NCATS Evolve to Next-Generation Accrual for Clinical Trials (ENACT)

Regulatory

ABSTRACT

The goal of the ENACT project is to build upon the federated network of sites from the National Clinical and Translational Science Award (CTSA) Consortium Accrual for Clinical Trials (ACT) project to allow for the performance of *in silico* trials and inform clinical care. To achieve this goal, we will leverage the widespread implementation of the electronic health record (EHR) and the well- established extensive informatics and regulatory expertise within the CTSA Consortium.

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1. Terms and Definitions

Belmont Principles: Derived from the Belmont Report[1], these are the principles of Beneficence, Justice, and Respect for Persons.

Central IRB: A single IRB will serve as the IRB of Record for ENACT in conformance with the requirement for Cooperative Research as laid out in the Common Rule §114. The Central IRB for ENACT enclaves will be the UC San Diego IRB.

Common Rule: 45 CFR 46 Subpart A.

Data Use Agreement (DUA): An agreement meeting the requirements of 45 CFR 164.514(e)(4). Data use agreements typically require or include the permitted uses and disclosures of the data by the recipient, no further use or disclosure of the data than that laid out in the data use agreement or required by law, use of appropriate safeguards to prevent unauthorized use and disclosure of the data, reporting of any unauthorized use to the covered entity that supplied the data, who may use or received the data, and that the individuals from whom the data is derived not be re-identified or contacted by the data recipient.

EHR: Electronic Health Record. Used in lieu of Electronic Medical Record (EMR) as well.

HIPAA Identifiers: Data elements which could be used to identify an individual as defined in 45 CFR 164.514(b)(2).

Institutional Review Board (IRB): A body established in accordance with 45 CFR 46.107 which reviews human subjects research on behalf of an institution.

Limited Data Set (LDS)[2]: A limited data set is protected health information that excludes certain direct identifiers of the individual or of relatives, employers, or household member of the individual. For a listing of excluded identifiers, see Section 5 of this document.

2. Regulatory Document

This document establishes the regulatory framework for ENACT that will enable ENACT Network Sites to contribute data from their EHRs to enable researchers at ENACT Network Sites to request and use an LDS in ephemeral (temporary) study-specific enclaves. Each ENACT Network Site will collaborate with other institutions within the ENACT Network consistent with a regulatory infrastructure that is required to leverage the EHR across designated CTSA sites nationwide. Each site will lend its expertise in the

[1] The Belmont Report
[2] 45 CFR 164.514(e)(2)

utilization of their EHR and regulatory expertise to navigate their institutional policies and procedures to launch the ENACT Network and conduct research studies. Previous guidance was provided to support research using only de-identified aggregated data. Future guidance will be provided to support research that requires direct identifiers.

3. Regulatory Principles

In developing the regulatory framework for ENACT, the Common Rule, the HIPAA Privacy Rule, and published guidance from the federal Office for Human Research Protections (OHRP) are adhered to in all cases. In addition, the Belmont Principles and general research ethics are incorporated.

4. Scope

The scope of ENACT requires each site to collaborate with other participating institutions within the CTSA consortium to leverage the EHRs across the ENACT network nationwide. Each site will lend its expertise in the utilization of their EHR, informatics infrastructure and regulatory expertise to navigate their institutional policies and procedures to support the ENACT Network and allow for the conduct of research studies using the Network. The scope of this document is to provide guidance on the creation and use of ephemeral enclaves that may contain an LDS imported from ENACT sites.

5. Regulatory Structure

The regulatory structure developed for ENACT is divided into two parts: approval of an ENACT-wide protocol for the creation of study-specific enclaves from data in EHRs from participating sites by a central IRB and reliance on the central IRB that allows a study-specific enclave.

Central IRB Approval of an ENACT-wide Protocol

The protocol for ENACT to create study-specific enclaves using an LDS from each participating site will be reviewed as human subjects research by the ENACT central IRB. The primary features for review of this enclave by the central IRB will center around privacy and confidentiality protections because the data to be transmitted will have been previously collected for non-research purposes. Studies to be conducted in enclaves will be eligible for review under Expedited Category 5[3]. The central IRB will issue waivers of consent and HIPAA authorization upon fulfillment of the applicable regulatory criteria.

Sites transmitting data may confer with their local IRB offices to determine whether local IRB review and approval is needed for transmission of the data is required. ENACT believes local IRB review and approval is not required because sites 1) would not be engaged[4] in the human subjects research as sites are not the prime awardee of the

[3] Expedited Review: Categories of Research that may be Reviewed Through an Expedited Review Procedure

[4] Engagement of Institutions in Human Subjects Research

ENACT grant, 2) will not interact or intervene with subjects for the purposes of this activity, 3) will not obtain the informed consent of subjects, and 4) will only be interacting with identifiable private information for the purposes of releasing it to investigators at another institution.

Sites will transmit requested data as an LDS and adhere to an executed ENACT DUA(s) and data transfer agreements that allows transmission of the data into the study-specific enclaves and use for the specific research project. As such, the only HIPAA identifiers that may be included in the LDS are all elements of dates, towns or cities, states, and zip codes. Per the HIPAA Privacy Rule at 45 CFR 164.514(e)(2), the following HIPAA identifiers may not be included in any LDS:

- Names
- Postal address information other than town or city, State, and zip code
- Telephone numbers
- Fax Numbers
- Electronic mail (e-mail) addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web Universal Resource Locators (URLs)
- Internet Protocol (IP) address numbers
- Biometric identifiers, including finger and voice prints, and
- Full face photographic images and any comparable images

Relying on the Central IRB for Study-Specific Enclaves

Upon agreeing to contribute their data to study-specific ENACT enclaves, researchers at ENACT sites will be able to request data for analysis be delivered to study-specific enclaves. Sites who request data will rely on the central IRB's approval of the ENACT protocol and adhere to the ENACT protocol procedures for use of, access to, and eventual deletion of the data. Reliance will be accomplished through the use of the SMART IRB agreement. If a site has not signed on to the SMART IRB agreement, the central IRB may execute a separate IAA with that site.

As a part of the reliance agreement, sites will be required to comply with central IRB SOPs for reporting of events of non-compliance, unanticipated problems, and not modifying the approved protocol without prior IRB approval except as needed to eliminate an apparent immediate hazard to subjects. As this is a secondary analysis of records only, it is not anticipated that there will need to be un-approved changes to eliminate apparent immediate hazards. Sites will also be required to enter into the ENACT DUA(s) to gain access to the data.

Upon execution of the reliance agreement and DUA(s), sites will be able to request data be provisioned in study-specific enclaves.

6. Regulatory Guidance

As a part of the privacy and confidentiality provisions of the ENACT protocol, each study-specific enclave requested by a site will be limited to the data requested. Sites will be required to work within the study-specific enclave to perform their analyses and will not be allowed to remove raw data from the study-specific enclave, though analyses and results may be removed.

After the analyses are complete and access to the data in the study-specific enclave is no longer required, the study-specific enclave will be terminated to ensure access is limited to only those who need it. Study-specific enclaves will be available for a period of one year from initiation. Researchers may request that ENACT renew access for longer than 1 year; however, such renewals cannot extend beyond 6 months after publication. Guidelines for such requests will be provided by the ENACT governance documentation.

Due to the nature of the approval of these ENACT data enclaves, study-specific enclaves may not be used to conduct research requiring the issuance of an IND, IDE, or abbreviated IDE. Researchers who are unsure whether their proposed research would require an IND, IDE, or abbreviated IDE should contact the central IRB for guidance.

7. Publication Guidance

Any study which utilizes data from the ENACT central enclave must cite the NCATS ENACT grants using the following statement: “The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant U24TR004111. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.”

Any publication must also include the specific query terms used to generate a study-specific enclave to enable rigor and reproducibility. Additional publication guidelines will be provided by the ENACT governance documentation.