EFIC AND WIC STUDIES

A Primer for Clinical Investigators

Report of the EFIC Subcommittee,
ACEP Research Committee

American College of Emergency Physicians®
ADVANCING EMERGENCY CARE

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1.0

Introduction

Emergency care researchers are at a disadvantage in enrolling patients into time-sensitive and potentially lifesaving studies. In more traditional clinical research, subjects are provided adequate information for a ***balanced assessment of the risks and benefits*** of the research prior to enrollment. Unfortunately, adequate education and dialogue are not always feasible in the prehospital and emergency department (ED) settings for subjects with an emergent medical condition. Medical conditions that alter a subject's sensorium, such as reduced cerebral perfusion or hemodynamic instability, prevent some ED patients from consenting to participation in research. Furthermore, the time-sensitive nature of emergent conditions sometimes makes obtaining consent from these patients or their legally authorized representatives (LARs) impractical. For these reasons, ED patients are often excluded from meaningful clinical research intended to evaluate diagnostic and treatment practices for their conditions. Federal guidelines have attempted to compensate for this inherent disadvantage in emergency care research by establishing exceptions and waivers that permit subjects to be enrolled in studies when they cannot provide informed consent. However, the rules on how to obtain an exception from informed consent (EFIC) or waiver of informed consent (WIC) may seem intimidating or indecipherable to emergency care researchers.

The primary goal of this document is to explain how to apply EFIC and WIC regulations in the conduct of emergency care research. To illustrate key concepts, examples have been taken from prior studies that used EFIC and WIC. For decades, the conduct of EFIC- and WIC-related research has remained within the purview of only a select group of emergency care researchers. Recognizing the highly complex nature of this type of clinical research and the need for improved understanding of its techniques, members of the Research Committee of the American College of Emergency Physicians (ACEP) have undertaken the present study to illuminate EFIC and WIC options for the wider emergency care clinical research community. This document includes protocols from **19 EFIC and WIC studies** completed during the period from 1999 to 2020 that were identified as potentially valuable to the current investigation. What follows is an exploration of how these studies were conducted and how future investigators can use them as examples to guide and refine clinical protocols. The ultimate hope is that with increased awareness of the federal guidelines, EFIC and WIC will be used more often and appropriately, and more patients will safely participate in and potentially benefit from emergency care research.

EFIC/WIC Studies Included in This Review

Short Title (Year)	Long Title (National Clinical Trial [NCT] Number)	EFIC/ WIC	Study Principal Investigator (PI) (Institution)
ACCESS (2016)[1,2]	Early Versus Standard Cardiac Catheterization Lab (CCL) Activation in Resuscitated Cardiac Arrest Survivors With Non-ST Segment Elevation MI (NCT03119571)	WIC	Yannopoulos (University of Minnesota), Aufderheide (Medical College of Wisconsin)
ALPS (2011)[3]	Amiodarone, Lidocaine or Neither for Out-Of-Hospital Cardiac Arrest due to Ventricular Fibrillation or Tachycardia (NCT01401647)	EFIC	May (University of Washington)
ASPIRE (2004)[4]	Autopulse Assisted Prehospital International Resuscitation Trial (NCT00120965)	EFIC	Hallstrom (University of Washington)
BOOST-3 (2019)[5]	Brain Oxygenation Optimization in Severe TBI, Phase 3 (NCT03754114)	EFIC	Barsan (University of Michigan)
COMBAT (2016)[6-9]	Control of Major Bleeding After Trauma (NCT01838863)	EFIC	Moore (Denver Health Medical Center)

Short Title (Year)	Long Title (National Clinical Trial [NCT] Number)	EFIC/ WIC	Study Principal Investigator (PI) (Institution)
DIRECT VS VIDEO LARYNGOSCOPY (2011)[10]	Laryngoscope Versus CMAC for Endotracheal Intubation in Patients Undergoing Emergent Airway Management (NCT01710891)	EFIC	Miner (Hennepin Healthcare Research Institute)
ERYTHROPOIETIN IN TBI (2006)[11]	Effects of Erythropoietin on Cerebral Vascular Dysfunction and Anemia in Traumatic Brain Injury (NCT00313716)	EFIC	Robertson (Baylor College of Medicine)
EROCA (2017)[12]	Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest (NCT03065647)	EFIC	Neumar (University of Michigan)
ESETT (2015)[13-14]	Established Status Epilepticus Treatment Trial (NCT01960075)	EFIC	Kapur (University of Virginia)
INTREPID (2016)[15]	A Randomized, Double-Blind, Placebo-Controlled, Study of NNZ-2566 in Patients With Traumatic Brain Injury (TBI) Conducted Under Exception From Informed Consent (EFIC) (NCT01366820)	EFIC	Bullock (University of Miami)
OSIRIS (2017)[16]	Inhaled Nitric Oxide After Cardiac Arrest (NCT03079102)	EFIC	Dezfulian (University of Pittsburgh)
PAD (1999)[17-21]	Public Access Defibrillation (PAD) Community Trial (NCT00004560)	EFIC	Ornato (Medical College of Virginia)
PREHOSPITAL AGITATION (2014)[22]	Ketamine Versus Haloperidol for Severe Agitation Outside the Hospital (NCT02103881)	EFIC	Miner (Hennepin Healthcare Research Institute)
PROPPR (2012)[23-25]	Pragmatic, Randomized Optimal Platelet and Plasma Ratios (NCT01545232)	EFIC	Holcomb (The University of Texas Health Science Center – Houston)

Short Title (Year)	Long Title (National Clinical Trial [NCT] Number)	EFIC/ WIC	Study Principal Investigator (PI) (Institution)
PROTECT III (2011)[26]	Progesterone for the Treatment of Traumatic Brain Injury (NCT00822900)	EFIC	Wright (Emory University)
RAMPART (2012)[27-30]	Intramuscular Versus Intravenous Therapy for Prehospital Status Epilepticus (NCT00809146)	EFIC	Silbergleit (University of Michigan)
REBOA (2019)[31,32]	The Use of REBOA as an Adjunct to ACLS in Non-Traumatic Cardiac Arrest: A Feasibility Trial (NCT03703453)	EFIC	Daley (Yale University)
ROC – CA (2011)[33,34]	A Trial of an Impedance Threshold Device in Out-of-Hospital Cardiac Arrest (NCT00394706)	EFIC	Weisfeldt (Johns Hopkins)
ROC – TXA FOR TBI (2020)[35]	Prehospital Tranexamic Acid Use for Traumatic Brain Injury (NCT01990768)	EFIC	May (University of Washington)

2.0

Abbreviations Used

ACEP	American College of Emergency Physicians
ACLS	Advanced cardiac life support
CFR	Code of Federal Regulations
DSMB	Data safety monitoring board
ED	Emergency department
EFIC	Exception from informed consent
ERCW	Emergency research consent waiver
FDA	United States Food and Drug Administration
GCP	Guideline for Good Clinical Practice
HHS	United States Department of Health and Human Services
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDE	Investigational device exemption
IND	Investigational new drug
IRB	Institutional review board
LAR	Legally authorized representative
NCT	National Clinical Trial
OHCA	Out-of-hospital cardiac arrest
PI	Principal investigator
REBOA	Resuscitative endovascular balloon occlusion of the aorta
sIRB	Single institutional review board
WIC	Waiver of informed consent
YCCI	Yale Center for Clinical Investigations

3.0

Informed Consent for Research

Vignette

Mr. X is a 47-year-old man who presents to your ED with an out-of-hospital cardiac arrest (OHCA). There is no suggestion of trauma. You would like to consider resuscitative endovascular balloon occlusion of the aorta (REBOA) for Mr. X. You consider him to be having a medical (ie, nontraumatic) cardiac arrest, and REBOA is believed to benefit this type of patient. REBOA is a hemorrhage control technique that is increasingly used to manage noncompressible intra-abdominal traumatic bleeding. By inflating an intra-aortic catheter, blood flow to the torso is occluded and redirected toward the heart and brain. This technique offers the benefit of increased blood flow in the aortic arch, which is intended to improve diastolic blood pressure and subsequent coronary perfusion. You wonder whether a small, noncontrolled, early feasibility trial of REBOA as an adjunct to advanced cardiac life support (ACLS) would be appropriate. This initial study could be used to design a subsequent pivotal clinical trial that could provide definitive guidance on the use of REBOA by emergency physicians in nontraumatic OHCA. However, you are unsure how to design or conduct such a clinical trial. Clearly, Mr. X and other patients experiencing OHCA will not be able to provide informed consent for the study. How should you design such a study? Will your institutional review board (IRB) allow you to proceed?

Informed Consent

The human right to bodily integrity has moral, political, and legal ramifications that affect all aspects of human interaction. The modern ethics of bodily integrity suggest that all medical research conducted on humans should be agreed to by the subjects or their LARs through a process of informed consent prior to their involvement in the research. As stated in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), **informed consent** is a process

in which "a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate."[36] Regulatory guidelines also state that researchers can enroll subjects without prospective informed consent when the proposed research falls within recognized informed consent exceptions.[37]

Historically, the right to bodily integrity has not been universally respected. Modern investigators are heirs to a legacy of scientific inquiry that has occasionally (and sometimes very conspicuously) been insensitive to research subjects' right to informed consent. However, it is now generally understood that subjects or their LARs must provide informed consent before researchers can use subjects' bodies, tissues, or medical information in research.

The United States **Code of Federal Regulations** (CFR) provides clear guidance to investigators on the required elements of informed consent.[38] The general requirements for informed consent mandate that investigators seek consent only under circumstances **that provide the prospective subject or their LAR sufficient opportunity to consider enrolling in a study and that minimize the possibility of coercion or undue influence**. The information given to the subject or LAR should be in language that they can understand. No informed consent may include any exculpatory language that waives or appears to waive the subject's or their LAR's legal rights or that releases or appears to release the investigator, sponsor, institution, or its agents from liability for negligence.

Before providing meaningful informed consent, subjects or their LARs must consider the risks and benefits of participating in the research study. However, **some medical conditions are characterized by a lack of decision-making capacity to provide informed consent**, and LARs are not always available to provide informed consent on behalf of these patients. Without a way to conduct clinical research in the absence of prior informed consent, prospective investigational research into certain acute medical conditions would be nearly impossible. Consequently, clinical research on emergent medical conditions that do not allow for prior informed consent is facilitated by federal regulations that permit an **EFIC** or a **WIC**. High-quality research into certain medical conditions (eg, cardiac arrest, severe trauma, and other conditions characterized by medical instability or time-sensitive intervention) is generally not feasible without the use of EFIC or WIC approaches. Despite growing interest, these approaches are not well understood by most clinical researchers and IRB members.

Acute care research often requires the collection of data and/or the initiation of experimental medical interventions before prospective informed consent can be obtained from the subject or their LAR. This situation creates a logistic and ethical dilemma for acute care researchers who must determine a medically unstable subject's decision-making capacity to provide informed consent; the degree or duration of cognitive impairment associated with an unstable medical condition is often unknown and sometimes unknowable. **Consent for research participation obtained from a subject with impaired decision-making capacity does not constitute adequate *informed* consent if the subject lacks decision-making capacity for that decision**. Furthermore, obtaining informed consent becomes increasingly difficult as the time window within which the emergent intervention must be initiated narrows.

These logistical challenges and their associated ethical and legal obstacles have led to fewer trials of emergency medical therapies compared to other areas of scientific inquiry.[39] This deficiency in acute care research deprives vulnerable patients of potentially effective strategies to stabilize their conditions and improve clinical outcomes. A lack of emergency care research has also led to the acceptance of emergency medical therapies that have not been adequately evaluated in well-controlled trials to prove that they are safe and effective.

Providing guidance on how to conduct high-quality emergency care research is an important step toward increasing the number and quality of acute care protocols submitted to IRBs. Additional and better-designed emergency research protocols will advance medical knowledge by subjecting conventional therapies to scientific rigor, improve therapies for medical conditions that have been associated with poor outcomes, and lead to novel, lifesaving therapies for critically ill patients.

Required Elements of Informed Consent

Informed consent is a required component of clinical research, unless IRBs approve an EFIC or a WIC. Current federal guidelines require that the following be provided to human research subjects when seeking informed consent for study enrollment (quoted from **21 CFR 50.25[a]**)[39]:

> (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
>
> (2) A description of any reasonably foreseeable risks or discomforts to the subject.
>
> (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
>
> (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
>
> (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.
>
> (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
>
> (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
>
> (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

These elements must be included in the **informed consent form (ICF)** signed by the participant or LAR to document authorization of participation in research. Depending on the specific intervention proposed in the protocol, additional elements of informed consent may also be required, including those outlined in **21 CFR 50.25(b)**[39]:

> (1) A statement that the treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.
>
> (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
>
> (3) Any additional costs to the subject that may result from participation in the research.
>
> (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
>
> (5) A statement that significant new findings developed during the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
>
> (6) The approximate number of subjects involved in the study.

In addition to these federally mandated components, the IRB of record for the study may also require that certain "boilerplate" language be included in the ICF.

Key Concepts

- The ability to provide prospective informed consent requires the subject to have a clear understanding of both the reasonably foreseeable benefits and risks of study participation.
- Patients with presenting medical conditions characterized by cognitive impairment, distracting symptoms, or hemodynamic instability are unlikely to be able to provide prospective informed consent for participation in research protocols.
- EFIC and WIC approaches allow for the enrollment of subjects in clinical research when they are unable to provide prospective informed consent at the time of their medical event.
- Valuable research into medical conditions associated with altered sensorium may not be feasible without the use of EFIC and WIC techniques.

3.1

The Code of Federal Regulations

Vignette

During your review of the federal guidelines governing the use of WIC and EFIC techniques, you recognize the importance of determining whether your proposed trial of REBOA in OHCA meets the initial EFIC requirements before submitting your protocol to the IRB. To obtain approval, you will need to convince the IRB that your study meets these criteria. You decide to create a document that addresses each requirement and clearly explains why your study satisfies each of them. You realize that you will need to write your proposal in layperson's terms, as it is unlikely that all members of the IRB will be as familiar with the federal regulations as you have become. So, where can you find these requirements, and what topics should you cover in your proposal?

The **CFR** is the codification of rules published in the *Federal Register* by the executive departments and agencies of the US government.[38] It is updated annually and divided into 50 titles that represent broad areas subject to federal regulation. The CFR contains the "rules" by which the US government operates. Because the federal government funds research activities and is responsible for protecting US citizens, several portions of the CFR apply to the conduct of clinical research.

Title 21 of the CFR is titled "Food and Drugs," with parts 1-1299 of 21 CFR pertaining to operations of the Food and Drug Administration (FDA) in the US Department of Health and Human Services (HHS). Part 50 (often referenced as **21 CFR § 50**) specifically addresses the protection of human subjects in research that involves **investigational drugs and devices**.[39] These protections have been in place since the passage of the Food, Drug, and Cosmetic Act in 1938 broadened the FDA's regulatory authority to require that manufacturers prove the safety of a drug before it can be sold.

Not all medical research involves investigational drugs or devices, however. In the 1980s, HHS began drafting a unified set of federal regulations that provided

guidance for the protection of all human subjects involved in medical research. **Title 45** of the CFR, "Public Welfare," with parts 1-199 pertaining to HHS Part 46 (often referenced as **45 CFR § 46**), is of great interest to the research community, as it relates to "Protection of Human Subjects."[40]

In 1991, 15 federal departments and agencies agreed to adopt the Federal Policy for the Protection of Human Subjects (**45 CFR § 46, Subpart A**), which provides uniform guidance for protecting human subjects across multiple federal departments and agencies.[40,41] This policy is often referred to as the "**Common Rule**," as it was intended to simplify and reduce the ambiguity of the variable language employed by different governmental agencies prior to that time. Since its adoption, the Common Rule has been revised in 2005 and 2018.[42] The revised 2018 version is often referred to as the "Final Rule." Although the FDA has harmonized its regulations with the Common Rule, the FDA continues to maintain its own regulations in **21 CFR § 50**.

In addition to Subpart A (ie, the Common Rule), **45 CFR § 46** also includes four other subparts that relate to special subject populations that may be at an increased risk of injury from research enrollment[40]:

- Subpart B (additional protections for research with pregnant women and fetuses)
- Subpart C (additional protections for research with prisoners)
- Subpart D (additional protections for research with children)
- Subpart E (requirements for IRB registration)

Within Subpart A, **45 CFR § 46.116** describes the general requirements for informed consent, and **45 CFR § 46.117** describes the requirements for documentation of informed consent.[40]

Recognizing the need for a waived informed consent requirement under specific circumstances, a "Dear Colleague" letter (OPRR Reports 93-3, August 12, 1993) from the Director of the Office for Protection from Research Risks (OPRR) authorized IRBs to alter or waive this requirement under a so-called "**Emergency Research Consent Waiver (ERCW)**" (**45 CFR § 46.116[c]-[d]**). Effective November 1, 1996, this policy permits an IRB to waive the requirement of informed consent "in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives (LARs) of the subjects, no legally effective informed consent can be obtained."[37]

The ERCW provision can be applied to research that involves a general population of human subjects, including children (Subpart D), but special regulatory limitations are applied to subjects covered by Subpart B (ie, fetuses, pregnant women, human *in vitro* fertilization) and Subpart C (ie, prisoners) of **45 CFR § 46**. Consequently, these categories of subjects are excluded from the waiver provisions and are ineligible for EFIC and WIC studies.

WIC is commonly used when **screening potential research subjects** by reviewing their medical records without obtaining prior informed consent. However, these regulations can also be applied to prospective research activities when deemed appropriate by the IRB.

Although most governmental agencies defer to the Common Rule for regulatory guidance, the **FDA maintains its own regulations** for investigational drugs and devices. As a result, two similar but different ERCW pathways exist:

- **EFIC** applies to research studies that involve investigational drugs and devices that are subject to FDA regulation (**21 CFR § 50.24**), including investigational new drug (IND) or investigational device exemption (IDE).[43]
- **WIC** applies to non-FDA studies (**45 CFR § 46.116**).[44]

Within acute care research, the EFIC pathway is more commonly encountered because most large interventional ERCW studies involve an investigational drug or device.

The Common Rule (**45 CFR § 46.116[f]**) allows an IRB to waive or alter some or all elements of informed consent if the proposed research activity meets all the following criteria[9]:

- The research involves no more than minimal risk to subjects;
- The research cannot be carried out practicably without the waiver or alteration;
- The waiver or alteration does not adversely affect the rights and welfare of the subjects; and
- When appropriate, the subjects or LARs are provided with additional pertinent information after participation.

For an ERCW study to be approved, however, the IRB must be satisfied that it qualifies for the waiver. In other words, the investigator must prove the following to the IRB's satisfaction (**21 CFR § 50.24**)[39]:

- The human subjects are in a **life-threatening situation**; available treatments are **unproven or unsatisfactory**; and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- **Obtaining informed consent is not feasible** because the subjects' medical condition renders them unable to give informed consent.
- The intervention involved in the research must be **administered before consent from the subjects' LARs is feasible**, and there is no reasonable way to identify prospectively the individuals who are likely to become eligible for participation in the research.
- Participation in the research holds out the **prospect of direct benefit** to the subjects because:
  - Subjects are facing a life-threatening situation that necessitates intervention;
  - Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
  - Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the

risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

- The research **could not practicably be carried out** without the waiver.
- The proposed research protocol **defines the length of the potential therapeutic window** based on scientific evidence, and the investigator has committed to attempting to contact an LAR for each subject within that window of time and, if feasible, to asking the LAR for consent within that window, rather than proceeding without consent. The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review.
- The IRB has **reviewed and approved informed consent procedures and an informed consent document** in accordance with Sections 46.116 and 46.117 of 45 CFR Part 46. These procedures and the informed consent document are to be used with subjects or their LARs in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph (b)(7)(v) of this waiver.
- Additional protections of the rights and welfare of the subjects will be provided, including, at least:
  - **Consultation** (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
  - **Public disclosure** to the communities in which the research will be conducted and from which the subjects will be drawn of plans for the research and its risks and expected benefits **prior to initiation of the research**;
  - **Public disclosure** of sufficient information **following completion of the research** to apprise the community and researchers of the study, including the demographic characteristics of the research population and its results;
  - Establishment of an **independent data monitoring committee** to exercise oversight of the research; and
  - If obtaining informed consent is not feasible and an LAR is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window a family member of the subject who is not an LAR and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

Although these provisions allow for subjects to be enrolled in a clinical research protocol without prior informed consent, the IRB requires that procedures are in place to **inform subjects (or their LARs if the subject remains incapacitated) at the earliest feasible opportunity** of their inclusion in the research, the details of the research, and other information contained in the informed consent document. If a subject's LAR is not reasonably available, this information must be provided to the subject's family.

According to these regulations, the IRB must also ensure that the subject, LAR, or family member is informed that the subject **may discontinue their participation at any time** without penalty or loss of benefits to which the subject is otherwise entitled. If an LAR or family member is told about the research and the subject's condition improves, the subject should also be informed of their participation in research and right to discontinue it as soon as possible. If a subject is entered into research with waived consent and the subject dies before an LAR or family member can be contacted, information about the research is to be provided to the subject's LAR or family member whenever feasible.

These regulations provide IRBs with mechanisms to approve the conduct of emergency care research that use EFIC or WIC approaches. Under these regulations, the IRB of record for the study is charged with reviewing and approving or denying investigators' requests for an ECRW. IRBs are not obliged to grant an ECRW and may impose reasonable requests on investigators to protect the rights of human subjects.

Key Concepts

- Federal guidelines allow for local IRB approval of an ECRW, allowing subjects to be enrolled in certain types of research without prospective informed consent.
- The EFIC approach is used in FDA-authorized research, while non-FDA research protocols use the WIC approach.
- EFIC and WIC regulations permit research to be conducted on subjects who cannot consent to study inclusion prior to enrollment but who are subject to life-threatening conditions for which available treatments are unsatisfactory.
- The subject's LAR should be contacted as soon as possible after study enrollment to provide informed consent on behalf of the subject.

3.2

Legally Authorized Representatives

Vignette

In writing your protocol for the REBOA trial, you realize that you will need to obtain informed consent for study inclusion from an LAR, rather than the patients themselves. After all, study participants will have experienced cardiac arrest and are unlikely to be capable of providing their own consent for study inclusion. You recognize that your protocol must include clear definitions of the therapeutic window and consent window as well as your proposed technique for identifying and contacting the LAR.

In many cases, subjects are incapable of providing their own informed consent due to new or preexisting cognitive impairment that prevents them from understanding the risks and benefits of inclusion in a research study. In such cases, an LAR may be authorized to provide informed consent on behalf of the patient.

An LAR is defined in **45 CFR 46.102(c)** as "an individual or judicial body or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."[40] In many cases, the LAR is a family member older than 18 years who fits into one of the following categories: spouse, parent, child (including adopted children), sibling, or another individual related by blood or affinity whose close association with the subject is equivalent to a family relationship (eg, the spouse of a sibling). In some instances, the LAR is the health care agent appointed by means of a medical power of attorney document or another individual authorized by a judicial body.

Local or state laws help to define who can serve as an LAR for purposes of providing informed consent for research, although many states have no law specific to research consent. Local IRBs can assist investigators by outlining appropriate methods for identifying the LAR in their specific state or locality. If the subject regains capacity to provide informed consent, consent for involvement in any further research activities should be obtained from the subject, and the consent of the LAR becomes invalid. Importantly, **informed consent obtained after enrollment has already occurred is consent for continued participation in the study, not consent for the**

initial enrollment. If enrollment was already initiated by an IRB-approved EFIC or WIC protocol, enrollment is considered to have already occurred. The distinction between *consent for enrollment* and *consent for continued participation* should be clearly explained to the subject. Subjects and their LARs should understand that they have the right to discontinue participation in the study at any time. Study participants and their LARs also have the right to ask for the subject's previously collected data to be destroyed at any time during their involvement in the study.

Protocol Description of LARs

When using LARs, EFIC protocols must clearly describe the plan for identifying and contacting a subject's LAR to seek informed consent. This process includes clearly defining the parameters of the **therapeutic window** (ie, the time during which the intervention must occur), proposing a **consent window** (ie, the time during which attempts to contact the LAR should begin and end), and identification of those research team members who will attempt to **identify and contact the LAR for consent**.

Depending on the specific intervention, a study's therapeutic window may be in the prehospital environment or within a predetermined number of minutes or hours after the subject has arrived at the hospital. If the therapeutic window is large (eg, hours or days), the IRB may reasonably request that researchers begin to obtain consent from an LAR prior to subject enrollment or may even refuse to grant EFIC/WIC if they believe that the investigators should have adequate time to identify an LAR before the intervention must occur. Although EFIC and WIC protocols do not require informed consent prior to initiating research, investigators are still required to make reasonable efforts to obtain informed consent from subjects or their LARs as soon as possible after enrollment. The IRB will want to know **when** the research team plans to begin efforts to obtain LAR consent and **its definition of impossible conditions for obtaining consent** (ie, the cutoff for the number of attempts over what time period). The research team must also include a detailed plan for how they intend to deal with situations in which informed consent cannot be obtained prior to the subject's death or discharge from the care environment. In cases of death, investigators are expected to make reasonable efforts to notify the LAR of the subject's involvement in their study.

All efforts to contact the LAR must be clearly documented by the researchers, including the identity of the LAR, the timing and number of attempts made, and whether the LAR was successfully contacted. Written guidelines for contacting LARs should be submitted with the study proposal. The study protocol should also include whether the investigator is seeking permission to obtain informed consent remotely (eg, by telephone or digital signature) or strictly in person. Some IRBs may not permit remote consent or may require that a physical (ie, "pen and paper") consent form be completed at the earliest feasible time after remote or virtual consent.

Key Concepts

- A subject's *LAR* should be identified as soon as possible after study enrollment.
- Informed consent for continued participation in the study should be sought from subjects as soon as they are able to provide it.

4.0

When Does a Study Require EFIC/WIC Protocols?

One early consideration for investigators wishing to use an ECRW is whether the proposed study is an **observational** study or an **interventional** study. According to the NIH's definition of a clinical trial[45]:

> An intervention is defined as a **manipulation of the subject or subject's environment** for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (eg, surgical techniques); delivery systems (eg, telemedicine, face-to-face interviews); strategies to change health-related behavior (eg, diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies.

The NIH also points out in their guidance that **measurements are *not* interventions**[45]:

> Measurements are used to collect data, while interventions are used to modify health-related endpoints. A manipulation or modification in one's behavior or environment for the purpose of measurement alone is not considered a clinical trial.

Thus, studies that do not include "manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints" are not considered interventional trials. Emergency care research protocols that merely collect data or observe subjects treated with routine standard-of-care interventions without introducing any study-specific intervention may not be subject to the same regulations as interventional trials. This distinction may influence how an IRB determines the appropriateness of EFIC or WIC approaches, as the risks inherent to an observational study often differ greatly from the risks of a study intervention.

Once a proposed study is determined to be interventional in nature, investigators must **consider the patient's presenting medical condition and the**

feasibility of obtaining informed consent without EFIC or WIC. To be eligible for EFIC or WIC, as defined by the federal regulations, investigators must justify their assertion that[45]:

> The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

In other words, non–life-threatening medical conditions or life-threatening conditions that can be treated satisfactorily with existing interventions are ineligible for studies that use EFIC or WIC. If research can be practicably carried out without such waivers, these waivers likely will not be granted.

Investigators must also demonstrate that "obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention involved in the research must be administered before consent from the subjects' LARs is feasible; and (iii) there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research."[39]

Many life-threatening medical conditions (eg, major trauma, cardiac arrest, stroke) are associated with some degree of cognitive impairment and require immediate intervention that cannot be delayed to obtain informed consent. However, when applying for EFIC or WIC approaches, investigators must clearly demonstrate in their rationale that[39]:

> ...participation in the research holds out the **prospect of direct benefit** to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

In other words, the investigator must provide the IRB with adequate scientific and medical evidence supporting the potential efficacy of the proposed intervention and their assertion that the intervention does not pose excessive risk to subjects over the risk of "standard therapy." Because most IRB members are not emergency physicians, investigators should explicitly describe their rationale for an informed consent waiver, including a thorough discussion of alternate therapies and their inherent risks and benefits. To adequately assess the relative risks and benefits of the proposed study, IRB members must be educated on the medical condition of interest as well as the pros and cons of the traditional and experimental therapies that are currently available to treat that condition.

The EFIC and WIC approaches also call for "additional protections of the rights and welfare of the subjects," specifically[43]:

- **Consultation** (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
- **Public disclosure** to the communities in which the research will be conducted and from which the subjects will be drawn, **prior to initiation** of the research, of plans for the research and its risks and expected benefits;
- **Public disclosure** of sufficient information **following** completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; as well as
- Establishment of an **independent data monitoring committee** to exercise oversight of the research.

These requirements are described in greater detail in the following sections.

Another important consideration is **whether the protocol requires FDA guidance**. Investigators should consider whether their protocol involves investigational drugs or devices that require FDA regulation and act accordingly when seeking guidance for their trial. Although harmonization has been established between the HHS and FDA on these guidelines, federal guidance for these two research entities may still differ. This distinction is most noticeable with IND and IDE applications. If such applications are required, information on the IND or IDE should be included in the IRB application for the EFIC or WIC study.

Key Concepts

- Investigators should determine whether their study is a clinical trial (ie, involves an intervention) or is merely observational.
- Investigators must provide adequate evidence to the IRB that potential subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the proposed intervention offers the prospect of direct benefit to participants.
- Investigators must determine whether their study involves interventions that are regulated by the FDA to determine whether their study is subject to FDA regulations.

5.0

Common Elements in EFIC/WIC Protocols

In this review, 45 completed EFIC/WIC studies were identified, including 19 studies with protocols available for analysis. Studies were included if they satisfied all the following criteria: (1) used EFIC or WIC; (2) were conducted in the United States; (3) were considered by their authors to be acute care research trials; and (4) were registered with the US National Library of Medicine Clinical Trials network (https://clinicaltrials.gov/). Most studies (41/45, or 91%) used the EFIC approach; only four used the WIC approach. The 19 studies with available protocols are described in greater detail in **Appendix 1**, while the remaining 26 studies without available protocols for review are listed in **Appendix 2**.

Although the reviewed studies do not represent a comprehensive list of all acute care EFIC and WIC trials conducted in the United States, they do reflect a wide variety of medical conditions, geographical regions, and clinical investigators. Despite their diversity, these study protocols contain common elements that can inform investigators about how to construct or review an EFIC or a WIC protocol. Common sections in the reviewed protocols include:

- **Introduction**. This section commonly describes the medical condition to be studied (with a focus on the difficulties of obtaining informed consent in acute care), introduces the concepts of EFIC and WIC, and emphasizes the importance of the knowledge to be gained from the study.

- **Defense for EFIC or WIC application to the present study**. This section commonly states whether the study is regulated by the FDA (requiring EFIC) or not (requiring WIC). It then explains how the study qualifies for EFIC or WIC status, based on patient populations that "are in a life-threatening situation, available treatments [that] are unproven or unsatisfactory, and the [need for the] collection of valid scientific evidence … to determine the safety and effectiveness of particular interventions" (**45 CFR § 46**). Data from precedent studies are referenced to explain what is already known in the field and how the proposed study will answer an important clinical question. An argument for the infeasibility of informed consent is provided

as well as an assessment of the study's potential to directly benefit the subject. Study authors then provide an explanation of why the research could not be completed without the requested waiver.

- **Additional protections for participants**. This section includes information on the five additional protection measures required for participants in EFIC and WIC trials, specifically:
  - The plan for community consultation;
  - The plan for pre-study public disclosure, including methods for patients to opt out (ie, refuse to participate in the trial);
  - The plan for post-study public disclosure;
  - The plan for contacting the LAR or family members to seek informed consent within the therapeutic window (if feasible) or as soon as possible after enrollment (when feasible); and
  - The formation of a Data Safety Monitoring Board (DSMB) to oversee the trial.

In addition to these common elements, many protocols also include other sections (as appropriate) related to:

- IND exemption;
- IDE; and the
- Rationale for inclusion or exclusion of vulnerable populations.

Each of these elements is described in greater detail in the following sections.

Key Concepts

- EFIC and WIC protocols generally include an introduction, defense of EFIC or WIC application to the present study, additional protections for subjects, and other sections.

- Investigators should consider whether their proposal requires an IND exemption or IDE.

6.0

Defense of EFIC/WIC Application in the Study Protocol

Vignette

> *You have reviewed the requirements for an EFIC study and are confident that your study requires such an approach. You recognize that you will need to explain your rationale for the use of EFIC to the IRB and other interested parties, including the community from which patients are enrolled. How should you structure your argument in defense of the need to use EFIC for this trial? Are there specific topics that must be included in the discussion?*

The use of EFIC or WIC to enroll subjects in a clinical research study is heavily scrutinized by the IRB and community members because it departs from the generally accepted practice of obtaining informed consent from subjects before they are enrolled in a research study. Consequently, investigators must provide justification for why the proposed research cannot be practically conducted without the exception or waiver. Citing precedent studies that have used EFIC or WIC to study the same or similar medical conditions can be helpful, as can describing anecdotal or previously published reports on the difficulties of obtaining informed consent among patients with the medical condition of interest. Investigators may also wish to provide references to previous studies with low enrollment due to consent failures to justify the need for a waiver in the proposed study.

Most of the protocols studied in this analysis addressed each portion of **21 CFR § 50.24** line by line, briefly explaining how the proposed study satisfies the specific requirements for EFIC or WIC approval. Generally, these comments fall into three categories:

- Description of the life-threatening condition of interest;
- Explanation of why informed consent is not feasible; and
- Description of the intervention's potential direct benefit to participants.

The following sections describe common responses to each of these categories in greater detail.

6.1

Description of the Life-Threatening Condition of Interest

Studies hoping to employ an EFIC or a WIC approach must describe the life-threatening nature of the disease being studied to the IRB and provide evidence that currently available treatments are unproven or unsatisfactory. This description is an essential part of the IRB application because it provides partial justification for the waiver.

Patients with traumatic brain injuries (TBIs) are commonly studied using EFIC and WIC approaches. In the BOOST-3 protocol, the authors pointed out that 52,000 patients die annually from TBI, while the Erythropoietin for TBI trial highlighted the 25% to 35% mortality rate in comatose TBI patients.[5,11] Cardiac arrest is another well-known, life-threatening condition that is commonly studied by using EFIC and WIC approaches. The REBOA EFIC plan reported that only 25% of both out-of-hospital and in-hospital cardiac arrest patients experience return of spontaneous circulation, with less than 10% surviving to hospital discharge. The ESETT trial referenced the nearly 17% mortality rate of the condition.[13,14,31] Other life-threatening conditions addressed by these protocols include major bleeding and emergent airway management. All trials examined in this report highlight the condition's prevalence, its morbidity, and its mortality in their IRB applications to show the seriousness of the condition under investigation. These trials also universally highlight that current standard-of-care treatments are unsatisfactory or unproven and that current interventions are in use because of traditional practice patterns or precedent observational data, which are subject to bias.

To apply EFIC or WIC approaches, solid scientific evidence confirming the safety and effectiveness of the proposed intervention must be provided to the IRB. A discussion of the intervention's risk to participants is crucial because IRBs will be concerned that the intervention is riskier than the current standard of care. In most cases, the inadequacy of current treatments should be described and supported with evidence from precedent studies. If a randomized controlled clinical trial is proposed, its potential benefits should be explained, and its risks and benefits should be contrasted with the risks and benefits of current treatments.

A randomized controlled clinical trial with a large study population is generally expected to provide sufficient statistical power. For example, the ALPS trial not only compared its intervention to the best available drug, but also included a placebo arm that was expected to detect which treatment would be both more beneficial and safer.[3]

Key Concepts

- Investigators must provide scientific evidence for the safety and efficacy of the proposed intervention in the study protocol.
- When available, evidence from precedent studies should be provided to illustrate that the benefits of existing interventions are inadequate or unproven.

6.2

Explanation of Why Informed Consent Is Not Possible

This section of the application generally highlights why subjects who will receive the proposed intervention are likely incapable of providing informed consent at the time of enrollment. To provide informed consent, **subjects must possess adequate cognitive ability to understand the risks and benefits of inclusion** in the research study — an uncommon ability among subjects with a life-threatening condition in need of emergent care. Investigators should justify why subjects with the medical condition of interest cannot provide informed consent early enough to employ standard informed consent practices. Although the reasons may be obvious to clinicians, investigators should keep in mind that most members of the IRB (and the public) do not work in the ED or prehospital setting and may not have experience treating patients with the condition of interest.

The timing of consent is an essential consideration in most EFIC and WIC protocols. With enough time for stabilization and recovery, many critically ill patients can eventually provide informed consent for study enrollment. However, the interventions that EFIC and WIC studies investigate are needed to stabilize the subject before they can consent. In addition, **LARs are often unavailable to provide informed consent in a timely manner under emergent conditions**. Investigators must, therefore, explain to the IRB why subjects and their LARs are unlikely to be able to provide informed consent prior to study enrollment. Investigators can highlight the subject's need for immediate intervention and the short time frame for the intervention that makes contacting the LAR impractical. Even when LARs are available in the ED, they often do not have enough time to carefully weigh the risks and benefits before the intervention needs to be performed.

In its justification for the use of EFIC, the BOOST-3 trial protocol refers to data from the precedent ProTECT III trial, in which 52% of participants had no available LAR for consent within 6 hours of presentation.[5,26] Lag times were expected to be as high as 30 hours, effectively making the BOOST-3 trial infeasible if prior LAR consent were required. Enrollment delays would have potentially excluded patients who wanted to enroll and would have led to an excessive loss of data.

Another common characteristic of EFIC and WIC studies is the inability to identify potential participants in advance of their presentation for emergent care. If potential subjects represented a small, easily identifiable cohort of patients (eg, patients with a previously identified condition who are all treated in a local clinic) who were expected to need acute care at some point, obtaining consent in advance of their ED presentation would be more practical. However, **it is often impossible to predict who will present to the ED for a given emergent medical condition**. Although it may seem desirable to seek universal consent from all citizens for involvement in human subject trials relating to cardiac arrest, for example, this action would not be feasible since each trial would have its own risk-benefit profile. It would be impossible for subjects to know in advance which studies they would be willing, and unwilling, to participate in.

To qualify for EFIC and WIC approaches, subjects must present emergently, unexpectedly, and unpredictably with a life-threatening condition. For example, TBI is an accidental injury that can, theoretically, happen to anyone at any time. Similarly, cardiac arrest can present suddenly as the first manifestation of cardiovascular disease.

The defined therapeutic window for the EFIC or WIC study's intervention should be supported by previous scientific evidence, when available. For example, the BOOST-3 trial protocol used previous evidence by referring to the precedent PROTECT III study's data to suggest that waiting for informed consent for at least 52% of the cases was not feasible.[5,26] The ACCESS trial that studied pulseless ventricular tachycardia or ventricular fibrillation cardiac arrest defined a therapeutic window based on evidence-based recommendations for STEMI, another cardiovascular condition for which the intervention of interest had already been used.[1,2] The authors of the Erythropoietin for TBI trial referred to their previous TBI study in which they prospectively tracked the availability of relatives for consent.[11] In this study, only 3% of patients had relatives who were present within the first hour — this provided adequate evidence to the IRB that LARs would likely be unavailable to give informed consent within the short therapeutic window for the intervention.

Key Concepts

- A key determinant for EFIC or WIC is the inability to obtain written informed consent prior to study enrollment.

- Investigators must provide adequate evidence and justification for their inability to obtain informed consent prior to study enrollment. Evidence and justification include the life-threatening nature of the patient's condition, the potential value of an immediate intervention, the short therapeutic window required for the intervention, the inability to identify and obtain consent from potential subjects prior to enrollment, and the infeasibility of informed consent from an LAR prior to the intervention.

6.3

Description of Potential Direct Benefit for Participants

Discussing the potential direct benefits subjects can receive from an intervention is crucial to justifying the use of EFIC or WIC. The proposed study intervention must have **the potential to provide greater direct benefit to participants than the current standard-of-care therapies available to the subject**. Although these theoretical benefits may be unproven, the investigator must provide the IRB with reasonable evidence that such additional benefit could exist.

Direct benefits to subjects differ from the potential indirect benefits to society offered by the research, or the potential for benefit to future patients by completing the study. **Although subjects may not actually realize direct benefit from participating in the study, the potential for direct benefit from the intervention is crucial to the IRB's consideration of the protocol**.

Examples of potential direct benefits cited in EFIC and WIC trials include the benefits of improved subject monitoring (as mentioned by the BOOST-3 trial) or of earlier intervention that potentially stabilizes subjects more quickly or leads to better clinical outcomes for patients with life-threatening conditions.[5] Whatever direct benefit is proposed should be something that potential subjects would not likely receive if they were excluded from the study. Although improved monitoring and accelerated medical attention are potential general direct benefits for all study participants and should be mentioned, investigators should also highlight the potential benefits of the intervention itself, as in the ACCESS trial when the investigators stated the potential benefit of early cardiac catheterization (versus ICU admission) for cardiac arrest survivors.[1,2]

When study interventions are new and lack FDA approval, investigators should provide preclinical data supporting their potential to directly benefit subjects. For example, in the OSIRIS trial that investigated inhaled nitric oxide for OHCA, data from previous animal studies were cited to support the neuroprotective and cardioprotective benefits of nitric oxide, in addition to safety and efficacy data from precedent human studies.[16]

Potential risks of the study intervention must be reasonable compared to the risks of no intervention or the current standard of care. In the PROPPR trial that investigated the most effective massive transfusion protocol for trauma victims, many of the intervention's risks were common to all blood product transfusions but were minimized through the local blood centers' protocols.[23-25] The trial's protocol mentioned the slightly increased risk of transfusion-related acute lung injury when transfusing plasma and platelets in amounts other than the usual 1:1:1 ratio and acknowledged that subjects in one arm or another could be at an increased risk of this occurring. However, the authors also carefully explained how they planned to mitigate and manage this risk.

Key Concepts

- A study intervention's reported direct benefits to subjects cannot include the potential for societal benefit from the knowledge gained by the research study, nor the potential for benefit to future patients.

- Improved monitoring and accelerated stabilization through early intervention are commonly cited examples of potential direct benefits to study subjects.

- Direct patient benefits and the risks of a study intervention must be compared to those of the currently available and anticipated standard of care.

6.4

Additional Protections for Participants

As EFIC and WIC studies seek to enroll subjects who present emergently with an unpredictable medical condition, these studies must engage the entire local community as potential participants. Five "additional protections" facilitating this community engagement are required for EFIC and WIC trials:

- Community consultation;
- Public disclosure *before* the trial begins, including methods by which patients can opt out or refuse to participate in the trial;
- Public disclosure *after* the trial has been completed;
- A plan for contacting the LAR or family members to seek informed consent within the therapeutic window (if feasible) or as soon as possible after the patient has been enrolled in the study (when feasible); and
- Formation of a DSMB to review study data.

These additional protections are intended to establish a dialogue between study investigators and community members and to raise awareness within the community about the trial. Although these requirements are mandated by the federal guidelines, the HHS and FDA do not dictate how these requirements are met. Rather, the IRB must review and approve the investigator's plan for implementing these protections. Since **individual IRBs have different metrics and requirements to meet these standards**, investigators should consult with their IRB of record for the study before formulating a plan for these requirements.

Community Consultation

Community consultation is an opportunity for the local community to learn about the risks and benefits of study participation, voice their own beliefs and concerns about the study, and have their questions answered by members of the study team.

In multicenter studies, the community consultation process is performed at each study site. Importantly, **successful completion of the community consultation does not constitute community consent** for the research study. In fact, a community cannot consent for an individual in the community to enter a research study. Rather, it is an opportunity for investigators to gain feedback on their protocol from the local community and for the IRB to use that feedback when assessing the study's risk and benefits from the community's perspective.

Multiple methods for community consultation exist, including focus groups, community meetings, and disseminated surveys. A plan for community consultation should be cited in the proposal and should be executed in accordance with local IRB policies. In general, **all materials used for community consultation must be reviewed and approved by the IRB before they can be used**.

Community consultation should include an explanation of how community members can opt out of inclusion in the study when a community is included in a protocol. For example, some studies offer opt-out bracelets to community members who do not wish to be enrolled. Such opt-out procedures are not required by the federal regulations but may be required by the IRB.

Public Disclosure

Public disclosure should begin before the trial starts and continue after the trial has been completed. Before the start of the trial, information about the study protocol, including the study's purpose and the risks and benefits of study inclusion, should be disclosed to the public. Disclosure can include visual aids, public advertisements, and direct contact with potential participants (when appropriate and permitted by the IRB). After trial completion, the public should be advised of the study results. For example, the investigators of the tranexamic acid for TBI trial disclosed their results through multimedia press releases after the trial was completed.[35] As with community consultation materials, **all materials used for public disclosure must be reviewed and approved by the IRB prior to their use**.

Plans for LAR Contact

Plans to obtain consent from the subject's LAR can vary according to the intervention and the environment where the study is conducted. For example, the BOOST-3 trial protocol designated an on-call study team to seek consent and initiate enrollment as soon as possible.[5] By contrast, the COMBAT trial protocol required the admissions department and social workers in the ED to locate the LAR for all study subjects.[6-9]

Data Safety Monitoring Board

Trials that use an EFIC or a WIC approach must outline a plan for monitoring the safety of study subjects in their initial protocol submission. Many studies use a DSMB, an independent group of experts that objectively reviews study data, to

ensure that the trial is not exposing subjects to excessive risk. For studies using a DSMB, investigators must submit to the IRB a description of who is on the DSMB, how often they will meet, and what role they will play in determining how the trial continues after their evaluation.

Key Concepts

- Public disclosure, including pre- and post-trial disclosure, is a major consideration for any IRB that reviews EFIC and WIC protocols.
- When subjects can opt out, the process for rejecting enrollment should be clearly described in the study protocol.
- If the use of a DSMB is being considered, investigators should provide the IRB with a description of who will constitute the DSMB, how often they will meet, and what role they will play in determining how the trial is conducted.

6.5

The Role of the Institutional Review Board

The IRB plays an important role in the application of EFIC and WIC regulations. Although federal regulations describe requirements for the use of an ERCW, the IRB is responsible for determining whether a study is eligible for these waivers. IRBs expect and require investigators to explain their rationale for requesting an ERCW and their plan for protecting community members from excessive exposure to the study's risks. Investigators need to remember that the primary function of an IRB is to protect the safety of participants in human subject research. Because obtaining informed consent is a major consideration in the protection of study participants, **many IRB members are uncomfortable with approving EFIC and WIC studies, especially if they have not reviewed these studies before**. Investigators planning to submit an EFIC or a WIC proposal to their IRB should expect to meet with IRB leadership to assess the IRB's history of review and approval of EFIC and WIC studies. If possible, investigators should consult with other researchers who have successfully applied for an ERCW through their IRB and learn how they satisfied the "additional protections" (eg, public disclosure, community outreach) requirements, which can vary widely among IRBs.

For single-center studies, the local IRB is often the IRB of record for the study. However, multicenter studies are increasingly using a **single IRB of record** (sIRB) model in which a single commercial, academic, or hospital-based IRB reviews the proposed research and makes decisions about the study on behalf of all involved sites. In this model, the individual local IRBs where the research will be conducted cede authority for review and approval to the sIRB. Importantly, local IRBs must have a reliance agreement, or authorization agreement, in place with the proposed sIRB to cede review. This reliance agreement can be highly customized and precisely delineates the roles of the sIRB and the local IRB in the initial review and ongoing oversight of the study. Even when an sIRB has provided the initial review and approval of a study protocol, local IRBs generally maintain some degree of oversight to ensure that the needs of the local community are met. For example, the local IRB still

approves and monitors the methods used for community consultation, public disclosure, and other local outreach activities while ceding authority for other aspects of the review to the sIRB.

Most of the trials included in this review used a central or regional IRB for study approval. This trend is likely to continue in the future, as federally funded multicenter studies have been required to use the sIRB model since January 2020. In the BOOST-3 trial protocol, the central IRB guided and defined acceptable options for community consultation.[5] When a central IRB is used, its representatives can choose to attend focus groups to ensure these meetings are effective. The IRB expects enrollment procedures, ICFs, and reports on adverse events to be evaluated by an independent committee throughout the data monitoring process.

Key Concepts

- The use of a central or regional IRB does not preclude the need for local IRB review and approval of an EFIC or a WIC proposal, including public disclosure of the study both before and after study execution.

- Community standards for pre- and post-study disclosure are defined by the local IRB and can differ widely between local IRBs.

6.6

Investigational New Drug and Investigational Device Exemptions

The FDA's **IND** program provides pharmaceutical manufacturers with authorization to ship the investigational drugs and begin human clinical trials before the FDA has approved a marketing application for the drug. Three types of IND approvals are commonly referenced:

- **Investigator IND** — submitted by a clinical investigator to study an unapproved drug or approved drug for a new indication or new patient population;
- **Emergency use IND** — used to emergently treat a patient with an experimental drug when the patient does not meet the criteria of an existing study protocol; and
- **Treatment IND** — used to treat a patient who has a serious or life-threatening condition with an experimental drug after the drug has been studied in human subjects but while it is still under FDA review.

Investigator INDs are generally used with EFIC protocols to study drug interventions for new medical indications or in new patient populations. If the proposed EFIC study intervention involves a drug, the investigator should plan to apply for a separate IND exemption from the FDA. When submitting the IND application to the FDA, the investigator should also submit a written copy of the proposed EFIC protocol. The IRB must receive documentation of the FDA's approval of the IND application before it can approve the EFIC protocol.

Although EFIC studies can involve either FDA-approved or unapproved drugs, the vast majority of EFIC trials include FDA-approved drugs that are being studied for a new medical indication or in a different patient population. However, conducting an EFIC trial inherently changes the patient population of interest because, unlike the original patient population the drug was tested on, these subjects have not provided their informed consent for study inclusion. Even if

investigators have already conducted the same study without using the EFIC pathway (ie, they obtained informed consent in advance of enrollment), the FDA and IRB will consider the patient population in the EFIC version of the trial to be different from those enrolled in the previous non-EFIC study.

Examples of drugs that have been studied using the EFIC pathway and required an associated IND exemption include hypertonic saline, diaspirin cross-linked hemoglobin, human polymerized hemoglobin, thawed plasma, vasopressin, monoclonal antibodies, progesterone, erythropoietin, neuropeptide NNZ-2566, thromboxane, levetiracetam, fosphenytoin, valproate, diazepam, and magnesium.

Similarly, an **IDE** should be obtained for EFIC studies in which the intervention of interest is a medical device.

Key Concepts

- Because they inherently involve studying the effects of a drug or device intervention, EFIC studies require submission of an IND or IDE application for FDA approval.

- ERWC studies that do not involve studying the effects of a drug or device intervention may be authorized by the WIC pathway.

- FDA approval of an associated IND or IDE application is required before an IRB can approve an EFIC study.

7.0

Community Consultation and Public Disclosure

Vignette

As part of your EFIC proposal on the use of REBOA for OHCA, you will need to include a description of your plan for community consultation and public disclosure of study results. You realize in your review of the federal regulations that much of the detail regarding this aspect of EFIC studies is left to the discretion of the IRB of record for the study, so you know that you will need to consult your local IRB for their assistance in crafting your approach. You wonder what the IRB will require and how they will decide whether your plan for community involvement in the study is adequate. What is required for community consultation, and how should you engage your community to ensure that your rationale for the use of EFIC is properly relayed to them?

The federal guidelines do not detail exactly how the community consultation and public disclosure process should be structured or implemented. As a result, this process can vary widely by community, and the local IRB is tasked with defining what qualifies as appropriate and adequate community consultation.

The CFR (**21 CFR § 50.24**) provides guidance that pertains to community consultation for EFIC as follows[36]:

> (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; (ii) public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.

Some IRBs may have extensive experience with ECRW community consultation and disclosure, while others may have little or no previous exposure. For this

reason, investigators who are planning to conduct an EFIC or a WIC study should reach out to their local IRB as well as other investigators who have performed this type of research in their local community for guidance on what prior community consultation process has been acceptable. **This process is meant to be tailored to the local community, so what works in one community may not be considered appropriate or adequate in a different community**. Local standards for this process should be considered heavily in preparing a proposed community consultation plan.

Community consultation and public disclosure can be thought of as two separate but related concepts with similar goals. Generally, **community consultation refers to the interaction of study investigators with the local communities that are expected to be affected by the proposed research**. In this phase, investigators solicit opinions from community members about the proposed research and then formally present this feedback to the IRB for their review. Exactly how "community" is defined will depend on a variety of factors, including the geographical region in which study subjects are to be enrolled, the type of subjects expected to be enrolled, and any special groups that may be disproportionately affected by the research.

Regardless of whether a study intends to target specific groups within the community, investigators should collaborate with community leaders to identify ways in which the conduct of the study could lead to disproportionate enrollment. For example, if a proposed intervention is expected to disproportionately impact a specific racial or ethnic group, investigators should discuss the proposal with and solicit feedback from local community leaders and organizations that represent those groups prior to initiating the research. Even when a trial is administered through a central IRB, local communities must be engaged because the local IRB must review the results of consultation before approving the research for local implementation.

Public disclosure refers to the broad dissemination of information on the proposed research protocol to the community at large, with the intent of reaching as many individuals as possible. Public disclosure is accomplished both ***before*** the research starts and ***after*** it concludes to disseminate study results. Public disclosure activities will vary by study and community but can include announcements on radio or television or flyers posted throughout the community.

The more specific goals of community consultation are:

- To provide a forum in which community members can express their opinions and concerns about the proposed study so that they can be addressed and incorporated into the IRB review process.
- To provide an opportunity for investigators to meet with study-specific groups of potential subjects within the study's catchment area and address their group-specific concerns. For example, investigators may meet with members of the local African American, Hispanic, or Jehovah's Witness communities when these groups are disproportionately represented in the study's population or are otherwise uniquely affected by the study.
- To ensure that community members understand the proposed study and its potential risks and benefits to subjects.

- To clearly communicate investigators' rationale for enrolling subjects without informed consent prior to enrollment.
- To show respect for the community and subjects' autonomy by soliciting and addressing their opinions and other feedback about the study prior to initiation.
- To discuss methods by which community members who do not wish to participate in the research may opt out in advance.

The more specific goals of public disclosure are:

- To provide sufficient information to the public at large to ensure that the broader community is aware of the research plans, expected risks and benefits, and enrollment of subjects who have not provided informed consent.
- To provide a method by which community members who do not want to participate in the research study can opt out in advance.
- To provide the public with the results of the proposed research in a way that is easily understood by laypersons.

Community consultation efforts generally consist of in-person educational meetings with some portion of the community believed to be representative of those individuals expected to participate in the research. **All communities that may be affected by the proposed research should be involved**. The advantage of an in-person discussion is that community members can offer their insights and opinions in real time, which may reflect the larger community's beliefs. After an educational session, community members provide feedback on their thoughts and feelings provoked by the session. Community members can also inform investigators about how patients' relatives or LARs may react when hearing about the study (eg, if they would allow their loved ones to participate in the study) and the rationale behind these opinions.

After receiving community member feedback on their initial presentation, the study team can modify its proposal before future community meetings. Community members can also share their opinions about how well additional materials (eg, ads and flyers) explain the study to a layperson. Community consultation allows many members of a diverse community to speak with investigators directly, express their concerns, share their personal stories, and ask questions. Importantly, it is acceptable for community members and investigators to have differing opinions on specific aspects of the proposed research. Although investigators would like community members to fully agree with the research plan, investigators are not obtaining "community consent." Rather, they are seeking consultation with the community through these efforts. Disagreement between investigators and the community should be well documented and presented to the IRB for arbitration. It is unnecessary for investigators to revise their study protocol based on feedback from the community outreach effort, although they may certainly do so. Rather, the IRB is ultimately responsible for determining whether community concerns or suggestions should be reflected in changes to the study protocol.

The community consent process allows researchers to gather unique information about individual community needs or concerns and to adapt their study protocol accordingly. For example, the community consent process for the diaspirin study revealed that many Jehovah's Witness patients sought care at one of the study's local hospitals.[46] Because the proposed trial involved a blood substitute for use in trauma patients, concerns were raised that this intervention may be inconsistent with that group's religious beliefs about receiving blood products. The results from their community consultation suggested that the proposed intervention should not be performed in that community.[47] In this case, the community consultation process ultimately changed the course of the study.

As Dr. Clifton Callaway described in *Critical Care Medicine*, "another function of community consultation is allowing the investigator to share responsibility with the community for subjects who are hurt in a trial or who are upset after the trial. Adverse outcomes are much easier to defend and accept for situations and risks that 'everyone knew about' and 'most people thought were a good idea.' The validity of this function requires that risks were adequately disclosed to community participants."[48]

Investigators planning an ERCW study should develop an organized approach to community consultation and public disclosure. The study protocol must be reviewed and approved by the local IRB prior to any research activities taking place. The IRB will likely request modifications to this protocol, and it may undergo several revisions prior to approval, which often takes 3 to 6 months to secure. A typical community consultation and public disclosure protocol may consist of:

- Development of educational materials (eg, advertisements, flyers, presentations);
- Community group consultation (eg, in-person meetings); or
- Additional means of dissemination (eg, electronic media, social media, written pamphlets).

Public disclosure is typically much less interactive than community consultation and is focused on the broad dissemination of the study's information to the general public. Community consultation can be thought of as using a small, representative sample of the community to gain an understanding of how other members in that community may react to the proposed research. The goal is not to meet with the entire community, but rather to seek feedback from specific community representatives. By contrast, public disclosure seeks to notify as many community members as possible about the impending research study and its results.

Public disclosure is accomplished through more passive means of information dissemination and occurs both before and after the research is conducted. Examples of passive dissemination of research information include publicly posted flyers, social media (eg, X [Twitter], Facebook), radio or television advertisements, mass email communications, and newspaper advertisements. Information presented in various forms must be consistent and should include: (1) a brief synopsis of the research; (2) risks and benefits; (3) a statement that most subjects

will be enrolled without informed consent; and (4) a method for members of the public to opt out of the research ahead of time.

Whenever a formal analysis of study data takes place, either at an interim or the conclusion of the study, it is advisable to update the community regarding the study's latest results. These updates can be provided via electronic media (eg, social media, mass email) or on paper (eg, flyer) rather than in person. In some cases, additional community meetings may be recommended by the IRB, such as when a new risk is identified.

Key Concepts

- Community consultation is intended to allow for direct communication between the research team and the community.

- Community consultation and public disclosure processes will vary by community, with the local IRB defining what constitutes appropriate and adequate community consultation.

7.1

Community Consultation and Public Disclosure Materials

The first step in the community consultation process is the development of educational materials to use at community meetings or to post in public locations. These materials should be directed at community members and written in layperson's terms. Included language should be as straightforward as possible and avoid the use of medical jargon or unfamiliar acronyms.

Community Consultation Meetings

In-person meetings are a vital component of the community consultation process.[47,48] Researchers should consider these meetings to be an opportunity to develop good rapport and a trusting relationship with community members. Federal guidelines do not specify how many meetings are needed to satisfy the requirements of community consultation. In general, researchers should plan enough meetings to ensure that all major demographic and geographic groups within the community have been consulted. In some cases, this goal can be accomplished in as little as four to six meetings. Additional community meetings may be required at the discretion of the IRB or other regulatory bodies if they judge that the study team has not achieved adequate community disclosure or if more meetings are needed to address specific concerns.

Previous studies have shown that ***interactive*** community consultation is associated with increased acceptance of the EFIC approach and greater recall of study information than non-interactive consultation, but surprisingly low recall of study risks.[49] These results suggest that how study information is shared can influence how community members perceive the risks associated with the study. Less interactive methods of community consultation (eg, handing out flyers) may provide a less representative and less accurate estimate of the public's opinion on study risks.

To achieve adequate attendance, investigators should schedule community meetings in conjunction with local organizations or at locations where regular,

predetermined meeting dates and times are possible. Local churches and religious organizations, the Rotary Club, Elks Club, VFWs, senior centers, and other community centers may be appropriate venues. Many nonprofit community organizations are eager to recruit local speakers for their meetings and may be willing to accommodate research presentations. This approach also ensures that there will be an audience for the question-and-answer portion of the presentation. By contrast, attempting a *de novo* meeting will most likely result in low turnout, lack of high-quality participation, and inadequate feedback. Lack of adequate attendance and participation undermines the goals of community consultation and may become problematic when the IRB assesses the community's perspective on the research. Prior to holding any meetings, researchers should obtain IRB approval of the meeting plan to maximize efficiency of the community consultation process.

Before community consultation meetings, investigators must establish an agenda, determine technology requirements, and discuss logistics with the organizer to ensure that the appropriate equipment is available and the presentation is provided within the specified time limit. Presenters must prepare and organize all required participant materials in advance, including flyers, a formal presentation, and all necessary informed consent documents. Participants should be provided with the materials they need to understand the presentation and can also be given information to take home to their families and friends to better disseminate study information within the community.

Dedicated research staff should attend community consultation meetings to document the number of community members in attendance as well as any feedback that is provided by attendees so that this information can be collated and delivered to the IRB for their review. Meeting minutes should include descriptions of interactions and dialogue between the participants and the researchers. Verbatim (ie, word-for-word) transcripts of meetings are not required for IRB submission; however, directly quoting comments by community members is encouraged when these statements are pertinent to the goals of the community consultation. Community member comments should be grouped by theme for ease of IRB review.

Slideshows

An electronic slideshow (eg, Microsoft® PowerPoint) may be a good way to present study information during a community meeting, although slideshows are not strictly required. Investigators can use whatever communication that they believe will be effective but should plan to provide a detailed written description of the information that was shared with attendees. Information shared with community members during the meeting should include, but may not be limited to, background on the medical condition of interest and currently available interventions, a description of the proposed study and the study population, the anticipated risks and benefits of enrollment in the study, economic considerations, treatment alternatives, and ways for community members to opt out of enrollment. The research team should also explain to the community that most participants will be enrolled before they can provide

meaningful, prospective informed consent. Presentations are typically followed by a question-and-answer session.

A slideshow outline could include:

- An overview of emergency research, EFIC, and informed consent
  - Many community members are unaware of the process for emergency research and exceptions to informed consent.
  - Community members often respond positively to the concept of EFIC once they understand the need for research to improve current therapies and the role they can play in furthering this research through these discussions.
  - It may be helpful to provide examples of prior studies that used an EFIC approach and how they have improved the standard of care for other medical conditions.
- Protocol design
  - This portion of the presentation explains why the study is being conducted and how its interventions will differ from the current standard of care.
- Study population
  - The population investigated in the study is identified. Subject screening measures and inclusion and exclusion criteria are reviewed.
- Informed consent
  - The fact that prospective informed consent will not be obtained prior to enrollment is explained.
  - The fact that the EFIC process is closely regulated by the FDA and local IRB based on input from the local community should be emphasized.
- Therapeutic window
  - The intervention's therapeutic window is explained in layperson's terms. The community's understanding of this concept is important in establishing their views on the proposed research.
- Rationale for EFIC
  - An explanation is given for why consent is not feasible and why a WIC is necessary for the study.
- LAR consent
  - A description is given of how the study will attempt to contact subjects' LARs or family members for informed consent on behalf of the subjects both before and after the intervention is administered.
- Opt-outs
  - Investigators explain how individuals can decline to participate in the research.
  - Investigators describe how community members who wish to opt out of the research will be identified by the study team. Examples include bracelets or an opt-out list.

- Study setting
  - A description of the research setting is provided, including information on the intervention to be administered, where it will be administered (eg, prehospital, ED), whether subjects will be followed in the hospital, and who will be involved in performing study activities.
- Risks, benefits, and adverse events
  - Attendees are provided with a balanced description of the study's risks and benefits, including any relevant information about known or potential adverse events.
  - Investigators should avoid minimizing any significant risks of the intervention. Minimization of risks can undermine trust between the research team and the community. Investigators should also emphasize the intervention's important potential benefits and why the current standard of care is insufficient.
- Patient health information
  - Community members should receive an explanation about the informed consent process for data collection, which patient health information will be collected, where it will be stored, risks associated with storage, and who will have access to their records.
- Community perceptions and open discussion
  - Attendees should be invited to ask questions and offer comments about the research.
  - Community members share their perceptions and understanding of the research. This discussion is an opportunity for the research team to clarify any misunderstandings and to address specific concerns. It allows the research team to gauge the acceptability of their responses to these concerns by attendees and to improve and refine future presentations to reduce ambiguity or miscommunication.
  - The community group is asked thought-provoking questions, such as whether the study was sufficiently explained and why the intervention's benefits outweigh the associated risks.
  - Community members should be invited to share any personal stories that may stimulate further conversation. During the presentation, they may be thinking of their own or a loved one's experience at the ED, which may affect how they view the proposed research.
  - It may be helpful for presenters to ask attendees if they or a loved one has experienced the medical condition of interest in the study to relate the importance of the knowledge expected to be gained from the study to future patients.

Flyers

One-page flyers are a traditional, familiar vehicle for information dissemination within most communities. Researchers can develop a flyer or handout that

summarizes the study's key information and includes a link (eg, a website or phone number) to additional resources for more information. Flyers can be printed and posted in public spaces, shared via email or social media, or modified for newspaper publication. Information included on flyers should succinctly describe the study's objectives, potential risks and benefits, methods for opting out, and a notice that most subjects will be enrolled without prior informed consent. Language that is difficult to misinterpret should be chosen, especially when mentioning that informed consent waivers will be used.

Written/Electronic Dissemination

- **Social media (X [Twitter]/Facebook/Instagram)**. Social media can increase the local community's awareness of the study. Researchers can use social media to develop an online presence, provide the community with easy access to information, rapidly disseminate updates on the study's progress, and provide opportunities for the community to interact with the research team. Communication through social media can be helpful even after the study ends to provide updates on the study results. Investigators should confer with their IRB to understand how involved the IRB will be with reviewing and approving the research team's social media posts. In most cases, the IRB will want to review and approve any materials that are posted to social media accounts prior to their release to the public.
- **Mass advertisement, demographic-targeted emails**. Advertisement emails sent to a specific demographic allow for more targeted information dissemination within the community. Emails should be sent to individuals in the community who are expected to be affected by the research. Flyers that were created for the study can be used as the email's template. Researchers can contact local media outlets or newspapers to determine the optimal approach for targeting their demographic group. This method is especially useful during public disclosure because it can potentially reach thousands of people at a relatively low cost. Investigators will need to justify to the IRB their rationale behind sending targeted emails, including how the targeted audience will be defined and how potential recipients will be identified.
- **Newspaper advertisements**. Advertisements can be placed in local newspapers, which may help reach older adults and people who do not use social media or the internet. Federal guidelines do not specify details such as the number and frequency of newspaper advertisements that can be placed; these topics should be discussed with the IRB and will depend largely on the available budget. Researchers should obtain price quotes from local newspapers on available advertisement packages, geographical distribution areas, and any associated costs. These costs will need to be considered when determining the study budget allocated to community outreach efforts.
- **Television and radio advertisements**. Television and radio advertisements are another method for public disclosure. Local or regional public television and

radio outlets offer advertisement packages for different budgets. However, for research trials with more limited budgets, this advertisement option may be cost prohibitive. Researchers who choose this route of advertisement must work with the media group to develop a script, and actors or vocalists may need to be recruited.

Email

Study-specific email accounts must be secure and regularly monitored. The study's email address should be provided on flyers, other disseminated material, and at community consultation meetings. Community members should be instructed to email the research team to ask questions, to provide feedback on materials, or to opt out of the study (when appropriate).

Telephone

A telephone number for the research team's secure phone line with voicemail should also be provided to community members who prefer communication over the phone or who do not have access to a computer. If a telephone number is provided, it should be adequately staffed, and timely responses to queries should be provided.

Key Concepts

- Investigators should consider scheduling meetings with community organizations at regular, predetermined times to increase attendance.
- Materials used in community consultations can include printed media, electronic media, and a wide range of communication strategies.
- Incorporating guidance and feedback from the IRB, the local study team should determine what type and frequency of community outreach is most appropriate for its study.

7.2

Post-Approval Public Disclosure

Requirements for public disclosure and dissemination of information continue through the duration of the study, even after the EFIC protocol is approved. The community should be updated throughout the study of any significant changes that may affect the risk-benefit ratio for participants. When a study amendment is proposed to the IRB, the local IRB will determine whether additional community consultation and public disclosure are required, although implementation of public disclosure remains the responsibility of the research team. Mid-study public updates can be announced through mass media (eg, social media, mass emails), although the IRB may require further community consultation through additional in-person meetings. The research team should consult the IRB of record and their local IRB on the best methods to inform the public of changes to the study protocol.

As described in **21 CFR § 50.24(a)(7)(iii)**, investigators must make the results of their trial publicly available to the community and other researchers after the study is completed.[43] A description of the proposed plan for post-approval public disclosure should be included in the initial IRB submission, either in the section pertaining to pre-approval public disclosure or in a separate section of the protocol. Post-enrollment public disclosure should be performed promptly after study enrollment is completed and may include:

- Publication of study results in a peer-reviewed research journal;
- Presentation of study results at local, regional, or national meetings;
- An email or letter to all trial participants;
- Press conferences; or
- Updated listings on the trial website.

In-person meetings are not generally required for public disclosure after study completion. However, investigators should consult their local IRB when developing or revising their post-study public disclosure plan to ensure that the plan is consistent with local IRB standards. When considering how to disclose the study

results, investigators must remember that it is unlawful to promote the safety or efficacy of a drug or technique that is still under investigation (**21 CFR § 312.7** and **21 CFR § 812.7**).

Key Concept

- Although the methods for post-approval public disclosure are not specifically described in federal guidelines, a detailed plan for public disclosure should be included in the study protocol.

8.0

Opt-Outs

Vignette

During your discussion with community members and other advisors to your study, you have learned that many potential subjects want the opportunity to decide in advance that they are not interested in participating in the study. You realize that "opt-out" methods have been used by other researchers for EFIC trials, but you are unfamiliar with those methods. How can you ensure that potential subjects for your study within the community can opt out of study inclusion if they want to do so?

Because the EFIC and WIC approaches are designed to comply with community standards and uphold community members' autonomy, potential subjects must be provided with a mechanism for opting out of the study. Details of the opt-out program must be provided in the study protocol and clearly communicated during the public disclosure process.

As described in **21 CFR § 50.25(a)(8)**, the basic elements of informed consent require that potential subjects be provided with "a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."[43] This statement is generally included in the ICF for the study but should also be mentioned in presentations to the community during the public disclosure process.

In the setting of community consultation, two possible hypotheses could be entertained. The first hypothesis is that most community members would want to participate in EFIC/WIC studies if offered the chance. Under this presumption, it would be most appropriate to offer "opt-out" options to community members, as this would seem to be the minority of potential subjects. The second hypothesis is that most community members would not want to participate; in this context, it would be most appropriate to offer "opt-in" options to community members. At the time that the original EFIC/WIC regulations were being developed, it was

presumed that most community members would want to participate when offered the chance to be enrolled in such studies. Consequently, the federal regulations offer "opt-out" mechanisms, rather than "opt-in" mechanisms. To date, the number of community members requesting to "opt out" of EFIC/WIC studies seems to be very small, supporting this assumption. In this way, community consultation establishes the reasonable presumption that most citizens would choose to participate when offered the chance to do so.

In the reviewed EFIC and WIC protocols, the most common ways for individuals to opt out were wearing a bracelet (59%), carrying a sticker or card in a wallet or purse (18%), wearing a dog tag (12%), or entering their refusal to participate into a secure database (12%). Many of these studies offered more than one method for opting out.

Additional information that can be included in the ERWC protocol includes: (1) further discussion of patients' right to preemptively withdraw their consent to participate in the trial; (2) a description of how prehospital employees will identify patients who have opted out; and (3) a disclaimer that in emergency situations, health care professionals may inappropriately enroll a patient in the trial if they do not understand that the patient wished to opt out.

Example of a Generic Opt-Out Statement

"Description of Refusal to Participate Procedure: Patients have the right to refuse to participate in the study prior to and during the trial and will not be enrolled in the study if they choose to opt out. In all the community consultation and public disclosure materials and at all trial events, community members will be educated on how to opt out of the study. Community members may communicate their decision to opt out of this study by wearing an opt-out bracelet available at study events or by contacting investigators via our website, who will then mail a bracelet to the individual. The bracelet has the words 'EFIC trial' on it and is the primary mechanism by which an individual can opt out."

Key Concepts

- Investigators of EFIC and WIC trials should offer community members a mechanism for opting out of a trial and should inform the community of how to opt out prior to the start of the trial.

- Common opt-out methods include the use of bracelets or other wearable signs and the use of databases listing opted-out community members that must be reviewed prior to each subject's enrollment.

9.0

Example EFIC Study

What follows is an example of how an EFIC study followed the methods outlined in previous sections.[31,32] Note that this process varies across institutions and that this is only one example of how to conduct an EFIC study.

Yale School of Medicine (New Haven, Connecticut): "The Use of REBOA in Out of Hospital Cardiac Arrest: An Early Feasibility Trial"

Trial Summary

REBOA is a hemorrhage control technique that is increasingly used to manage noncompressible intra-abdominal traumatic bleeding. In this technique, an intra-aortic catheter is inflated to occlude blood flow to the torso and redirect it toward the heart and brain. This technique improves diastolic blood pressure and subsequent coronary perfusion by increasing blood flow in the aortic arch, which can benefit patients with nontraumatic cardiac arrest. Investigators at Yale New Haven Hospital initiated an EFIC trial to study this technique as a novel intervention for medical cardiac arrest patients. The research goal is to conduct a small noncontrolled early feasibility trial (n = 5) of REBOA as an adjunct to ACLS. This study will be used to design a subsequent pivotal clinical trial that provides definitive guidance on the use of REBOA by emergency physicians in nontraumatic OHCA.

Initial Steps

Early and frequent consultation with one's local IRB is essential in conducting an EFIC study, especially if the IRB does not have significant experience with EFIC research. Prior to approaching the IRB, the investigator should create a detailed study outline and plan. Many IRBs offer templates to help create these documents in a manner familiar to the local institution.

The REBOA study team elected to conduct a noncontrolled early feasibility trial. Other options such as a small controlled trial were considered; however, it was determined that because the procedure had not been attempted in humans, safety and feasibility were the primary goals, and the inclusion of a control group would limit the ability to enroll patients and gather this data.

The trial design went through multiple iterations over the course of 18 months prior to receiving IRB approval. Investigators provided extensive documentation as to why the study met EFIC criteria, addressing each point found in Section 3.1 as well as a clear plan as to how the LAR would be approached for informed consent after enrollment. A provision was also included to allow family or a "significant other" to provide informed consent if the LAR was unavailable.

The investigator should expect increased IRB oversight of their EFIC trial compared to non-EFIC studies due to the inability of patients to provide informed consent. Maintaining a good working relationship with the IRB and open lines of communication is imperative to obtaining approval and conducting a successful trial. It is best that researchers be as forthcoming as possible about potential risks to patients and how their trial design will mitigate these risks. It is likely that the IRB will have concerns that the investigator has anticipated; efficient and careful responses to these concerns are crucial. In addition to trial design and risk mitigation, the Yale IRB had a significant role in designing the community consultation process, as detailed in the subsequent section.

Community Meetings

At the beginning of the EFIC process, the study team aimed to set up at least four community meetings with different groups at various places throughout the county. After the initial four meetings were completed, the Yale IRB reviewed the minutes and concluded that a sufficient representation from the county was not obtained. The Yale IRB asked the research team to hold another two meetings in different geographic areas to increase community awareness and knowledge, specifically for the local African American and Hispanic communities, and to ensure that all geographic areas were represented. A total of six meetings were held by the research team.

The research coordinator inquired about meeting availability with various community groups to begin scheduling meetings. The groups contacted were the local VFWs, Rotary Clubs, Elks Club, Community Centers, YMCAs, Senior Citizen Centers, and institutional cultural centers. The Yale research team hosted two Rotary Club meetings, one 5k run for a cardiac arrest nonprofit organization, and three Yale cultural center meetings.

The research team began each of the six meetings with a brief slide presentation and used any remaining time for open discussion. Participants were encouraged to ask questions both during and after the presentation, and conversations were facilitated between participants and the research team to discuss the participants' comments and concerns. The research coordinator recorded key statements from the participants and the research team during these discussions. Comments were initially organized by speaker and later by the key themes that emerged from all the meetings combined, and they were submitted for IRB review. Each community meeting lasted approximately 60 minutes and included time for the welcome, review of the study's details and risks, and participants' questions.

Notably, the study's researchers were able to take advantage of resources already in place through Yale University to schedule three of the six meetings.

Yale University, through the Yale Center for Clinical Investigations (YCCI), has developed a Cultural Ambassadors Program with the goal of connecting Yale's researchers with community leaders for increasing community involvement in Yale's research endeavors. The YCCI Cultural Ambassadors meet monthly, and many members have been regularly attending meetings for several years. This group is educated in research so that they can more fully understand the research proposals when disseminating this information to the local community.

From their community meetings, the Yale research team found that researchers should be prepared to have difficult discussions about the potential risks of the proposed research and the community's concerns about research conducted without informed consent. They also found that many communities have a long-standing distrust of the medical system, often for legitimate reasons. For some community groups, repeat meetings were helpful in developing trust between the group and the research team. For example, some members of the community group were not able to reframe their opinions of the research and approve of it until the second or third meeting with the YCCI Cultural Ambassadors. Developing a sense of trust over several meetings likely helped change their opinion. Although approval of all community members (ie, community consent) is not the goal of community meetings, researchers should interact with the local community enough so that more of the community supports the research, which helps during the regulatory review process.

Newspaper Advertisements and Flyers

The REBOA investigators created flyers that detailed the study's objectives, risks, procedure, and background information and handed them out at community informational sessions. Flyers were adapted for print media and published in several local New Haven County publications for a total circulation of 63,630 homes and businesses.

Flyers were also disseminated across New Haven County, including at public boards, bulletin boards, anywhere that bills were posted, libraries, clinics, city and town halls, laundromats, post offices, senior centers, community centers, gyms, coffee shops, grocery stores, YMCAs, restaurants, lamp posts, and bus benches.

Digital Media

In addition to print media, investigators used targeted digital ads. These ads were sent to the study's desired demographic of individuals over the age of 50 and reached approximately 33,000 individuals in the New Haven County area. The targeted ads were a digitized version of the flyer and were created after contacting one of the local New Haven newspapers.

Social Media

Advertising the study on social media provided several distinct advantages over conventional media, including lower costs and access to a larger audience with specific demographics. The Yale team considered using:

- **Facebook**. Investigators had initially planned to advertise on Facebook but decided to purchase demographic-targeted digital ads instead. Facebook

permits demographic-specific advertising and would have been a good option if digital ads had not been possible.

- **X (Twitter)**. A handle was created that allowed community members to stay apprised of the study's progress. Investigators tweeted general study information and changes and updates throughout the investigation. However, each tweet required IRB approval before posting.

Broadcast Media and Television

The Yale investigators had planned to advertise their study on local radio and television stations. However, when they contacted several local media outlets to obtain price estimates on their radio and television advertising spots, they found their budget would not cover the costs, so they stayed with local print and digital publications instead.

Opt-Out Email and Phone

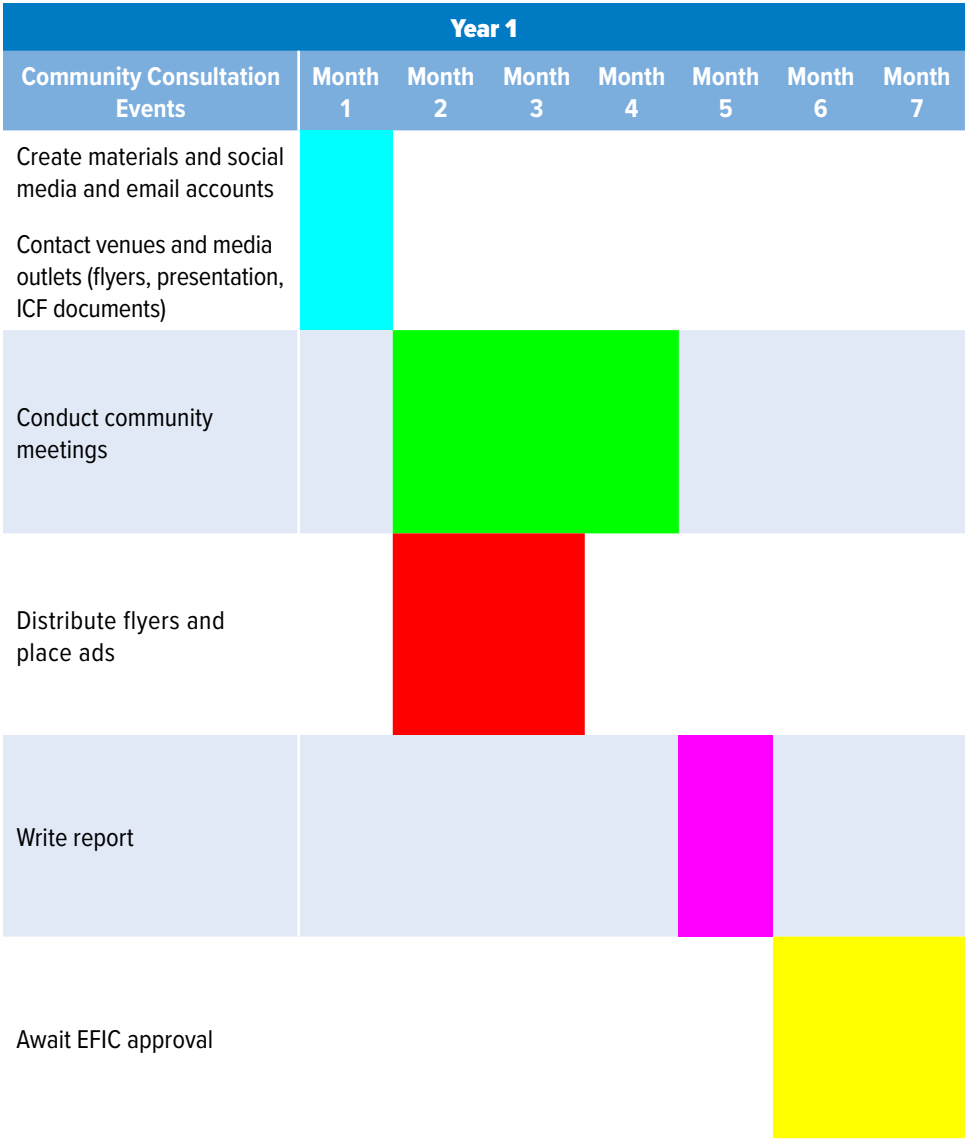
During each community consultation, attendees were given instructions on how to opt out of study participation. Community members had the option to add their name and birth date to an opt-out list that was provided at each meeting. A HIPAA-compliant email address and phone number were created and disseminated to community members through flyers and mass email advertisements so that community members could communicate with the research team and submit their opt-out information. The research staff monitored this email account daily.

*Anticipated Budget**

Item	Cost (Estimates)	Description
Banner	$600	Table banner to be used at events
Printed materials	$300-$500	Flyers, presentations, ICF documents
Newspaper ads	$1,000	One ad in three newspapers
Email ads	$900	Three email deployments
X (Twitter) account	$0	Free to create account
Facebook ads	$0.27/click	Contact Facebook for up-to-date pricing
Presentation	$0	Free to those with a Microsoft Office subscription
Television ads (local public station)	$4,800 $7,000	48, 15-second spot ads 28, 15-second spot ads

* This budget is provided as an example only; prices will vary based on location and timing.

Timeline



Timelines will vary from this example because they should be tailored to each study. Six months is typically the shortest timeline possible, and it is not unusual for the EFIC process to take more than 1 year.

10.0

Resources for Investigators

Other groups have also published insightful resources to help investigators create an EFIC or a WIC protocol. A list of these resources is provided below along with a brief description of why they are particularly useful in this type of research.

- **Aero Data Lab. Research conducted with an "Exception From Informed Consent": a map of the EFIC trial landscape. Published June 17, 2019. Accessed January 24, 2023.**
  - The Aero Data Lab provides a summary of EFIC studies from the last 2 decades, including the number of subjects enrolled and the time frame of their enrollment.[49]
- **Halperin H, Paradis N, Mosesso V Jr, et al. Recommendations for implementation of community consultation and public disclosure under the Food and Drug Administration's "Exception From Informed Consent Requirements for Emergency Research": a special report from the American Heart Association Emergency Cardiovascular Care Committee and Council on Cardiopulmonary, Perioperative and Critical Care. *Circulation*. 2007 Oct 16;116:1855-1863.**
  - This landmark reference from 2007 for EFIC use in emergency care research includes a helpful description of the requirements for community consultation and of assessing the incremental risk of a potential EFIC study.[50] It offers community consultation options according to the level of risk involved in the proposed study.
- **Klein L, Moore J, Biros M. A 20-year review: the use of exception from informed consent and waiver of informed consent in emergency research. *Acad Emerg Med*. 2018 Oct;25(10):1169-1177.**
  - This study describes the use of the EFIC and WIC techniques in 28 studies of emergency care research between 1999 and 2016; it also describes the types of medical conditions these precedent studies explored.[51] The authors include detailed discussions about how these studies justified EFIC and WIC use once published and discussions on the characteristics of patients included in the studies.

- **SIREN. Model operational procedures for the implementation and review of NIH sponsored multicenter clinical trials with exception from informed consent (EFIC) for emergency research. Published January 2021. Accessed January 24, 2023.** https://deepblue.lib.umich.edu/bitstream/handle/2027.42/166478/Model%20EFIC%20Procedures%20Final%20Version%201.pdf
  - This document is provided by SIREN (Strategies to Innovate Emergency Care Clinical Trials Network) to guide EFIC investigators on how to construct appropriate trial protocols.[52] It provides three subdocuments that can be used as a model for designing and documenting an EFIC protocol:
    - Investigator's EFIC Implementation Plan;
    - Standard Operating Procedure for Trial Applications Involving EFIC to a Single/Central IRB; and
    - Guidelines for Centralized Review of Community Consultation and Public Disclosure.
  - Supplemental material is also provided, including sample site EFIC activity reports for IRB submission.
  - The authors note that this is a template for developing an EFIC protocol based on those used in SIREN studies, specifically BOOST-3 and HOBIT.[5,53]
- **US Food and Drug Administration (FDA). Exception from informed consent requirements for emergency research. Updated March 29, 2018. Accessed January 24, 2023.** https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research
  - This document (last revised April 2013) provides the FDA's guidance, including "nonbinding recommendations," on the use of EFIC in emergency care research.[54] It also includes a thorough report on the history and evolution of EFIC regulations, with a sizeable question-and-answer section.
- **Feldman WB, Hey SP, Kesselheim AS. A systematic review of the Food and Drug Administration's 'Exception From Informed Consent' pathway. *Health Aff (Millwood)*. 2018 Oct;37(10):1605-1614.**
  - This systematic review reports on 41 approved EFIC trials from 1996 to 2017, including meta-analyses of 46,694 subjects enrolled in 29 EFIC trials. The authors discuss many important ethical and administrative issues that investigators should consider when planning and implementing an EFIC protocol.

APPENDIX 1

List of Included Studies (With Brief Descriptions)

ACCESS (2016)

- **Title:** Early vs Standard Cardiac Catheterization Lab (CCL) Activation in Resuscitated Cardiac Arrest Survivors With Non-ST Segment Elevation MI
- **Study PI(s):** Demetri Yannopoulos, MD (University of Minnesota); Tom Aufderheide, MD (Medical College of Wisconsin)
- **Emergency care network:** ACCESS Network
- **Study description:** The purpose of this trial was to determine which of two standard treatments, if any, led to better outcomes: (1) Initial cardiac catheterization laboratory (CCL) admission or (2) initial intensive care unit (ICU) admission in adults 18 to 80 years old who were successfully resuscitated from OHCA without signs of a heart attack on tracings of the heartbeat. This study was performed at 26 sites in the United States and Canada. Patients were included in the study after informed consent was obtained from either them or their next of kin or after using EFIC under emergency circumstances when patients were unable to provide informed consent and their next of kin could not be located.
- **Study population:** Adults who were successfully resuscitated from OHCA without signs of a heart attack on tracings of the heartbeat
- **Actual enrollment:** 65 subjects
- **Intervention/comparator:** Early cardiac catheterization versus ICU admission
- **Primary outcome/measures:** Survival to hospital discharge with a Modified Rankin Score less than or equal to 3 (time frame of up to 3 weeks)
- **Data collection period:** December 2017 to November 2019
- **Type of ECRW:** WIC
- **Study findings:** Between January 2018 and July 2019, 65 patients were enrolled in the ACCESS trial. The trial was stopped early in July 2019 because the rate of subject enrollment was too low. Study results showed no

difference in patient outcomes between treatment with initial CCL admission and treatment with initial ICU admission, including in survival and functionally favorable survival at hospital discharge and 3 months after hospital discharge.

- **ClinicalTrials.gov identifier:** NCT03119571
- **References:**
  - ACCESS Trial. Medical College of Wisconsin. Accessed April 13, 2022. https://www.mcw.edu/departments/emergency-medicine/research/resuscitation-research-center/access-trial
  - ACCESS Trial. University of Michigan. Accessed April 12, 2022. https://medicine.umich.edu/dept/emergency-medicine/access-trial

ALPS (2011)

- **Title:** Amiodarone, Lidocaine or Neither for Out-of-Hospital Cardiac Arrest due to Ventricular Fibrillation or Tachycardia
- **Study PI:** Peter J. Kudenchuk, MD (University of Washington)
- **Emergency care network:** Resuscitation Outcomes Consortium (ROC)
- **Study description:** This randomized double-blind trial compared parenteral amiodarone, lidocaine, and saline placebo with standard care in adults who had nontraumatic OHCA due to shock-refractory ventricular fibrillation or pulseless ventricular tachycardia after at least one shock and who had vascular access. Paramedics enrolled patients at 10 North American sites. The primary outcome was survival to hospital discharge, while the secondary outcome was favorable neurologic function at discharge. The per-protocol (primary analysis) population included all randomly assigned participants who met eligibility criteria, who received any dose of a trial drug, and whose initial cardiac arrest rhythm of ventricular fibrillation or pulseless ventricular tachycardia was refractory to shock.
- **Study population:** OHCA due to ventricular fibrillation or ventricular tachycardia
- **Actual enrollment:** 3,204 subjects
- **Intervention/comparator:** Amiodarone or lidocaine versus placebo
- **Primary outcome/measures:** Survival to hospital discharge
- **Data collection period:** May 2012 to January 2016
- **Type of ECRW:** EFIC
- **Study findings:** Overall, neither amiodarone nor lidocaine was associated with a significantly higher rate of survival or favorable neurologic outcome compared to placebo in patients with OHCA due to initial shock-refractory ventricular fibrillation or pulseless ventricular tachycardia.
- **ClinicalTrials.gov identifier:** NCT01401647
- **Reference:**
  - Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016 May 5;374(18):1711-1722.

ASPIRE (2004)

- **Title:** Autopulse Assisted Prehospital International Resuscitation Trial
- **Study PI:** Alfred P. Hallstrom, PhD (University of Washington)
- **Emergency care network:** N/A
- **Study description:** The AutoPulse™ Assisted Prehospital International Resuscitation (ASPIRE) Trial compared the efficacy of circulatory assist by manual chest compression to an automated chest compression device (AutoPulse™) during the resuscitative attempt after OHCA.
- **Study population:** OHCA presumed to be of cardiac origin
- **Actual enrollment:** 1,837 subjects
- **Intervention/comparator:** AutoPulse™ device versus manual chest compressions
- **Primary outcome/measures:** Survival to 4 hours post cardiac arrest
- **Data collection period:** June 2004 to March 2005
- **Type of ECRW:** EFIC
- **Study findings:** This study enrolled 1,837 participants from June 2004 to March 2005. Study enrollment was terminated after an independent DSMB conducted the first planned interim monitoring. No difference was found in the primary end point of survival to 4 hours between the group that received manual chest compressions and the group that received treatment with the AutoPulse™ device (N = 1071; 29.5% vs 28.5%; *P* = .74) or among the primary study population (n = 767; 24.7% vs 26.4%, respectively; *P* = .62). However, among the primary population, survival to hospital discharge was 9.9% in the manual chest compressions group and 5.8% in the AutoPulse™ device group (*P* = .06), adjusted for covariates and clustering. A cerebral performance category of one or two at hospital discharge was recorded in 7.5% of patients in the manual chest compressions group and in 3.1% of the AutoPulse™ device group (*P* = .006). Overall, use of the AutoPulse™ device in this study was associated with worse neurologic outcomes and worse survival than manual chest compressions.
- **ClinicalTrials.gov identifier:** NCT00120965
- **Reference:**
  - Hallstrom A, Rea TD, Sayre MR, et al. Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial. *JAMA*. 2006 Jun 14;295(22):2620-2628.

BOOST-3 (2019)

- **Title:** Brain Oxygenation Optimization in Severe TBI, Phase 3 (BOOST-3)
- **Study PI:** William Barsan, MD (University of Michigan)
- **Emergency care network:** Strategies to innovate emergency care clinical trials network (SIREN)

- **Study description:** TBI is a major cause of death and disability in developed societies. Every year, approximately 3.5 million Americans sustain a TBI, of which 50,000 die and another 300,000 are hospitalized and survive the injury. BOOST-3 is a randomized clinical trial that set out to compare the effectiveness of two strategies at monitoring and treating patients with TBI in the ICU. The study will determine and compare the safety and efficacy of a strategy that has treatment goals based on both intracranial pressure (ICP) and brain tissue oxygen ($PbtO_2$) with a strategy that has treatment goals based on ICP monitoring alone. Both strategies are currently used in standard care, but it is unknown if one is more effective than the other. The monitoring and goals included in both strategies help doctors adjust treatments, including the type and dose of medications, amount of intravenous fluids given, ventilator settings, need for blood transfusions, and need for other medical care. The results of this study are meant to help doctors discover if one of these strategies is safer and more effective.
- **Study population:** Patients with TBI
- **Actual enrollment:** 1,094 subjects (per ClinicalTrials.gov as reported April 12, 2022)
- **Intervention/comparator:** Treatment goals based on a strategy that includes both ICP and $PbtO_2$ versus a strategy guided by ICP monitoring alone
- **Primary outcome/measures:** Neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury
- **Data collection period:** August 2019 to July 2023
- **Type of ECRW:** EFIC
- **Study findings:** The study is currently enrolling subjects.
- **ClinicalTrials.gov identifier:** NCT03754114
- **Reference:**
  - SIREN. BOOST-3. Accessed April 12, 2022. https://siren.network/clinical-trials/boost-3

COMBAT (2016)

- **Title:** Control of Major Bleeding After Trauma (COMBAT)
- **Study PI:** Ernest E. Moore, MD (Denver Health Medical Center)
- **Emergency care network:** N/A
- **Study description:** Bleeding is the most avoidable cause of death in trauma patients. Up to one-third of severely injured trauma patients are found to be coagulopathic, and 40% of deaths following severe injury are from uncontrollable hemorrhage in the setting of coagulopathy. Mortality after a severe injury is decreased by early administration of fresh frozen plasma, replacing lost coagulation factors, improving the coagulopathy, and restoring blood volume. This study intended to determine if giving plasma to severely injured trauma patients during ambulance transport instead of after arrival at the hospital reduced hemorrhage and, thus, decreased both total blood product administration and mortality. Severely injured trauma patients with

a systolic blood pressure ≤70 or a systolic blood pressure ≤90 with a heart rate ≥108 bpm at the scene were enrolled and randomized to receive either two units of frozen plasma thawed in the field or normal saline (the current standard of care) as the initial resuscitation fluid. After this initial resuscitation fluid, both groups received the same standard of care treatment, including packed red blood cells, additional normal saline, or plasma as needed based on laboratory and clinical evidence of coagulopathy. Blood samples and clinical information were collected throughout the hospital stay up to 28 days after the injury. The main outcome was 28-day mortality.

- **Study population:** Trauma patients with hemodynamic instability
- **Actual enrollment:** 144 subjects
- **Intervention/comparator:** Prehospital infusion of two units of frozen plasma versus normal saline as the initial resuscitation fluid
- **Primary outcome/measures:** 28-day mortality
- **Data collection period:** April 2014 to April 2017
- **Type of ECRW:** EFIC
- **Study findings:** The COMBAT trial was terminated for futility, but results were subsequently combined with those from a similar trial. The Prehospital Air Medical Plasma (PAMPer) clinical trial showed a nearly 30% reduction in mortality with plasma transfusion in the prehospital environment, while the Control of Major Bleeding After Trauma (COMBAT) clinical trial showed no survival improvement. Thus, a post hoc analysis that included both trials was done to examine questions that could not be answered by either clinical trial alone. This post hoc analysis included 626 patients (467 men [74.6%] and 159 women [25.4%]; median [interquartile range] age, 42 [27-57] years) who had trauma with hemorrhagic shock. A Cox regression analysis showed a significant overall survival benefit in patients who received plasma (hazard ratio [HR], 0.65; 95% CI, 0.47-0.90; *P*=.01) after adjustment for injury severity, age, and clinical trial cohort (COMBAT or PAMPer). A significant association with prehospital transport time was detected (from arrival on scene to arrival at the trauma center). Increased mortality was observed in patients in the standard care group when prehospital transport was longer than 20 minutes (HR, 2.12; 95% CI, 1.05-4.30; *P*=.04), while increased mortality was not observed in patients in the prehospital plasma group (HR, 0.78; 95% CI, 0.40-1.51; *P*=.46). No serious adverse events were associated with prehospital plasma transfusion. These data suggest that prehospital plasma transfusion is associated with a survival benefit when transport times are longer than 20 minutes and that the risk-benefit ratio favors its use.
- **ClinicalTrials.gov identifier:** NCT01838863
- **References:**
  - Pusateri AE, Moore EE, Moore HB, et al. Association of prehospital plasma transfusion with survival in trauma patients with hemorrhagic shock when transport times are longer than 20 minutes: a post hoc analysis of the PAMPer and COMBAT clinical trials. *JAMA Surg*. 2020 Feb 1;155(2):e195085.

- Moore HB, Moore EE, Chapman MP, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. *Lancet*. 2018 Jul 28;392(10144):283-291.
- Reynolds PS, Michael MJ, Cochran ED, Wegelin JA, Spiess BD. Prehospital use of plasma in traumatic hemorrhage (The PUPTH Trial): study protocol for a randomised controlled trial. *Trials*. 2015 Jul 30;16:321.
- Chapman MP, Moore EE, Chin TL, et al. Combat: initial experience with a randomized clinical trial of plasma-based resuscitation in the field for traumatic hemorrhagic shock. *Shock*. 2015 Aug;44 suppl 1(0 1):63-70.

DIRECT VS VIDEO LARYNGOSCOPY (2011)

- **Title:** Laryngoscope Versus CMAC for Endotracheal Intubation in Patients Undergoing Emergent Airway Management
- **Study PI:** James R. Miner, MD (Hennepin County Medical Center)
- **Emergency care network:** N/A
- **Study description:** Direct laryngoscopy (DL) has long been the most common approach for emergency endotracheal intubation, although the use of video laryngoscopy (VL) is becoming more widespread. Current observational data suggest that VL has higher first-pass success, although randomized trials are lacking. The objective was to compare first-pass success in patients undergoing emergency intubation with DL or VL using a C-MAC device. This study was an open-label, prospective, randomized controlled trial in an academic ED where patients underwent emergency intubation with a plan of DL on the first attempt. Patients were randomly assigned in a 1:1 ratio to either DL or VL using a C-MAC device for the first intubation attempt. The primary outcome was first-pass success. Secondary outcomes included time to intubation, development of aspiration pneumonia, and hospital length of stay (LOS).
- **Study population:** Patients requiring intubation in the ED
- **Actual enrollment:** 198 subjects
- **Intervention/comparator:** VL using a C-MAC device versus DL
- **Primary outcome/measures:** First-pass intubation success rate
- **Data collection period:** October 2011 to June 2013
- **Type of ECRW:** EFIC
- **Study findings:** A total of 198 patients were enrolled and intubated with either DL (n = 95) or VL (n = 103). First-attempt success was 86% for the DL group and 92% for the VL group (difference = 5.9%; 95% CI, 14.5%-2.7%; *P* = .18). Time to intubation, rates of aspiration pneumonia, and hospital LOS were not different between the two groups. For patients in whom DL was the planned first attempt for emergency intubation, the researchers did not detect a difference between DL or VL using the C-MAC device in the first-pass success rate, duration of intubation attempt, aspiration pneumonia, or hospital LOS.
- **ClinicalTrials.gov identifier:** NCT01710891

- **Reference:**
  - Driver BE, Prekker ME, Moore JC, Schick AL, Reardon RF, Miner JR. Direct versus video laryngoscopy using the C-MAC for tracheal intubation in the emergency department, a randomized controlled trial. *Acad Emerg Med*. 2016 Apr;23(4):433-439.

ERYTHROPOIETIN IN TBI (2006)

- **Title:** Effects of Erythropoietin on Cerebral Vascular Dysfunction and Anemia in Traumatic Brain Injury
- **Study PI:** Claudia S. Robertson, MD (Baylor College of Medicine)
- **Emergency care network:** N/A
- **Study description:** TBI causes a spectrum of cerebrovascular dysfunction, ranging from impaired pressure autoregulation to severe global ischemia (inadequate blood flow). Pressure autoregulation is the ability of an organ to maintain a constant blood flow despite changes in perfusion pressure. Impaired pressure autoregulation causes TBI patients to be more vulnerable to secondary ischemic attacks. Erythropoietin (EPO) is a substance that is normally made by the kidneys and stimulates the production of red blood cells. It is usually given to patients to treat anemia. Scientists discovered that EPO is also made in the brain after injury. In animal models of TBI, the brain's production of EPO has numerous protective effects, including reducing inflammation in the brain, reducing brain cell death, and improving blood flow to the brain. In the laboratory, the effects of EPO can be enhanced by giving additional amounts of it intravenously. Because of the results from this laboratory research, scientists are studying the effects of EPO in patients with severe TBI. The primary objective of this randomized placebo-controlled study was to determine the effect of early administration of recombinant human EPO (rhEPO) on long-term neurologic outcomes in patients with severe TBI. The researchers also examined the effects of rhEPO administration on the cerebrovascular system, hemoglobin concentration, brain oxygenation, the need for blood transfusion, and systemic complications. The two parts of the study were the treatment phase and monitoring phase. In the treatment phase, participants were randomly assigned to one of four groups: a low- or high-dose rhEPO treatment group or a low- or high-dose placebo group (control group). All other aspects of treatment during the acute post-injury phase followed the standard treatment protocol for individuals with severe TBI: The treatment phase lasted 1 to 2 weeks or however long treatment in the ICU was required. The monitoring part of the study lasted up to 6 months after the TBI and included recording information from tests performed as part of the standard TBI treatment as well as some additional tests performed for the study.
- **Study population:** Patients with TBI
- **Actual enrollment:** 200 subjects
- **Intervention/comparator:** Intravenous EPO 500 IU/kg versus saline
- **Primary outcome/measures:** GOS-E dichotomized as favorable (good recovery and moderate disability) and unfavorable (severe disability, vegetative, or dead) at 6 months post injury

- **Data collection period:** April 2006 to March 2013
- **Type of ECRW:** EFIC
- **Study findings:** There was no EPO-transfusion threshold interaction. Compared to placebo (favorable outcome rate: 34/89 [38.2%]; 95% CI, 28.2%-49.1%), both EPO groups were futile (first dosing regimen: 17/35 [48.6%]; 95% CI, 31.4%-66.0%; *P* = .13 and second dosing regimen: 17/57 [29.8%]; 95% CI, 18.4%-43.4%). The dosage of 10 g/dL resulted in improved neurologic outcome at 6 months, and its threshold was associated with a higher incidence of adverse events. These findings do not support either approach in this setting.
- **ClinicalTrials.gov identifier:** NCT00313716
- **Reference:**
  - Robertson CS, Hannay HJ, Yamal JM, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. *JAMA*. 2014 Jul 2;312(1):36-47.

EROCA (2017)

- **Title:** Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest
- **Study PI:** Robert W. Neumar, MD, PhD (University of Michigan)
- **Emergency care network:** N/A
- **Study description:** OHCA is a life-threatening condition in which the heart suddenly stops beating and blood flow to the body ceases. If cardiac arrest is not treated immediately, it causes sudden death. In the United States alone, over 300,000 people per year have OHCA, and less than 1 out of 10 survive. Therefore, finding new ways to treat cardiac arrest patients is important to improving survival. The current standard for treating OHCA is CPR and ACLS at the scene until either the heart is restarted or resuscitation efforts are considered hopeless, at which point they would be discontinued. This practice is supported by paramedics in the field who can deliver these CPR therapies. However, promising new strategies have emerged that are more feasible to initiate in the hospital. One such strategy is extracorporeal cardiopulmonary resuscitation (ECPR). In ECPR, catheters that are connected to a machine are placed in large blood vessels and take over the work of the heart and lungs. The purpose of this study was to examine the feasibility and potential benefit of ongoing mechanical CPR for patients with refractory OHCA during expedited transport to EDs that are capable of initiating ECPR.
- **Study population:** Refractory OHCA
- **Actual enrollment:** 15 subjects
- **Intervention/comparator:** ECPR versus standard of care
- **Primary outcome/measures:** ED arrivals less than 30 minutes after cardiac arrest; ECPR initiations less than 30 minutes after arrest
- **Data collection period:** May 2017 to March 2020

- **Type of ECRW:** EFIC
- **Study findings:** Fifteen subjects from 151 OHCA 911 calls (10%) were enrolled. Five of 12 subjects who were randomized to expedited transport had an ED arrival time of less than or equal to 30 minutes (overall mean 32.5 minutes [SD 7.1]), and 5 were eligible for and treated with ECPR. Three of 5 ECPR-treated subjects had blood flow initiated in less than or equal to 30 minutes of arrival (overall mean 32.4 minutes [SD 10.9]). No subject in either group survived with a good neurologic outcome. The EROCA trial did not meet predefined feasibility outcomes for selecting OHCA patients for expedited transport and ECPR initiation in the ED, and treatment did not demonstrate benefit. The FDA approved this study as a staged feasibility study to enroll 15 participants and submit their data prior to enrolling another group of 15 participants. After enrolling the first 15 participants, the PI chose not to pursue an amendment to enroll additional participants due to slow accrual and research restrictions related to COVID-19.
- **ClinicalTrials.gov identifier:** NCT03065647
- **Reference:**
  - Hsu CH, Meurer WJ, Domeier R, et al. Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest (EROCA): results of a randomized feasibility trial of expedited out-of-hospital transport. *Ann Emerg Med*. 2021 Jul;78(1):92-101.

ESETT (2015)

- **Title:** Established Status Epilepticus Treatment Trial
- **Study PI:** Jaideep Kapur, MD (University of Virginia)
- **Emergency care network:** Neurological Emergencies Treatment Trials (NETT)
- **Study description:** Benzodiazepine-refractory, or established, status epilepticus is thought to have a similar pathophysiology among patients, but differences in underlying etiology and pharmacodynamics may differentially affect the response to therapy. The Established Status Epilepticus Treatment Trial (ESETT) compared the efficacy and safety of levetiracetam, fosphenytoin, and valproate in established status epilepticus. The posterior probabilities that each drug was the most or least effective were calculated. Safety outcomes included life-threatening hypotension or cardiac arrhythmia, endotracheal intubation, seizure recurrence, and death.
- **Study population:** Patients with status epilepticus
- **Actual enrollment:** 478 subjects
- **Intervention/comparator:** Levetiracetam versus fosphenytoin versus valproate
- **Primary outcome/measures:** The absence of clinically evident seizures and improvement in the level of consciousness by 60 minutes after the start of drug infusion, without additional anticonvulsant medication
- **Data collection period:** October 2015 to May 2019
- **Type of ECRW:** EFIC

- **Study findings:** The study enrolled 478 patients; 462 unique patients were included in the analysis: 225 children (aged <18 years), 186 adults (18-65 years), and 51 older adults (>65 years). One hundred seventy-five (38%) patients were randomly assigned to levetiracetam, 142 (31%) to fosphenytoin, and 145 (31%) to valproate. The primary efficacy outcome was met in those treated with levetiracetam for 52% of children (95% credible interval, 41-62), 44% of adults (33-55), and 37% of older adults (19-59); with fosphenytoin for 49% of children (38-61), 46% of adults (34-59), and 35% of older adults (17-59); and with valproate for 52% of children (41-63), 46% of adults (34-58), and 47% of older adults (25-70). No differences were detected in efficacy or primary safety outcome by drug within each age group. Except for endotracheal intubation in children, secondary safety outcomes did not significantly differ by drug within each age group. Children, adults, and older adults with established status epilepticus respond similarly to levetiracetam, fosphenytoin, and valproate, with successful treatment in approximately half of patients.
- **ClinicalTrials.gov identifier:** NCT01960075
- **References:**
  - Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet*. 2020 Apr 11;395(10231):1217-1224.
  - Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019 Nov 28;381:2103-2113.

INTREPID (2016)

- **Title:** INvestigating TREatments for the Prevention of Secondary Injury and Disability Following Traumatic Brain Injury (INTREPID) or a Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of NNZ-2566 in Patients With Traumatic Brain Injury (TBI) Conducted Under Exception From Informed Consent
- **Study PI:** Ross R. Bullock, MD, PhD (University of Miami)
- **Emergency care network:** N/A
- **Study description:** The purpose of this study was to determine whether the drug NNZ-2566 (ie, trofinetide, Neuren Pharmaceuticals), an analogue of the neuropeptide IGF-1, is safe and effective in treating TBI.
- **Study population:** Adults with traumatic brain injury
- **Actual enrollment:** 261 subjects
- **Intervention/comparator:** An intravenous bolus infusion of NNZ-2566 20 mg/kg over 10 minutes followed by a continuous intravenous infusion of 6 mg/kg/h (n = 133) of NNZ-2566 for a total of 72 consecutive hours versus placebo (saline)
- **Primary outcome/measures:** Compared to placebo, reduced incidence of adverse events and serious adverse events (time frame: adverse events to

discharge or day 30 post randomization, whichever occurs first, and serious adverse events through 3 months [defined as 12-14 weeks] post randomization)

- **Data collection period:** February 2013 to January 2016
- **Type of ECRW:** EFIC
- **Study findings:** NNZ-2566 has a favorable safety profile. The baseline severity, as measured by the Composite Baseline Severity Score (CBSS), was strongly associated with all primary outcomes. A significant imbalance in baseline severity between active and placebo treatment was found in all cohorts. No evidence of dose response or a consistent pattern of improvement in the GOS-E or Mayo-Portland Adaptability Inventory – Version 4 (MPAI-4) was detected in the drug or placebo groups. The overall mortality rate was lower than those reported in comparable TBI clinical trials, but the difference in mortality rates between the drug and placebo groups was not significant. The treatment group had evidence of improvement in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for patients with a CBSS above the median. Compared to prior studies, a higher drug clearance rate (+24%) in this study's population resulted in a lower-than-predicted drug exposure (–20%). There was also evidence of positive pharmacokinetic/pharmacodynamic associations.
- **ClinicalTrials.gov identifier:** NCT01366820
- **Reference:**
  - Intrepid: investigating treatments for the prevention of secondary injury and disability following traumatic brain injury: a randomized, double-blind, placebo-controlled, dose-escalation study of NNZ-2566 in patients with traumatic brain injury. Presented at: 6th Annual TBI Conference; May 12, 2016; Washington, DC. Accessed April 13, 2022. https://www.neurenpharma.com/pdf/8b017201-d48d-4811-8b32-dfda2fd3d9bc/Presentation-at-6th-Annual-TBI-Conference-Washington-DC.pdf

OSIRIS (2017)

- **Title:** Inhaled Nitric Oxide After Cardiac Arrest (iNOOHCA)
- **Study PI:** Cameron Dezfulian, MD (University of Pittsburgh)
- **Emergency care network:** N/A
- **Study description:** This study was a phase II, double-blind, placebo-controlled, randomized (1:1) clinical trial of inhaled nitric oxide 20 ppm administered over 12 hours within 4 hours of return of spontaneous circulation (ROSC) from OHCA. Planned enrollment was 180 subjects over 48 months at University of Pittsburgh Medical Center hospitals, with randomization stratified in blocks of 8. Patients were recruited using EFIC approaches to facilitate early enrollment and treatment. The study had a prespecified safety analysis at the midpoint (after 1 year or 60 patients, whichever occurred first). Subjects were screened by members of the University of Pittsburgh post–cardiac arrest service, who were also study coinvestigators, and by the research coordinators. A member of the study's team notified surrogates as soon as possible of subjects' inclusion under EFIC (subjects themselves were not notified because they were comatose after OHCA).

- **Study population:** OHCA with ROSC
- **Actual enrollment:** 57 subjects
- **Intervention/comparator:** Inhaled nitric oxide versus placebo
- **Primary outcome/measures:** Death or significant neurologic or cardiac impairment (time frame: hospital discharge [+/– 3 days])
- **Data collection period:** August 2017 to June 2020
- **Type of ECRW:** EFIC
- **Study findings:** The study was terminated in June 2020 because enrollment was slow and the PI moved to a new institution. The study enrolled only 57 of the planned 180 subjects.
- **ClinicalTrials.gov identifier:** NCT03079102
- **References:**
  - Magliocca A, Fries M. Inhaled gases as novel neuroprotective therapies in the postcardiac arrest period. *Curr Opin Crit Care*. 2021 Jun 1;27(3):255-260.
  - Inhaled Nitric Oxide After Out-of-Hospital Cardiac Arrest (iNOOHCA). ClinicalTrials.gov identifier: NCT03079102. Updated April 25, 2022. Accessed February 24, 2024. https://www.clinicaltrials.gov/study/NCT03079102

PAD (1999)

- **Title:** Public Access Defibrillation (PAD) Trial
- **Study PI:** Joseph P. Ornato, MD (Virginia Commonwealth University)
- **Emergency care network:** Public Access Defibrillation Clinical Trial Center
- **Study description:** This study intended to measure survival to hospital discharge of patients with OHCA who received public access defibrillation (ie, trained nonmedical responders using automated external defibrillators [AEDs]) and those who received the traditional optimum community standard of care (ie, rescuers trained to recognize a cardiac emergency, call 911, and initiate CPR).
- **Study population:** OHCA in community units (eg, apartment or office buildings, gated communities, sports venues, senior centers, shopping malls)
- **Actual enrollment:** 993 community units that responded to 3,413 events
- **Intervention/comparator:** Public access defibrillation versus standard of care
- **Primary outcome/measures:** Number of survivors of definite OHCA in each community unit
- **Data collection period:** September 1999 to February 2004
- **Type of ECRW:** EFIC
- **Study findings:** More than 19,000 volunteer responders from 993 community units in 24 North American regions participated. The two study groups had similar unit and volunteer characteristics. Patients with treated OHCA in the two groups were similar in age (mean, 69.8 years), proportion of men (67%), rate of cardiac arrest in a public location (70%), and rate of witnessed cardiac

arrest (72%). No inappropriate shocks were delivered. More patients survived to hospital discharge in the units that were assigned to volunteers trained in CPR and AEDs (30 survivors among 128 cardiac arrests) than in the units that were assigned to volunteers trained only in CPR (15 among 107; *P* = .03; relative risk, 2.0; 95% CI, 1.07-3.77). Only two patients survived in residential complexes. Functional status at hospital discharge did not differ between the two groups. Training and equipping volunteers to attempt early defibrillation within a structured response system can increase the number of survivors to hospital discharge after OHCA in public locations. Trained laypersons can use AEDs safely and effectively.

- **ClinicalTrials.gov identifier:** NCT00004560
- **References:**
  - Hallstrom AP, Ornato JP, Weisfeldt M, et al; Public Access Defibrillation Trial Investigators. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med*. 2004 Aug 12;351(7):637-646.
  - Ornato JP, McBurnie MA, Nichol G, et al; PAD Trial Investigators. The Public Access Defibrillation (PAD) trial: study design and rationale. *Resuscitation*. 2003 Feb;56(2):135-147.
  - Mosesso VN Jr, Brown LH, Greene HL, et al; PAD Trial Investigators. Conducting research using the emergency exception from informed consent: the Public Access Defibrillation (PAD) Trial experience. *Resuscitation*. 2004 Apr;61(1):29-36.
  - Nichol G, Wells GA, Kuntz K, et al. Methodological design for economic evaluation in Public Access Defibrillation (PAD) trial. *Am Heart J*. 2005 Aug;150(2):202-208.
  - Richardson LD, Gunnels MD, Groh WJ, et al; PAD Trial Investigators. Implementation of community-based public access defibrillation in the PAD trial. *Acad Emerg Med*. 2005 Aug;12(8):688-697.

PREHOSPITAL AGITATION (2014)

- **Title:** Ketamine vs Haloperidol for Severe Agitation Outside the Hospital
- **Study PI:** James R. Miner, MD (Hennepin County Medical Center)
- **Emergency care network:** N/A
- **Study description:** This study was intended to determine if one of two drugs, ketamine or haloperidol, is better for treating agitation. Agitation is a state of extreme emotional disturbance in which patients can become physically aggressive or violent, endangering themselves and those who care for them. Chemical substances or severe mental illness is often involved in dangerous levels of agitation. The investigators were specifically interested in studying agitation that is treated by paramedics in the prehospital setting. Their hypothesis was that ketamine is superior to haloperidol in treating agitation in the prehospital environment.
- **Study population:** Severely agitated patients treated in the prehospital environment
- **Actual enrollment:** 146 subjects
- **Intervention/comparator:** Intramuscular ketamine (5 mg/kg) versus haloperidol (10 mg)

- **Primary outcome/measures:** Time from drug injection to adequate sedation, defined as a score of 0 or less on the Altered Mental Status Scale (AMSS) (time frame: 2 hours)
- **Data collection period:** October 2014 to July 2015
- **Type of ECRW:** EFIC
- **Study findings:** One hundred forty-six subjects were enrolled: 64 received ketamine, and 82 received haloperidol. Median time to adequate sedation for the ketamine group was 5 minutes (range 0.4-23 min) versus 17 minutes (range 2-84 min) for the haloperidol group (difference 12 min; 95% CI, 9-15). Complications occurred in 49% (27/55) of patients who received ketamine vs 5% (4/82) in the haloperidol group. Complications specific to the ketamine group included hypersalivation (21/56, 38%), emergence reaction (5/52, 10%), vomiting (5/57, 9%), and laryngospasm (3/55, 5%). Intubation was also significantly higher in the ketamine group: 39% of patients receiving ketamine were intubated versus 4% of patients receiving haloperidol. Ketamine is superior to haloperidol in terms of faster adequate sedation for severe prehospital acute undifferentiated agitation but is associated with more complications and a higher intubation rate.
- **ClinicalTrials.gov identifier:** NCT02103881
- **Reference:**
  - Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol (Phila)*. 2016 Aug;54(7):556-562.

PROPPR (2012)

- **Title:** Pragmatic, Randomized Optimal Platelet and Plasma Ratios
- **Study PI:** Gerald van Belle, MD (University of Washington)
- **Emergency care network:** Resuscitation Outcomes Consortium (ROC)
- **Study description:** Forty percent of in-hospital deaths in injured patients involve massive truncal hemorrhage. These deaths may be prevented with rapid hemorrhage control and improved resuscitation techniques. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial was designed to determine if a mortality difference exists between subjects who received different ratios of FDA-approved blood products. Multiple observational studies have reported that blood product component ratios (ie, plasma:platelets:red blood cells) that approach the 1:1:1 ratio of fresh whole blood are associated with significant decreases in truncal hemorrhagic death and in the overall 24-hour and 30-day mortality of injured patients. The rationale for the 1:1:1 ratio is that the closer a transfusion regimen approximates whole blood, the faster hemostasis will be achieved, with minimum risk of coagulopathy. The current Department of Defense guideline specifies the use of the 1:1:1 ratio, and it is followed for almost all combat casualties. However, in other observational studies, leading centers have reported good outcomes across a range of different

blood product ratios. For example, a 1:2 plasma:red blood cell ratio is used with little guidance on platelets. The proposed randomized trial is intended to resolve debate and uncertainty on optimum blood product ratios.

- **Study population:** Subjects predicted to receive massive transfusion (defined as receiving 10 units or more of red blood cells within the first 24 hours)
- **Actual enrollment:** 680 subjects
- **Intervention/comparator:** 1:1:1 ratio (plasma:platelets:red blood cells) of massive transfusion product administration versus 1:1:2 ratio
- **Primary outcome/measures:** 24-hour and 30-day mortality
- **Data collection period:** August 2012 to December 2013
- **Type of ECRW:** EFIC
- **Study findings:** Six hundred eighty patients were randomized between August 2012 and December 2013. The overall median time from admission to randomization was 26 minutes. PROPPR enrolled at higher-than-expected rates with fewer-than-expected protocol deviations and was the largest randomized study to enroll severely bleeding patients. The study showed that rapidly enrolling and successfully providing randomized blood products to severely injured patients in an EFIC study is feasible. PROPPR was able to achieve these goals by utilizing a collaborative structure and developing successful procedures and design elements that can be part of future trauma studies.
- **ClinicalTrials.gov identifier:** NCT01545232
- **References:**
  - Henry B, Perez A, Trpcic S, Rizoli S, Nascimento B. Protecting study participants in emergency research: is community consultation before trial commencement enough? *Trauma Surg Acute Care Open*. 2017 Jul 12;2(1):e000084.
  - Holcomb JB, Tilley BC, Baraniuk S, et al; PROPPR Study Group. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015 Feb 3;313(5):471-482.
  - Baraniuk S, Tilley BC, del Junco DJ, et al. Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial: design, rationale and implementation. *Injury*. 2014 Sep;45(9):1287-1295.

PROTECT III (2011)

- **Title:** Progesterone for the Treatment of Traumatic Brain Injury
- **Study PI:** David W. Wright, MD (Medical University of South Carolina)
- **Emergency care network:** Neurological Emergencies Treatment Trials (NETT)
- **Study description:** The ProTECT study was intended to determine if intravenous progesterone, when started within 4 hours of injury and given for a total of 96 hours, is more effective than placebo for treating victims of moderate to severe acute TBI.
- **Study population:** Subjects with moderate to severe acute TBI

- **Actual enrollment:** 882 subjects
- **Intervention/comparator:** Intravenous progesterone started within 4 hours of injury and given for a total of 96 hours versus placebo
- **Primary outcome/measures:** Favorable outcome as determined by the GOS-E (time frame: 6 months post randomization)
- **Data collection period:** March 2010 to July 2014
- **Type of ECRW:** EFIC
- **Study findings:** Eight hundred eighty-two of the planned 1,140 patients underwent randomization before the trial was stopped for futility of the primary outcome. The study groups had similar baseline characteristics; the median age of the patients was 35 years, 73.7% were men, 15.2% were black, and the mean Injury Severity Score was 24.4 (on a scale from 0 to 75, with higher scores indicating greater severity). The most frequent mechanism of injury was a motor vehicle accident. No significant differences were observed between the progesterone group and placebo group in the proportion of patients with a favorable outcome (relative benefit of progesterone, 0.95; 95% CI, 0.85-1.06; *P* = .35). Phlebitis or thrombophlebitis was more frequent in the progesterone group than in the placebo group (relative risk, 3.03; CI, 1.96-4.66). There were no significant differences in the other prespecified safety outcomes. This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI.
- **ClinicalTrials.gov identifier:** NCT00822900
- **Reference:**
  - Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med*. 2014 Dec 25;371(26):2457-2466.

RAMPART (2011)

- **Title:** Intramuscular Versus Intravenous Therapy for Prehospital Status Epilepticus
- **Study PI:** Robert Silbergleit, MD (University of Michigan)
- **Emergency care network:** Neurological Emergencies Treatment Trials (NETT)
- **Study description:** This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus who were treated by paramedics.
- **Study population:** Children and adults in status epilepticus who were treated by paramedics
- **Actual enrollment:** 1,023 subjects
- **Intervention/comparator:** Intramuscular injection of midazolam (5-10 mg) versus intravenous injection of lorazepam (2-4 mg)
- **Primary outcome/measures:** Termination of seizures before arrival to the ED without the need for rescue therapy provided by paramedics
- **Data collection period:** June 2009 to January 2011

- **Type of ECRW:** EFIC
- **Study findings:** At the time of arrival to the ED, 329 of 448 subjects (73.4%) in the intramuscular midazolam group and 282 of 445 subjects (63.4%) in the intravenous lorazepam group did not require rescue therapy for their seizures (absolute difference, 10 percentage points; 95% CI, 4.0-16.1; $P < .001$ for both noninferiority and superiority). The two treatment groups were similar with their need for endotracheal intubation (14.1% of subjects with intramuscular midazolam and 14.4% with intravenous lorazepam) and their seizure recurrence (11.4% and 10.6%, respectively). Among subjects whose seizures ceased before arrival to the ED, the median times to active treatment were 1.2 minutes in the intramuscular midazolam group and 4.8 minutes in the intravenous lorazepam group; corresponding median times from active treatment to cessation of convulsions were 3.3 minutes and 1.6 minutes. Rates of adverse events were similar in the two groups. For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation.
- **ClinicalTrials.gov identifier:** NCT00809146
- **References:**
  - Silbergleit R, Lowenstein D, Durkalski V, Conwit R; NETT Investigators. Lessons from the RAMPART study — and which is the best route of administration of benzodiazepines in status epilepticus. *Epilepsia*. 2013 Sep;54(suppl 6):74-77.
  - Silbergleit R, Biros MH, Harney D, Dickert N, Baren J; NETT Investigators. Implementation of the exception from informed consent regulations in a large multicenter emergency clinical trials network: the RAMPART experience. *Acad Emerg Med*. 2012 Apr;19(4):448-454.
  - Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012 Feb 16;366(7):591-600.
  - Silbergleit R, Lowenstein D, Durkalski V, Conwit R; Neurological Emergency Treatment Trials (NETT) Investigators. RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial): a double-blind randomized clinical trial of the efficacy of intramuscular midazolam versus intravenous lorazepam in the prehospital treatment of status epilepticus by paramedics. *Epilepsia*. 2011 Oct;52(suppl 8):45-47.

REBOA (2019)

- **Title:** The Use of REBOA as an Adjunct to ACLS in Nontraumatic Cardiac Arrest: A Feasibility Trial
- **Study PI:** James M. Daley, MD (Yale University)
- **Emergency care network:** N/A
- **Study description:** REBOA is an endovascular technique that has become more widely used for severe trauma. It is a procedure in which the Seldinger technique is used to advance a balloon-tipped catheter into the femoral artery and then the aorta. The balloon is then inflated to fully occlude blood flow to the distal aorta. Study investigators hypothesized that this technique may be beneficial for medical cardiac arrest. By occluding the aorta and preventing distal blood flow during CPR, physicians may maximize perfusion to the heart and brain and promote ROSC and neurologic recovery.

Investigators conducted an IDE-approved early feasibility study using the ER-REBOA catheter in five patients who were in cardiac arrest of medical etiology (ie, nontraumatic etiology). Primary outcomes were feasibility and safety. Secondary outcomes were procedural performance, hemodynamic response to aortic occlusion, and patient-centered outcome variables.

- **Study population:** Subjects with witnessed cardiac arrest of suspected medical etiology (nontraumatic) and CPR initiation within an estimated 6 minutes of collapse
- **Actual enrollment:** 5 subjects
- **Intervention/comparator:** REBOA (single group assignment) without comparator
- **Primary outcome/measures:** Feasibility of aortic occlusion (time frame: the time expected for the procedure, typically between 10 to 15 minutes) and the safety of the procedure (time frame: time of procedure to 90 days post discharge)
- **Data collection period:** January 2020 to April 2021
- **Type of ECRW:** EFIC
- **Study findings:** Results of this trial are not yet available
- **ClinicalTrials.gov identifier:** NCT03703453
- **References:**
  - Daley J, Cannon K, Buckley R, et al. A research protocol and case report of emergency department endovascular aortic occlusion (REBOA) in non-traumatic cardiac arrest. *J Endovasc Resusc Trauma Manag*. 2020 Nov;4(2):88-93.
  - Daley J, Morrison JJ, Sather J, Hile L. The role of resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct to ACLS in non-traumatic cardiac arrest. *Am J Emerg Med*. 2017 May;35(5):731-736.

ROC-CA (2011)

- **Title:** A Trial of an Impedance Threshold Device in Out-of-Hospital Cardiac Arrest
- **Study PI:** Myron L. Weisfeldt, MD (Johns Hopkins University)
- **Emergency care network:** Resuscitation Outcomes Consortium (ROC)
- **Study description:** This study compared the use of an active impedance threshold device (ITD) with a sham ITD in patients with OHCA who underwent standard CPR at 10 sites in the United States and Canada. Patients, investigators, study coordinators, and all care clinicians were unaware of the treatment assignments. The primary outcome was survival to hospital discharge with satisfactory function (ie, a score of ≤3 on the Modified Rankin Scale, which ranges from 0 to 6; higher scores indicate greater disability).
- **Study population:** Patients with OHCA
- **Actual enrollment:** 11,738 subjects
- **Intervention/comparator:** Active ITD versus sham ITD
- **Primary outcome/measures:** Survival to hospital discharge with satisfactory function (Modified Rankin Scale ≤3; time frame: hospital discharge or death prior to discharge)

- **Data collection period:** June 2007 to July 2010
- **Type of ECRW:** EFIC
- **Study findings:** Of the 8,718 patients included in the analysis, 4,345 were randomly assigned to treatment with a sham ITD and 4,373 to treatment with an active device. A total of 260 patients (6.0%) in the sham-ITD group and 254 patients (5.8%) in the active-ITD group met the primary outcome (risk difference adjusted for sequential monitoring, –0.1 percentage points; 95% CI, −1.1-0.8; *P* = .71). No significant differences were observed in secondary outcomes, including rates of ROSC on arrival at the ED, survival to hospital admission, and survival to hospital discharge. Use of the active ITD did not significantly improve survival with satisfactory function among patients with OHCA who received standard CPR.
- **ClinicalTrials.gov identifier:** NCT00394706
- **References:**
  - Aufderheide T, Nichol G, Rea T, et al. A trial of impedance threshold device in out-of-hospital cardiac arrest. *N Engl J Med*. 2011:365:798-806.
  - Stiell IG, Nichol G, Leroux BG, et al; ROC Investigators. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med*. 2011 Sep 1;365(9):787-797.

ROC-TXA FOR TBI (2020)

- **Title:** Effect of Out-of-Hospital Tranexamic Acid Versus Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury
- **Study PI:** Susanne May, MD (University of Washington)
- **Emergency care network:** Resuscitation Outcomes Consortium (ROC)
- **Study description:** This study was a multicenter, double-blind, randomized controlled trial that included subjects with moderate to severe TBI defined as a Glasgow Coma Scale (GCS) score of less than or equal to 12 due to either blunt or penetrating trauma. The study included three treatment arms: (1) a 1-gram prehospital bolus of TXA followed by a 1-gram infusion over 8 hours, (2) a 1-gram prehospital bolus of TXA, or (3) a placebo.
- **Study population:** Subjects 15 years and older with a TBI and prehospital GCS score less than or equal to 12 prior to randomization
- **Actual enrollment:** 967 subjects
- **Intervention/comparator:** TXA 1-gram prehospital bolus followed by 1-gram maintenance infusion versus 2-gram prehospital bolus versus placebo
- **Primary outcome/measures:** Dichotomized GOS-E at 6 months (time frame: 6 months post injury)
- **Data collection period:** May 2015 to November 2017
- **Type of ECRW:** EFIC

- **Study findings:** Treatment with TXA as an out-of-hospital bolus with or without in-hospital infusion led to a favorable neurologic outcome (defined as a GOS-E score >4) in 65% of patients compared to 62% of patients in the placebo group that received an out-of-hospital bolus and in-hospital infusion. The difference between the two groups was not statistically significant. In patients with suspected moderate or severe TBI, out-of-hospital administration of TXA compared with placebo did not significantly improve 6-month neurologic recovery.
- **ClinicalTrials.gov identifier:** NCT01990768
- **Reference:**
  - Rowell SE, Meier EN, McKnight B, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. *JAMA*. 2020;324(10):961-974.

APPENDIX 2

List of Other EFIC/WIC Studies

Study Title (NCT #)	PI (Institution)	Subjects (# enrolled)	Year(s)	Summary	EFIC/ WIC
Acute Coronary Syndrome (ACS)					
Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial (NCT00091507)[55]	D'Agostino and Udelson (Tufts)	Acute coronary syndrome (911)	2011-2012	Early administration of intravenous glucose-insulin-potassium vs placebo	EFIC
Agitation					
Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam (N/A)[56]	Martel (Hennepin)	Agitation (144)	2003-2004	Treatment of agitation with droperidol vs ziprasidone vs midazolam	EFIC

Study Title (NCT #)	PI (Institution)	Subjects (# enrolled)	Year(s)	Summary	EFIC/ WIC
Cardiac Arrest					
A preliminary study of CPR by circumferential compression of the chest with use of a pneumatic vest (VEST-CPR)[57]	Halperin (Johns Hopkins)	Cardiac arrest (34)	1992	Comparison of CPR with external compression vest vs manual compressions	N/A
Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest (N/A)[58]	Longstreth (University of Washington)	Cardiac arrest (300)	1998-2001	Magnesium, diazepam, or both given immediately after resuscitation	EFIC
Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial (NCT00120965)[59]	Hallstrom (University of Washington)	Cardiac arrest (1,071)	2004-2005	Automatic vs manual compressions in CPR	EFIC
ResQ Trial: Comparison of standard CPR alone vs active compression-decompression CPR plus an ITD on survival from out-of-hospital cardiac arrest (NCT00189423)[60]	Lurie (Advanced Circulatory Systems)	Cardiac arrest (1,653)	2005-2010	Standard CPR vs active compression-decompression CPR with an ITD	EFIC
Vasopressin rescue for pediatric intensive care unit cardiopulmonary arrest refractory to initial epinephrine dosing: a prospective feasibility pilot trial (NCT00628550)[61]	Raymond (UT Southwestern)	Cardiac arrest (10)	2008-2010	Vasopressin vs epinephrine given as second vasopressor	EFIC

Study Title (NCT #)	PI (Institution)	Subjects (# enrolled)	Year(s)	Summary	EFIC/ WIC
Trial of continuous or interrupted chest compressions during CPR (NCT01372748)[62]	Resuscitation Outcomes Consortium (ROC)	Cardiac arrest (23,711)	2011-2015	Continuous chest compressions with positive-pressure ventilation vs chest compressions interrupted for ventilations at 30:2 ratio	EFIC
Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial (NCT00391469)[63]	Kim (University of Washington)	Cardiac arrest (1,359)	2014	Standard care with or without prehospital cooling	WIC
Pragmatic airway resuscitation trial (PART) (NCT02419573)[64,65]	Wang (University of Alabama at Birmingham)	Cardiac arrest (3,004)	2015-2017	Initial endotracheal intubation vs laryngeal tube airway	EFIC
Hemorrhagic Shock					
Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality (N/A)[66]	Dutton (University of Maryland)	Hemorrhagic shock (110)	1996-1999	Fluid resuscitation with systolic blood pressure goal of 100 vs 70 mm Hg	EFIC
Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial (N/A)[46]	Sloan (University of Illinois at Chicago)	Hemorrhagic shock (112)	1997-1998	Diaspirin cross-linked hemoglobin vs saline during resuscitation	EFIC

Study Title (NCT #)	PI (Institution)	Subjects (# enrolled)	Year(s)	Summary	EFIC/ WIC
Human polymerized hemoglobin for the treatment of hemorrhagic shock when blood is unavailable: the USA multicenter trial (NCT00076648)[67]	Moore (University of Colorado)	Hemorrhagic shock (714)	2004-2006	Resuscitation with PolyHeme vs crystalloid fluid	EFIC
Low-dose vasopressin in traumatic shock (NCT00420407)[68]	Cohn (University of Texas at San Antonio)	Hemorrhagic shock (78)	2011	Normal saline vs normal saline plus vasopressin for resuscitation	EFIC
A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial (NCT01411852)[69]	Resuscitation Outcomes Consortium (ROC)	Hemorrhagic shock (192)	2012-2013	Controlled 250-mL bolus vs standard resuscitation (2,000 mL)	EFIC
Arginine vasopressin during the early resuscitation of traumatic shock (AVERTShock) (NCT01611935)[70]	Sims (University of Pennsylvania)	Hemorrhagic shock in traumatic injury that requires 6+ units of blood products during first 12 hours (101)	2013-2016	Vasopressin vs placebo	EFIC
Study of tranexamic acid during air and ground medical prehospital transport (STAAMP) trial (NCT02086500)[71]	Sperry (University of Pittsburgh)	Hemorrhagic shock (903)	2015-2019	Prehospital infusion of TXA vs placebo	EFIC

Study Title (NCT #)	PI (Institution)	Subjects (# enrolled)	Year(s)	Summary	EFIC/ WIC
Respiratory Failure					
Prehospital CPAP vs usual care for acute respiratory failure (NCT00405314)[72]	Thompson (University of British Columbia)	Respiratory failure (71)	2002-2006	Continuous positive airway pressure ventilation mask vs usual care	EFIC
Ketamine vs etomidate for sedation of emergency department patients during rapid sequence intubation (NCT01823328)[73]	Driver (Hennepin)	Respiratory failure (143)	2013-2015	Ketamine vs etomidate for RSI	EFIC
Status Epilepticus					
Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial (NCT00621478)[74]	Chamberlain (Canadian Children's National Research Institute)	Status epilepticus (273)	2008-2012	Lorazepam vs diazepam for seizure termination in pediatric subjects	EFIC
Stroke					
Mechanical embolus removal in cerebral ischemia (MERCI™) (Multi-MERCI) (NCT00318071)[75]	Smith (University of California, San Francisco)	Stroke (164)	2004-2006	Use of the MERCI L5 Retriever device (no comparator) for large vessel occlusion	EFIC
Mechanical retrieval and recanalization of stroke clots using embolectomy (MR RESCUE) (NCT00389467)[76]	Kidwell (Georgetown), Jahan (University of California, Los Angeles)	Stroke (127)	2004-2012	Mechanical embolectomy with the MERCI Retriever or Penumbra System plus standard medical care vs standard medical care alone for large vessel occlusion	EFIC

Study Title (NCT #)	PI (Institution)	Subjects (# enrolled)	Year(s)	Summary	EFIC/ WIC
Field administration of stroke therapy — magnesium (FAST-MAG) trial (NCT00059332)[77]	Saver (UCLA)	Stroke (1,700)	2005-2013	Intravenous magnesium sulfate vs placebo	EFIC
TBI					
Lack of effect of induction of hypothermia after acute brain injury (N/A)[78]	Clifton (University of Texas Houston Health Science Center)	TBI (392)	1994-1998	Normothermia vs induced hypothermia	WIC
Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial (NCT00178711)[79]	Clifton (University of Texas Houston Health Science Center)	TBI (232)	2005-2009	Normothermia vs induced hypothermia	WIC
Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial (NCT00316004)[80]	Bulger (University of Washington)	TBI (1,331)	2006-2009	Prehospital hypertonic saline/dextran vs hypertonic saline vs normal saline	EFIC
Hyperbaric oxygen brain injury treatment (HOBIT) trial: a multicenter, randomized, prospective phase II adaptive clinical trial evaluating the most effective hyperbaric oxygen treatment paradigm for severe traumatic brain injury (NCT02407028z)[53]	Rockswold (Hennepin), Barsan (University of Michigan), Gajewski (University of Kansas), Korley (University of Michigan), SIREN Network	TBI (recruiting)	2018-present	Hyperbaric oxygen (at various atmospheres absolute) with or without normobaric hyperoxia vs usual care	EFIC

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