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The Emergency Medicine Specimen Bank: An Innovative Approach To Biobanking In Acute Care

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Abstract

The Emergency Medicine Specimen Bank (EMSB) was developed to facilitate precision medicine in acute care. The EMSB is a biorepository of clinical health data and biospecimens collected from all adult, English- or Spanish-speaking individuals who are able and willing to provide consent and are treated at the UCHHealth – University of Colorado Hospital Emergency Department (UCH-ED). The EMSB is the first acute care biobank that seeks to enroll all patients, with all conditions who present to the ED. Acute care biobanking presents many challenges that are unique to acute care settings such as providing informed consent in a uniquely stressful and fast-paced environment and collecting, processing, and storing samples for tens of thousands of patients per year. Here, we describe the process by which the EMSB overcame these challenges and was integrated into clinical workflow allowing for operation 24 hours a day, seven days a week at a reasonable cost. Other institutions can implement this template, further increasing the power of biobanking research to inform treatment strategies and interventions for common and uncommon phenotypes in acute care settings.

Introduction

Precision medicine aims to customize treatment strategies based upon individual patient variability¹. Population-level data allows researchers to characterize the phenotypic differences within conditions and specifically identify patients who do not respond to standards of care¹. Omics techniques (genomics, metabolomics, proteomics, etc.) are powerful tools that can help define clinical phenotypes. Capturing treatment effects within these phenotypes helps clinicians target individual patients with a more informed therapeutic strategy² (Figure 1).

The use of omics analyses to discover novel biomarkers and/or genetic variants that can predict individual drug responsiveness requires a considerable number of research subjects^{3,4}. This requisite for large sample sizes in precision medicine has been one of the major driving forces behind the recent movement towards biobanking^{5,6}. Thousands of participants might take years to accumulate, delaying research efforts. Emergency Departments (EDs) admit tens-of-thousands of patients every year; therefore, ED biobanking has the potential to accrue significant sample sizes in a short amount of time thereby accelerating discovery potential.

To increase the capacity for precision medicine in the ED, the University of Colorado, Department of Emergency Medicine (CU-DEM) in partnership with the CU Center for Personalized Medicine (CCPM) Biobank has established The Emergency Medicine Specimen Bank (EMSB)); a repository of clinical health data linked to biological specimens collected on acute care patients. With the development of the EMSB, paired with the university-wide efforts in personalized medicine, and federal grant funding for discovery in the field of acute care precision medicine, we hope to personalize acute care medicine.

Our objective here is to describe the process by which we established the EMSB, and how we integrated operations into ED clinical workflow allowing for operation 24 hours a day, seven days a week (24/7) at a reasonable cost. We believe other institutions can implement this acute care biobanking template, further increasing the power of biobanking research to inform treatment strategies and interventions for common and uncommon phenotypes in acute care settings.

Overview of the process

A major goal of the EMSB is to obtain patient biological samples from ED patients at presentation and after treatment without interfering with patients' clinical care and enabling biological analysis of individual therapeutic responses. Our approach has therefore been to 1) integrate both the informed consent and sample collection processes into the clinical workflow of the UCH-ED (Figure 2), and 2) collect biological samples and briefly store those samples under a temporary waiver of consent. All procedures described below were approved by COMIRB #17-1642.

Consent process: Utilizing a self-consent process that is distributed by registrars enables participation from the majority of patients.

When patients enter the UCH-ED, either through intake ("walk-in") or by ambulance, they immediately interact with a registrar. During this "rapid registration," baseline patient information is obtained. This initial contact between registrar and patient is the first touch point of the EMSB; all conscious, English- and/or Spanish-speaking, adult patients who are not prisoners receive a research informed consent form during rapid registration. The EMSB utilizes a self-consent process, where patients are asked to read over the research informed consent form during their stay to inform their decision around participation in the EMSB. All registrars are trained on frequently asked study questions and are instructed to refer to senior research staff to answer more complex questions. To facilitate this consent process, undergraduate student research assistants participating in a for-credit internship provide eligible patients with more detail, re-orient the patients to the consent form, and answer study-related questions. Registrars then capture the consenting signature at a later time when obtaining more detailed registration data. If the patient has read through the research informed consent and has no further questions, he/she may consent to participate and an electronic signature is captured and stored in the EHR. If the patient declines participation, the registrar will also document this decision in the EHR. If the patient has not had a chance to read over the consent, he/she has one final contact with a registrar at discharge or during the hospital admission process. Registrars do not approach patients who are incapacitated as a result of their medical condition, patients who do not speak English or Spanish, or patients who are prisoners for participation in the EMSB. Registrars document and track these patients in the EHR as "unable to consent".

Over the first 6 months of operations, 47% of the entire UCH-ED population have documented EMSB eligibility and consent status. From those that have documented consent status, 4,219 individuals have consented to the EMSB while 8,727 have declined

participation. Because of medical incapacitation or language barriers, 22% of the ED population with EMSB documentation was ineligible for study participation.

Sample collection: Linking sample collection with IV placement and discharge streamlines research efforts with clinical workflow.

To minimize risk to patients, samples are only collected on individuals who have intravenous lines (IVs) placed for clinical purposes. Nurses and/or technicians draw the first (4 mL) research sample when they place IVs and the second at the time of patient discharge or admission to the hospital, on all patients who receive an IV. 24/7 operations make it difficult to have research staff on site to manage research samples at all times. Thus, temperature-monitored -20°C mini-freezers were placed at all nurse care stations for temporary storage of research samples. The waiver of consent covers sample collection and storage up until this point; however, documentation of research participant consent must be validated in the EHR prior to processing samples for long-term storage.

Consent validation and sample storage: Integration of consent status into EHR allows for scanning of patient stickers and immediate consent verification by research staff.

Research personnel scan the patient barcode from each sample into the EHR, verify EMSB eligibility and consent status, and sort the samples appropriately. Samples from patients who do not have documentation of consent in the EHR are discarded. Samples from patients with verified eligibility and consent are logged into the EMSB database (OnCore, Table 1), where the link between patient identity and sample barcode are stored. De-identified samples are then aliquoted into 1.0 mL Matrix™ (ThermoFisher) 2D barcoded tubes and stored in Matrix™ racks. Long-term sample storage for the EMSB is housed under a collaborative effort at the CCPM Biobank. All samples are transferred to the CLIA-certified CCPM Biobank and stored in -70°C freezers. The Matrix™ system allows for rapid automated or instrument-assisted sample tracking, storage, and distribution.

Sample and clinical health data retrieval: University-wide data integration simplifies sample identification and data retrieval.

The University of Colorado utilizes OnCore, a clinical trials management system which houses clinical research data, across the university and the UCHHealth system. Once COMIRB (the Colorado Multiple Institutional Review Board) approves a research protocol, data analysts from Compass (Health Data Compass - an enterprise health data warehouse within the CCPM) can access information stored in OnCore, including the linked patient ID and sample barcode information for subjects participating in the EMSB (Table 1). Compass analysts can also provide de-identified phenotypic clinical outcomes data from the EHR linked to the EMSB samples. As part of the CCPM efforts, the CCPM Biobank generates pharmacogenomic and germline genetic mutations that are stored in the EHR for precision medicine implementation. For instance, among the many genetic variants stored and reported in the EHR are hepatic cytochrome (CYP) drug metabolizing enzyme polymorphisms and BRCA mutations. Researchers also have an opportunity to access these pharmacogenomic and mutation data linked to EMSB clinical health data and biological specimens through Compass. Therefore, Compass serves as the central resource for all investigators interested in utilizing EMSB samples and linked patient health data (Figure 3).

Once researchers identify a cohort, staff from EMSB and Compass sends samples and de-identified patient health data, respectively, directly to the investigator. Although the EMSB is set up for precision medicine applications, researchers may also use this resource for general discovery, such as biomarker determination in acute care conditions.

Ethical Considerations for Consent:

Using a non-traditional self-consent process required careful consideration of all human subjects' research policies and procedures to ensure respect, beneficence, and justice for each potential participant. The self-consent process is amenable to relatively short visit timeframes, minimizes the burden to patients who may be feeling extremely stressed or ill, and is integrated into clinical workflow to allow for 24/7 recruitments (Table 2). Below we outline our approach to maintaining ethical standards for informed consent while optimizing a process suitable for the UCH-ED environment.

Respect: The consent form incorporates the new Common Rule elements of broad consent to ensure honesty and transparency around EMSB procedures and future research.

Biobanks necessitate an unorthodox consent process, where true "informed consent" is not possible because the research has yet to be defined⁷. This has led to many biobanks adopting an open or "broad" consent form that is not tied to one specific research study; however, this approach has not mitigated the ethical concerns around consenting for biobanks. In attempt to formulate regulatory structure around broad consent processes, in January of 2018, the US government implemented policies for performing broad consent for future unspecified human subject research in the new Common Rule⁸. Per these regulations, consent forms for future unspecified research must disclose: 1) if biospecimens will or will not be used for commercial profit, 2) if research will include human genome sequencing, 3) what types of research could be done using identifiable information or specimens, 4) if and with whom any identifiable information or specimens will be shared with other researchers, 5) a statement that the subject will not be informed of the exact types of research to be performed with their information or specimens, 6) a statement that the subject will not receive results from the research unless it is already known that clinically relevant results will be shared with the participant, and 7) contact information for subjects to use if questions arise⁸. To align with these new regulations and promote transparency around potential future research, all points outlined above are included in the EMSB research informed consent form. Additionally, utilizing a self-consent process facilitated by highly trained student research assistants and clinical staff (registrars) aims to preserve patient autonomy in accomplishing the research informed consent process.

Beneficence: The temporary waiver of consent for sample collection and storage minimizes risks to patients while maximizing the research potential for the EMSB.

Due to the urgency to treat in acute care settings, a waiver of consent for sample collection is essential for biobanking in the ED if the goal is to obtain samples before treatment has occurred on *most* patients without interfering with patient care. COMIRB approved a waiver of consent for the collection and short-term storage of all research samples for the EMSB

because the research protocol met all requirements for waiver of consent set forth by the Common Rule⁸. The consent waiver permits EMSB consenting to occur separately from sample collection. When discussing the study with patients, we inform them that nurses and technicians collect samples that researchers only use *if* they provide consent. Later, we confirm consent status for all research samples prior to processing for long-term storage in the biobank.

Understanding the differences in the workflows of an ED compared to other clinics or departments were essential for recognizing the importance of this waiver. Most individuals outside of acute care do not clearly understand the unique clinical workflows that take place in the ED. Therefore; it is imperative to provide details around ED workflow to the IRB of record in order to create transparency with the IRB when communicating the needs of the study, the patient, and the clinical staff. The consent waiver for EMSB is a key element to integrating sample collection into clinical workflow, maximizing research potential while minimizing interruption to clinical care.

Justice: Tracking individuals who are unable to consent will inform our ability to understand populations that are systematically excluded from participation.

The critical nature of incapacitated patients makes this patient population particularly important from a research perspective, as many of these patients fail to respond to treatments given in the ED. Additionally, racial and ethnic background can have a major influence on individual response to treatments^{9–11}. Therefore, our goal for the EMSB is to be inclusive of all acute illnesses and as many demographic groups as possible. Obtaining proxy research informed consent from family or friends who accompany patients to the ED may prove an ethical solution for consenting otherwise ineligible subjects. However, Colorado State Law is silent on the subject of proxy decision-makers for medical research and only provides a definition of proxy decision-makers for medical treatment (Colorado Revised Statute§ 15–18.5–103:¹²). To align with Colorado State Law, COMIRB does not permit proxy consent for research unless one can show that the research falls under medical treatment or the research meets the following criteria: 1) only incompetent/incapacitated persons are suitable as research subjects, 2) the research entails no significant risks or there must be a greater probability of direct benefit to the participant than harm, and 3) descriptions of the proposed research and the obligations of the person's representatives must be provided¹³. The undefined nature of biobanking research does not satisfy the third requirement and therefore our request to include patients who are accompanied by a proxy decision maker, but unable to provide consent themselves, was denied. Exclusion of these patients may result in systematic omission of important acute conditions and/or demographic groups from future research. To address this possibility, we are tracking these ineligible patients and will retrospectively analyze those conditions/languages from de-identified data. Future plans include utilizing these data to investigate the impact of the current interpretation on researchers' ability to collect samples for future unspecified research in critically ill, non-English-, or non-Spanish-speaking populations.

Clinical Integration:

ED biobanks have the potential to quickly accrue significant samples sizes from a diverse population of patients. To capitalize on the large ED patient population, biobanking efforts must operate in parallel to (or within) 24/7 clinical operations. Clinical integration has been essential to the sustainability of the EMSB and was made possible through early engagement of key stakeholders and strong education efforts for clinical staff to support the implementation of the program (Table 2).

Stakeholder support: Early engagement of key stakeholders secured the necessary support for integration into clinical workflow.

There remains no consensus in the field regarding ethically appropriate biobank consent models. The ethical matters brought forward by COMIRB ultimately resulted in a commitment to place the rights of the research participants at the center of our decisions. Involving key stakeholders in CU Regulatory Compliance and clinical administration was essential for successfully creating a consent form and a clinically integrated process. Monthly research implementation meetings are held with clinical staff to discuss the progress of the EMSB integration and navigate barriers to research implementation. A clear investment in the EMSB from the clinical management team is necessary because of the additional workload for the nurses, technicians, and registrars in the UCH-ED.

Education of clinical staff: Longitudinal electronic, hard copy, and in-person resources maintain compliance.

Education and training for clinical staff was implemented prior to study initiation and will continue throughout the life of the biobank. Our first step in educating the clinical team was to provide protocol information electronically to all faculty and staff prior to the EMSB go live. Emails specifically address the changes in clinical workflow for each clinical group and are meant to provide a general introduction to the EMSB. Teams are then educated in person. We utilized the educational mechanisms already in place for each clinical team (including nurses, techs, and registrars). We attend quarterly in-person meetings for registrars, distribute protocol booklets to all registrar stations, and provide on-site support on a daily basis. To access and educate the entire UCH-ED nursing/technical team, EMSB research staff provides protocol information at the Nurses' Annual Compliance/Competency Training, attend bi-weekly nurse/technician huddles prior to each shift, and check in with on-shift nurses and technicians daily. Finally, we employed two tools in the EHR to help maintain and track protocol compliance for consent: 1) a pop-up that reiterates eligibility criteria and provides a reminder to upload a signed consent form when registrars attain EMSB consent and 2) record of registrar name, date, and time associated with EMSB consent documentation. This allows the research team to generate quality assurance reports that can be linked back to individual registrars for re-training purposes. Employing a robust educational program, stringent quality assurance procedures, and providing support from highly trained research staff helped operationalize this research integration into the clinical workflow.

Financial Sustainability:

The ultimate goal of the EMSB is to generate a financially sustainable biobank that can become a resource to both academic and industry partners; however, implementing a massive biobanking effort on a modest budget was a major challenge. Clinical integration decreased the research budget cost significantly, though some logistic barriers prohibited our ability to integrate all research procedures into the clinical workflow (Table 2). The estimated start-up costs for this biobank were around \$30,000 for equipment and supplies. An estimate of our yearly expenses includes salary support for research staff (\$40,000/year) and consumable supplies (\$12,500/year) totaling less than \$75,000 per year. Leveraging the clinical staff allows a budget decrease outlined below.

Clinical integration: Employing clinical practices to minimize costs.

Utilizing clinical staff to collect blood samples for the EMSB enabled 24/7 collections on most patients and eliminated the need for research staff to be employed for this task. This kind of clinical integration has reduced the overall biobanking budget by at least the salary and benefits for three research assistants (~\$150,000/year). However, integrating sample processing into clinical workflow was cost-prohibitive at our organization. The UCH Clinical Laboratory offers 24/7 research services including sample processing and temporary storage at a significant cost geared toward clinical trial implementation. Utilizing this service for such a large sample size was prohibitive for our budget. Using hospital laboratories for sample processing may, however, be a cost-effective and efficient way to implement a biobank at other institutions and should be explored when possible.

Selection of samples: Adapting specimen type to eliminate the need for 24/7 processing.

We adapted our approach to sample processing to accommodate a budget-friendly and scientifically-sound method by choosing to store whole blood rather than plasma/serum and cellular fractions. Whole blood samples are immediately frozen and then processed into aliquots for long-term storage within 48 hours of initial sample collection from the research participant. This allows for capture of a snapshot of the clinical illness at a particular time, while facilitating flexibility in the timing around sample processing. Whole blood is versatile and has been validated in numerous 'omics methodologies^{14,15} and is used for most clinical assays; however, whole blood may not be ideal for all studies. Thus, strategies to augment sample processing so that serum/plasma samples can also be stored within a reasonable timeframe are currently being explored. Adjusting our process enabled cost savings by eliminating the need for 24/7 sample processing and halving storage tube needs.

Broadening the scope: Creating a departmental resource to leverage additional funds.

Many investigators at CU collect biospecimens for research purposes. Individual investigators mostly hold these samples in their own purchased freezers leading to limited visibility to potential collaborators on campus and significant wasted storage space due to numerous partially filled freezers. A seed grant through the CU-DEM (~\$10,000 for start-up costs) established a laboratory space in the UCH-ED that helped facilitate clinical integration efforts and provided a departmental resource for all ED investigators. Storing samples in the CCPM biorepository and tracking through On-Core, allows all investigators

across campus to access samples through the EMSB infrastructure while centralizing storage leading to greater efficiency.

Conclusions

We describe the ethical, logistical, and financial challenges of running an ED biobank. Most challenges were overcome through mapping clinical processes, meetings with key stakeholders, a multi-faceted educational plan for clinical staff, and a robust quality assurance plan. Integrating the EMSB-related activities into the clinical workflow has minimized cost.

The overarching goal of the EMSB is to generate a biorepository of biological samples and clinical health data that investigators interested in improving healthcare in acute-care environments can use. The EMSB will serve as a powerful discovery tool for researchers wishing to identify new biomarkers of acute care conditions, determine mechanisms of drug response, and elucidate pathophysiology of acute disease. Pairing samples with data from the electronic medical record can more precisely determine phenotypes researchers would like to examine. Coupling these data with individual patient genomics allows for determination of the genetic underpinnings of clinical presentation and/or treatment response variability. Omics analyses have led to numerous discoveries allowing clinicians to understand disease subtypes more completely, and thus treat those disease subtypes more effectively. For example, genetic testing has resulted in risk-reducing guidelines that have significantly decreased mortality rates in breast cancer patients¹⁶ and FDA-approved drug labeling that recommends genetic testing for drugs such as clopidogrel, abacavir, and carbamazepine to maximize drug effectiveness and safety. Although Emergency Medicine, as a specialty, has not adequately explored patient variability in order to improve health outcomes through genetic testing and biomarker discovery, we believe that ED biobanks like the EMSB will serve as a vital resource to begin this work.

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Figure 1.

Figure 2.

Figure 3.

Table 1.

Information systems utilized by the EMSB

System	Uses	Reference
Epic	Electronic health record; stores all patient health data including EMSB consent status	https://www.epic.com
Compass	A health data warehouse that serves as a resource for obtaining patient data stored in Epic; EMSB studies will use COMPASS to obtain patient data with paired samples	http://www.ucdenver.edu/about/departments/healthdatacompass/Pages/default.aspx
OnCore	An application for managing clinical research data; EMSB database storing the link between research participant ID and sample ID	https://forteresearch.com/enterprise-research-oncore/
Laboratory Information Management System	Laboratory tracking system that links patient health information with stored biologic samples.	In progress

Table 2.

The ethical, logistical, and financial challenges and solutions of implementing the EMSB

Challenges		Solutions
Ethical	Non-traditional Self-Consent	<ul style="list-style-type: none"> - Incorporated all new requirements of the Common Rule for broad consent forms - Strong educational efforts and engagement for Registrars on study protocol - Stringent quality assurance procedures - Onsite support from research staff to answer questions
	Waiver of Consent - Sample Collection	<ul style="list-style-type: none"> - Followed regulations set forth by the New Common Rule - Educated IRB panel on UCH-ED clinical workflow - Minimized risk and inconvenience to patient via using patients with an IV only
	Proxy Consent–Critically Ill/Language barrier	<ul style="list-style-type: none"> - No solution found - tracking numbers of patients for future evaluation
Logistical	Timely, low impact, 24/7 Consent	<ul style="list-style-type: none"> - Self-consent process - Consent status stored in EHR - UCH-ED Registrars obtain e-signature for consent
	24/7 Sample Collection	<ul style="list-style-type: none"> - Integrate into ED nurses/technician workflow - Supply storage freezers to all nursing stations - Strong educational efforts for nurses/technicians on study protocol - Weekly check-in at nurses' huddle - Daily support from research staff - Support from key stakeholders and clinical management
Financial	Reduce Research Staff	<ul style="list-style-type: none"> - Integrate consent and sample collection into clinical workflow - Support from key stakeholders and clinical management
	Sample Processing	<ul style="list-style-type: none"> - Collect whole blood to reduce labor burden - Enlisted Departmental financial support for laboratory space and furnishings