Good afternoon and welcome to this Webinar. My name is Jeremy Brown, and I work in the Office of Emergency Care Research.

Today we will be discussing issues relating to three Funding Opportunity Announcements:
1. Clinical Coordinating Center - CCC
2. Data Coordinating Center - DCC
3. Hubs & Spokes

We will discuss frequently asked questions that pertain to all three FOAs, and then open up the discussion to questions which may be sent in via email to Jeremy.brown@nih.gov.

Before going on I’d like to acknowledge the NIH SIREN team who are here to serve the research community.

From NINDS we have Drs. Robin Conwitt and Scott Janis, as well as Shanta Rajaram.
From NHLBI we have Drs. George Sopko and Debra Egan.

From NCATS we have Dr. Todd Wilson

And from the Dept. of Defense we have Lt. Col. Jennifer Hatzfeld and Savita Nigam

Now is an appropriate time to acknowledge and thank Dr. Pat Walicke, who served as the lead NINDS SIREN manager, and who has since left NIH. We would not be here today without her help.

BACKGROUND AND FUNDERS

SIREN, which is an acronym of *Strategies to Innovate EmERgENcy Care Clinical Trials* is an emergency care clinical research network supported by NINDS, which is the lead Institute at NIH, NHLBI, and NCATS. The Office of Emergency Care Research contributes personnel, and the Dept. of Defense will contribute funding to support trauma studies, about which we will have some more to say. The network will focus on three areas of emergency care research:

i) Neurological emergencies – with the exception of acute stroke, because acute stroke is under studied by NINDS’ Stoke Net

ii) Cardiopulmonary emergencies, with the exception of ARDS, because ARDS is studied by NHLBI’s PETAL network and

iii) Trauma.
It is important to remember that the goal of the SIREN network is to implement a total of at least four large, and by large we mean >1,000 patients, simple, pragmatic clinical trials in the emergency department and pre-hospital settings. The clinical trials will be awarded under separate funding announcements, using an R01 or similar mechanism.

**FUNDING FOR SIREN**

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<th>Component</th>
<th>Year 1</th>
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<td>The DCC</td>
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<td>Hubs &amp; Spokes</td>
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The direct funding amounts for each of the SIREN components are as follows:

- The CCC: Year 1: $680,000. Years 2-5: $415,000
- The DCC: Year 1: $430,000. Years 2-5: $250,000
- Hubs & Spokes: Year 1: $160,000. Years 2-5: $98,000

**ROLES AND RESPONSIBILITIES OF THE NETWORK**

**The CCC:**

The Clinical Coordinating Center is the administrative center of SIREN, with responsibilities for contracts with the hubs for performance of clinical trials, producing master trial agreements with the hubs, planning the budgets for
proposed clinical trials, disbursing payments to sites, and managing the SIREN website. The CCC also leads and manages the key SIREN governance committees:

- The SIREN Steering Committee (SSC),
- The SIREN Management Committee (SMC) and
- The SIREN Operations Committee (SOC)

The CCC will also establish and managing the central IRB. will oversee the SIREN central IRB, the master contract agreements, trial performance at the hub sites, recruitment plans, enrollment tracking and quality improvement.

One very important aspect of the CCC is its flexibility: Since each clinical trial will be unique, the CCC must be flexible in providing tailored solutions. Remember to demonstrate this in your applications. In addition, remember to demonstrate how your CCC can provide all of the other roles and responsibilities listed in the FOA. For example, be sure to show how you will

- Provide scientific leadership
- Promoting the visibility and awareness of SIREN and encourage the submission of clinical trial applications.
- Coordinate and support all the SIREN Steering Committee (SSC)
- Participate in the CTSA Network Executive Committee (NEC) activities
- Developing SIREN Standard Operating Procedures (SOPs)
- Provide instruction and training to clinical sites regarding Good Clinical Practice
- Provide a mechanism (like a call in center, a hot line, or web chat) for promptly addressing procedural queries from sites and prehospital providers, both for general SIREN processes and for processes specific to each clinical trial.
- Monitor human subjects' protection among participants enrolled at all SIREN clinical sites.
Applicants should remember to show how they will interact with their CTSAs, if present at their institution.

A good tip here is to carefully read all of the examples of the responsibilities of the CCC outlined in the FOA, and address them in the application.

The DCC:

The Data Coordinating Center, the DCC, will provide the scientific and organizational leadership to SIREN in all aspects of data management, data quality, statistical design and statistical analysis. Responsibilities of the DCC include management and support of the DSMB, and reporting to regulatory authorities such as the central IRB and the FDA. The DCC will also provide data summaries to external groups.

Like the Clinical Coordinating Center, the DCC needs to be innovative: it will need to support tools such as a modular Case Report Form (CRF), risk based monitoring and web based data capture. The DCC will also need to support work performed in the pre-hospital settings. Applicants are strongly encouraged to provide examples of how they used these tools in prior work.

Applicants are also encouraged to provide examples of how they will address the work of the DCC in these areas which include:
• **SIREN DSMB.** The DCC has the primary responsibility for the Data and Safety Monitoring Board (DSMB), including meeting facilitation in addition to preparation of reports and provision of interim analyses.

• **Regulatory and other External Reporting**

• **Quality Assurance**

Another important aspect of the DCC will be its role in the assessment phase of a proposed clinical trial. In this area, the DCC will be responsible for:

• Providing information and guidance to all potential investigators as they apply for NIH funding for a clinical trial to be performed in SIREN: (e.g., assess protocol synopsis and schedule of activities), particularly regarding statistical design;

• Performing a feasibility study of the proposed clinical trial, particularly in relation to any challenges in data management; and

• Developing the components of the clinical trial budget.

**The Hubs and Spokes**

![The SIREN Network](image)

The **Hubs** will provide scientific leadership and conduct clinical trials in the ED and pre-hospital settings. A Hub is envisioned as a regional academic medical center or tertiary care facility which will enroll patients itself along with providing clinical and organizational leadership to its network of 2-10 satellite sites which we call the Spokes. The Hub must be capable of providing physicians with expertise in
emergency medicine, neurology, cardiology, pulmonology, hematology, general surgery, trauma surgery, neurosurgery, cardiovascular surgery or other subspecialties, as required.

So what does a SIREN Hub look like?

Well, a typical SIREN Hub is envisioned as a medical center with full multidisciplinary 24/7 coverage. The Hub might be
- a level 1 trauma center or
- a major neurologic or cardiovascular academic referral medical center or
- a tertiary care facility.

Now, if a Hub is not itself a Level 1 trauma center, it must either be co-located with one or have a committed Spoke which is a Level 1 trauma center. Remember that a Hub must function as an exemplary clinical research site itself, while concurrently providing leadership, organizational oversight and research support to its Spokes.

The Hubs are expected to participate as a clinical site in every clinical trial performed in SIREN, whether the focus is neurological, heart/lung/blood or trauma. This means that each Hub must be able to:
- execute clinical trials in the ED setting;
- provide and coordinate the multiple medical and surgical specialties which may participate in the clinical trials, such as neurology, cardiology, pulmonary, neurosurgery, trauma surgery, cardiothoracic surgery, anesthesia and hospital intensivists;
• demonstrate a strong working relationship with pre-hospital providers (e.g., EMS);
• Propose and oversee a network of Spokes.

So what do these spoke sites look like?

The principal role of the Spokes is to provide access to a larger patient population for trial enrollment. Spokes also increase access to patients with a particular disease or injury, and very importantly, they provide access to patients from underserved communities.

For each clinical trial, the Hub would be expected to construct a network of 2-10 Spokes specifically tailored to the needs of that particular trial. Since the requirements of each clinical trial will be somewhat different, the identity and configuration of Spokes will be unique for each clinical trial. So it is important that the Hub has a relationship with a number of potential Spokes, and the ability to add Spokes as appropriate.

A number of applicants have asked about the detail that they need to provide regarding the spokes, and how many spokes they should detail, since the FOA calls for each Hub to have 2-10 spokes. We suggest that in the grant submission, the applicant Hub identifies five Spokes committed to participation in at least one clinical trial. However, since these five Spokes are unlikely to meet all the possible clinical trial requirements, the Hub should show what plans and mechanisms it has for recruiting and adding other Spokes, when needed.
Spoke hospitals may be academic emergency centers or community hospitals. They may be geographically related or geographically distant centers. The Spokes should be located in North America, and if a spoke is outside of the United States the applicant must explain how the Spoke will coordinate with the SIREN central IRB. Spokes may enroll and treat patients on-site or may identify patients to transfer to the Hub for enrollment. There is no ideal or preferred arrangement.

Active participation of pre-hospital providers is also critical to achieving the recruitment of at least 100 subjects per year into the planned four concurrent trials. Remember too that an EMS system may serve as one of the Spokes.

Hub applicants should also demonstrate that they can

- support recruitment of at least 100 subjects per year into each of the planned four concurrent trials;
- provide physicians with expertise in cardiology, neurology, pulmonary, hematology, trauma surgery, thoracic surgery, neurosurgery, intensive care and anesthesia.

Just as the CCC and DCC need to show flexibility, the Hubs and Spokes should also be flexible. In your application be sure to show how your Hub and Spokes can be resourceful and innovative depending on the clinical trial that is being carried out. You may want to note how you might conduct a study in which:

- children or adolescents are included
- you are enrolling patients with a relatively infrequent condition, such as spinal cord injury or acute pulmonary edema secondary to decompensated heart failure
- or in which management continues from the ED into subsequent care settings such as the intensive care unit, operating room or hospital floor, or
- in which outcome measures are collected well beyond the ED encounter, perhaps at 30 or 90 days or longer after the intervention;
- another example you may want to address is how your Hub and Spokes will enroll patients who need diagnostic or therapeutic interventions with aggressive time goals, like an MRI that may have nonstandard acquisitions or a patient who requires interventional cardiology.
- You are also advised to address your pre-hospital capabilities, and include any telemedicine or air transport that your Hub and spokes may provide.

A number of applicants have asked about the way that Hubs and Spokes will be paid.

SIREN will use Master Contracts and Payments to speed the implementation of clinical trials in SIREN. The CCC will negotiate and maintain a master contract with each Hub and each Spoke. Payments will be on a per-patient basis, according to clinical trial budgets and the master trial agreement, and will be directly distributed by the CCC to each Hub and Spoke. All the clinical centers, both Hubs and Spokes, are expected to work cooperatively with the CCC and to accept the master contract and payment system. You should consult with your institutions regarding the acceptability of these master contracts. Applicants who cannot accept master contracts and payments will need to justify this in the application, but be aware that this may make your application less competitive.
Another frequent question is about the role of the central IRB. The central IRB will be established and managed by the CCC which will create reliance agreements with each Hub and spoke. We expect that all the hubs and spokes will use the central IRB for standard clinical trials. We prefer that the Hubs and Spokes use the central IRB for EFIC studies, but we also understand that the fulfillment of community based requirements may require collaboration with local IRBs, and with local community liaisons or representatives.

Applicants are strongly encouraged to consult with their institution, potentially including their institutional IRB, regarding the acceptability of a central IRB for emergency care clinical trials that are not EFIC, and the acceptable approaches to EFIC trials under a central IRB. We would like to see a letter of support from your hospital’s Chair of the IRB and the CEO agreeing to use the CCC IRB.

Now the FOA states the following: “Applicants who do not accept the central IRB should provide an alternative which preserves efficient study initiation, along with a justification for this choice.” This means that technically, you may apply to be a Hub or Spoke without agreeing to use the central IRB. However, if you choose to do this please realize that your application will not be very competitive. Remember too that NIH will soon mandate the use of a central or single IRB of record as policy, and this will apply to new grants awarded after Jan 25th, 2017

**RECEIPT DATES AND LETTERS OF INTENT**

In order to help NIH, we encouraged, though we did not require, a letter of intent to submit an application in response to any of the three funding opportunity announcements.

The receipt date for the SIREN CCC, DCC and Hubs and Spokes was May 1st.
The receipt date for all the SIREN FOAs is June 1, 2016, by 5:00 PM local time of applicant organization.

We strongly encourage applicant organizations not to wait until the last minute to submit their applications. Computer errors and network connectivity issues do occur and NIH cannot accept late applications, so please plan accordingly.

Now that we’ve covered the basics of the CCC, DCC and Hub-Spoke sites, we will use the rest of this hour to address the questions that arise from the FOAs.

**Do I need to have been part of NETT or ROC to apply?**

No. We encourage applications from any qualified group, whether or not they were previously part of NETT or ROC. Experience with research in emergency medicine will be a component of the evaluation by independent peer review. Other criteria such as innovation, organizational skill, relationships with emergency medical services, and leadership will also be components of the review process. So please consider applying even if you have not been part of ROC or NETT.
What is the relationship between SIREN and DoD?

The Combat Casualty Care Research Program (CCCRP) in the US Army Medical Research and Materiel Command (USAMRMC) provided input and consultation for the SIREN. The Combat Casualty Care Research Program has expressed interest in performing clinical trials in SIREN, either as a co-funding agency or a sole funding agency. Such studies will be consistent with military priorities for trauma research. We hope that a separate funding opportunity for trauma studies will be announced by the DOD. These studies will be reviewed and supported by the DOD, but will use the SIREN network to carry them out.

What the role will NCATS and the CTSA Trial Innovation Centers serve in the SIREN network? Do I need to show how we will work with them?

NCATS will provide resources and operational expertise to the SIREN network from the NCATS or other NCATS programs. These resources include, but are not limited to, support for the single IRB and master contracts, such as standard operating procedures, document templates and software tracking and management programs. The NCATS Trial Innovation Centers, or TICs, should be operational in the summer of 2016.

What this means is that sites that have a CTSA should include a letter of support from PI of the CTSA. They may also wish to outline the CTSA resources if appropriate. How sites will actually work with their CTSAs will vary depending on the way that the CTSA works at the site. And remember that you need not be a site with a CTSA in order to respond to any of the SIREN FOAs.

Now some questions we've received about the Hub-and Spoke sites:

Can a site be included as a potential Spoke on grant submissions from more than one Hub?
The answer is yes. The Spokes identified in the Hub grant submission are meant to be representative and illustrative, not definitive. The FOA states that the actual Spoke sites will be selected based on the specific needs of each study, and therefore will be different for each clinical trial. So a single clinical center could be a Spoke in more than one Hub application. However, the same reviewers will be assessing the Hub applications and are likely to note the duplication in Spokes across applications.

**Can multiple institutions collaborate in forming one Hub?**

Yes, multiple academic or other institutions may collaborate in formation of a single Hub. There should be a rationale for doing so, such as geographic proximity or a history of collaboration. There can be only one lead, contact PI for the Hub. The other institutions may be led by a co-PI or a co-investigator as the applicants judge suitable.

**The FOA mentions that we need to include a description of up to 10 multicenter trials in which we participated - what if we are a new site with a deep interest in joining but no multicenter experience yet?**

The PD/PI for the Hub should be a clinical trials expert with a track record of successfully implementing clinical trials; experience with clinical trials in the ED and prehospital settings is desirable but not required. Other important experience includes clinical trials in neurology, cardiovascular, respiratory, hematology or trauma, whether or not in the emergency setting. While industry supported clinical trial experience is useful, it is very important that the team has experience in conducting NIH supported trials.

If you don’t yet have the expertise to serve as a Hub, there are other ways to participate in SIREN. For example, you could join another Hub application as a committed Spoke. Once SIREN is established, you could approach a Hub PI to join a clinical trial as a Spoke or a clinical trial PI to join as an ad hoc site. You can also
submit a grant application as a PI to perform a clinical trial in SIREN. SIREN will provide support and mentoring to new clinical trial PIs.

**Must the PI be an emergency physician? Could she be an intensivist, trauma surgeon, neurologist or cardiologist?**

The PD/PI for the Hub will be a clinical trials expert with a track record of successfully implementing clinical trials. Experience with clinical trials in the ED and prehospital settings is most relevant. However, experience in neurology, cardiovascular, emergency medicine, respiratory, hematology or trauma clinical trials, whether or not in the emergency setting, is also important. Past experience in emergency trial networks suggests that successful PIs are those who have a strong relationship with ED and EMS staff, which typically requires a spending considerable portion of their working day in the ED setting. So no, the PI need not be an ED physician.

**The FOA for the Hubs and Spokes mentions up to ten clinical hubs in one section (SIREN organization and Funds available) and up to 15 clinical hubs in another (Purpose). Which is it?**

The answer is ten.

**How will Hubs be funded after the first year?**

After the first year, there is a decrease in funding because Hubs are expected to obtain additional support from clinical trials.

The U24 grant mechanism we will use is a cooperative agreement with milestones. After the first year, a portion of the Hub’s annual budget will depend on the Hub’s performance against milestones and on quality metrics. It is anticipated that
enrollment will be one of the criteria; Hubs and Spokes together are expected to enroll a minimum of 100 subjects per year in SIREN clinical trials.

**What types of collaborations should Hubs demonstrate?**

Because some studies conducted in the network are likely to include the enrollment and randomized treatment of subjects by EMS providers, Hubs are expected to demonstrate effective collaboration with local Emergency Medical Services. As we mentioned, one of the Hubs may be a EMS system.

Hubs are expected to demonstrate effective collaborations among emergency care specialists, neurologists, cardiologists, pulmonologists, anesthesiologists, neurosurgeons, trauma surgeons, cardiothoracic surgeon and intensivists. Not all collaborators need not have substantial effort on the Hub’s grant, but all should demonstrate a willingness to assist, to allow their patients to participate, and to comply with protocol standardized patient care within the confines of what they feel to be appropriate clinical care. The applicant may wish to consider including Letters of Support from specialists.

Hubs are expected to demonstrate the ability to collaborate with sufficient Spokes to meet their enrollment targets and to provide access to diverse subject populations and environments. Hubs should include a minimum of 5 committed Spokes in the application. It is NOT required that every Spoke participate in every trial. For each trial, a number of Spokes will be selected based on the requirements of that particular clinical trial.

Here are three new questions we received:

**How will the process for selecting clinical trials for execution within the SIREN network work, including the details of when and how the CCC/DCC will be involved?**
The answer is that the selection and prioritization of meritorious clinical studies which have been awarded grants will be performed by the SIREN governance committees. Prioritization will take into account the utilization and availability of SIREN facilities and resources, as well as public health priorities. A flow chart of this process will be produced by the SIREN leadership team soon after the selection of the CCC and DCC.

Is there a target for the number of trial applications that will receive strategic support and budget estimates from the CCC/DCC?

Yes. We expect the SIREN network to manage at least four clinical trials at once, each with a target enrollment of at least 1,000 patients. But note that the peer review of submitted trials will continue independent of the SIREN network.

Are there target characteristics for the trials that NIH would like to fund?

We addressed this earlier, but it is worth reviewing this again. The question asks about NIH funding of trials, which will undertaken by the usual peer review method, and it is important to note that currently there are no special set aside funds for trials that which to use the SIREN network. But if we focus on the kinds of trials that SIREN will carry out, there are broadly three characteristics:

i) Neurological emergencies – with the exception of acute stroke, because acute stroke is under studied by NINDS’ StokeNet

ii) Cardiopulmonary emergencies, with the exception of ARDS because ARDS is studied by NHLBI’s PETAL network and

iii) Trauma.
Another way to think about the kinds of trials in SIREN is to consider the mission of NINDS and NHLBI as they pertain to patients in the pre-hospital arena, the emergency department and perhaps the OR or ICU. Additionally, trauma studies will be funded by DOD. These are likely to be studies for which the DOD has published a specific FOA. More details about the kinds of trials SRIEN and the DOD are looking to undertake will be outlined in future program announcements.

Is Year 1 of the Network grant intended for set up of the Network and initiation of committees, or would trial applications and awards also be anticipated during this time as well?

We understand and expect that in the first year of the grant cycle, sites will be heavily involved in setting up their infrastructure, and the DCC and CCC will be involved with developing protocols and standard operating procedures. However, we expect that the time to the initiation of the first study will be very, very soon after the SIREN network is established. The last thing that we want to see is a long delay between the funding of SIREN and the network initiating its first study. And finally, we should point out that there are already clinical studies that have been reviewed at NIH that wish to use the SIREN network. So all the SIREN awardees – the hubs and Spokes, the DCC and the CCC, should be ready to enroll patients as quickly as possible, and certainly sooner than the end of Year 1.

Here’s another set of questions

How will funding flow for investigators at community hospitals without an academic affiliation? We have a community hospital partner that staffs its ER with a private group, which is an LLC entity. Likewise for our EMS agencies– their director is a county employee.
The funds will flow from the CCC to the community hospitals just as they would flow to a Hub or spoke that had an academic affiliation. For EMS agencies funds would flow from the CCC to the agency itself, in line with federal and local laws.

**How much funding for research staff anticipated from actual trial grants?**

As we explained above, after Year 1, the SIREN infrastructure funding decreases slightly. This is because there will be additional funding from the budgets of the clinical studies. Precisely how much will flow from the study funds into the various components of SIREN will vary, dependent on the nature of the study being undertaken. The SIREN CCC will play a major role in helping the PI of a proposed clinical study to formulate a budget that is realistic and appropriate to get the clinical answer.

**Will funding from the CCC be in the form of a Grant from NIH or subcontract with the CCC institution?**

This will be a subcontract with the CCC.

**How will data monitoring of each individual spoke work- Will this be done by hubs or from CCC?**

There are two possibilities here: either the data flows from the Spokes directly to the DCC, or it flow to the Hub and from there is sent to the DCC. We suspect that the first model, with each Spoke directly submitting data to the DCC, is the one that will be used, but this is not a final ruling and the final model will be decided by the winning CCC and DCC.

**Is it permissible to include more than one hospital from the same health system together as a single “spoke”? In this particular case, these hospitals are community affiliates of the Hub’s health system.**
No. Each hospital should be a single on of the spokes in the Hub and Spoke model.

We are now at the close of the hour. Thank you for your questions and for your interest in SIREN. Let’s remember that SIREN is here to improve the treatment of patients with medical emergencies, and that the goal of all of us is to serve these patients in the very best way possible.

Please feel free to contact us with any remaining questions that you may have. Our contact information is on the FOAs and the announcement for this Webinar.

We wish each of you the very best of luck with your applications. Goodbye.