Board (IRB) may inspect identifying records and, therefore, absolute confidentiality cannot be assured.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

This study is not designed to be of direct benefit to the subjects. Results may aid diagnostic and prognostic assessment of DOC patients and may provide ICU clinicians with an efficient, reliable and validate tool for assessing conscious awareness. The minimal risks associated with this study are reasonable relative to the anticipated results.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The subjects are expected to be ethnically diverse and include participants of both genders.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Non-English speakers are excluded from the study because the CRSR-FAST is currently available only in English.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English

http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

An independent member of the study team (i.e., not an examiner) will screen patients at MGH (Lunder 6, Ellison 4 and Blake 12) for eligibility through a medical chart review. When a patient meeting the inclusion/exclusion criteria is identified, the study PI and study coordinator will be notified. The study coordinator will work with the patient's clinical team to determine an appropriate time to approach the family for consent. Once consent is obtained, the coordinator will work with the family and clinical team to determine an appropriate time to conduct the CRSR-FAST and CRS-R assessment(s).

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

There will be no cost to subjects for participation in this study. Subjects will not be paid for participation.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician

investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

All consent meetings for patients will be conducted either remotely (via telephone or Enterprise Zoom) or at MGH and will be conducted by trained members of the research staff. Remote consent procedures will comply with the MGB IRB guidance (https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/Documents/Policy%20on%20Conduct%20of%20Human%20Research%20Activities%20During%20COVID-19%20Operations.pdf and https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Informed-Consent-of-Research-Subjects.pdf). Specifically, when verbal consent procedures are used, subjects will be provided with a copy of the written informed consent document, fully informed about the study and given the opportunity to have all questions answered. Study staff will adhere to the relevant sections of the remote visit guidelines provided by the MGB IRB (i.e., the Clinical Research Virtual Visit Checklist). A script will be used to obtain surrogate consent and document the verbal consent. All email communications with surrogates will comply with the MGB IRB guidelines (https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/FAQs-Email-Communication-with-Research-Participans-and-Potential-Research-Participants.pdf).

Consent will be obtained from the patient's surrogate decision-maker as all subjects will, by definition, lack capacity. Surrogates approached about participation in the study will be clearly informed that participation is voluntary, that a decision not to participate will not jeopardize clinical care or participation in rehabilitation, and that study participation can be discontinued at any time during the study. If a surrogate withdraws from the study, they may request that the data be discarded. After discussing the terms of participation, procedures, and potential outcomes with the surrogate, consent will be obtained by a member of the research team.
No time limit will be placed on the surrogates to consider participation, though only patients within 3 weeks of injury will be enrolled.
The attending physician and nurse will be notified once the patient has been enrolled.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

An internal audit of all case report forms and database entries will be performed upon completion of study activities for each subject to ensure accuracy and completeness.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

In the unlikely case of an adverse event, the PI will follow all steps in the Partners IRB Adverse Event Reporting Protocol.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in

accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

As the PI of this study, Dr. Yelena Bodien will oversee and monitor all aspects of this study on an ongoing basis and will be accountable to the Partners IRB. In this capacity, Dr. Bodien will conduct regular (weekly) meetings of the research team and will notify the IRB in advance of any desired alterations to the study protocol or its early cessation.

To monitor and assure the validity and integrity of data and adherence to the IRB-approved protocol, prior to opening enrollment, meetings will be held with all members of the research team to review the protocol and address questions and concerns.

For guidance, refer to the following Partners policies:
Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/guidance.htm#13

Reporting Unanticipated Problems (including Adverse Events)
http://healthcare.partners.org/phsirb/guidance.htm#7

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Privacy and Confidentiality

Once family members sign the Informed Consent, or provide verbal consent, all participants will be assigned an identification number. Any identifying information will be stripped from study documents. A separate file will be maintained for cross-reference to allow for follow-up contact. Identifying information will be kept in a locked cabinet in a separate office accessible only by study staff. All research staff will have completed up-to-date CITI training prior to their involvement in this study.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

A limited data set (e.g., including dates of admission to MGH) will be shared with Dr. Ni Pengsheng, Research Associate Professor of Health Law, Policy and Management at Boston University who will assist with statistical analyses.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

No data will be stored at research collaborators outside of partners.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

No data from outside of Partners will be sent to Partners investigators.

RERERENCES

1. Giacino, J., K. Kalmar, and J. Whyte, *The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility.* Arch Phys Med Rehabil, 2004. **85**(12): p. 2020 - 2029.
2. Schnakers C., Vanhaudenhuyse A., Giacino J. et al. *Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment.* BMC Neurology 2009 9:35
3. Prisco, L., Ganau , M., and Berlot, G. Proposal of a new behavioral scoring system in neurointensive care unit: the NEUROSCORE. *Abstract* International Brain Injury Association's Ninth World Congress on Brain Injury, 2012

Statistical Analysis Plan

Examiners documented the start and end time of each assessment to determine the feasibility of the CRSR-FAST (goal: mean ≤10 minutes). We tested concurrent validity by comparing CRS-R and CRS-FAST diagnostic ratings (conscious [MCS or eMCS] vs. unconscious [coma or VS/UWS]), using the simple Kappa coefficient and CRSR-FAST test-retest and inter-rater reliability using Mak's ρ (Statistical Analysis System [SAS v9.4]). We established an a priori threshold of ≥ 0.60 to indicate substantial validity and reliability