University of Minnesota NETT Hub

February 20, 2013

Minnesota Spoke Splash

Welcome!

The Minnesota Spoke Splash is the monthly newsletter of the Minnesota NETT Hub. If you know of others who should receive this newsletter directly, if you would like to change your email subscription, or if you have comments or suggestions, please submit them to Marinda Bland (blan0181@umn.edu).

Exception from Informed Consent in Emergency Research

Michelle Biros, MD, MS
Minnesota NETT Hub PI

SINCE the mid-1990s federal regulations have been available that allow enrollment of critically ill or injured patients into clinical trials using Exception from Informed Consent (EFIC). These regulations are applicable only under narrow clinical circumstances when prospective informed consent is not possible. Examples would include a patient–subject whose critical condition makes it impossible for the patient to give meaningful prospective consent, and it is also not feasible to obtain meaningful prospective consent from the patient's Legally Authorized Representative (LAR).

Innovative patient safeguards are built into the EFIC regulations, including pre-study community consultation and public notification. For the ProTECT trial, and RAMPART before it, the Minnesota Hub did extensive consultation with thousands of members of the general public and a more targeted group at risk of the diseases under study (status seizures). Our results suggest a general support of emergency research with and without consent, and an appreciation that the investigators were seeking the community' s opinion.

Continued on page 2

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Contents

Neurological Emergencies Treatment Trials

Continued from page 1

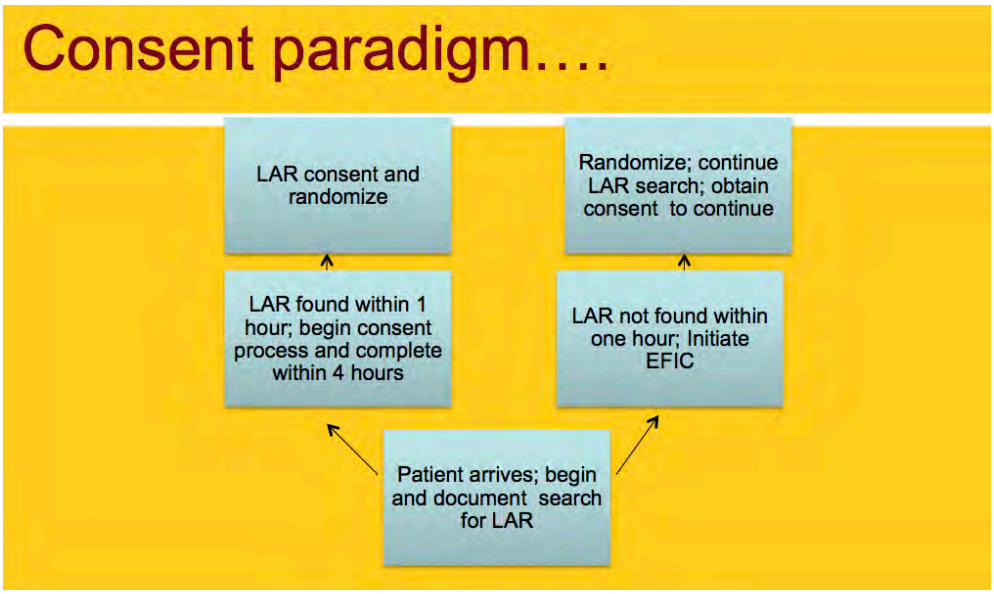
It is also necessary, when conducting EFIC trials, for investigators to develop an informed consent process in the event that prospective informed consent may somehow be possible for an individual case. In such severe critical circumstances as those for which EFIC was developed, any prospective informed consent, if possible at all, would likely come from the patient's LAR. In many EFIC circumstances, prospective consent is not feasible from the LAR because the LAR is not present within the intervention's time window, the subject (and hence the LAR) is not identifiable, or it is felt that the LAR is too distraught or otherwise incapacitated to render an informed prospective decision regarding the participation of the patient-subject in the trial.

Our current NETT study, ProTECT, is being conducted with EFIC. ProTECT is an interventional study involving patients with moderate to severe traumatic brain injury. Minnesota Spokes are HCMC, Regions and North; within the national NETT, there are about 60 level one trauma centers involved in ProTECT. Because patients eligible for this study are too injured to be able to provide meaningful prospective informed consent for research participation, and because the application of treatment has to be done in a narrow time frame that may preclude identification and contact with LARs, the trial is being conducted with EFIC. However, consenting protocols are available in the event that LARs can be identified and are present to provide informed consent.

The consenting mechanism of the trial is shown in Figure One. The investigators proposed a one-hour window after the patient's ED arrival to attempt to locate the LAR so that the patient might be eligible for enrollment with prospective consent. This time window was felt to be respectful of patient autonomy and consistent with the spirit of the regulations; this time frame would allow a good faith effort to attempt to locate and inform the LAR and proceed with prospective surrogate consent. If the LAR is located within the hour, enrollment proceeds with prospective consent, within the first 4 hours after injury. However, if no LAR is present within one hour of patient arrival, patients are entered into the study under EFIC. Consent for continued participation is then obtained from the patient or from the LAR when feasible. The aim is to obtain consent for continued participation in this EFIC study within 24 hours.

If the patient is unidentified, the hour after arrival should be used to attempt to identify the patient, and then the LAR. These attempts should be documented. However, NETT experience suggests that the patients' identity is likely to remain unknown beyond the one-hour window allotted to LAR arrival. An unidentified patient can be enrolled in ProTECT under EFIC.

Figure One: The ProTECT study protocol for surrogate consent or EFIC enrollment



The Human Subjects Coordinator of the NETT carefully tracks all enrollments into the trial and monitors for adherence to the study protocol. When ethical issues related to EFIC and ProTECT arise, the Human Subjects Working Group adjudicates and develops recommendations to prevent similar issues in future enrollments. The majority of violations of the EFIC regulations have to do with identification of the correct LAR when enrolling patients under the consent arm of the protocol. Some of these interesting challenges will be presented in a paper that is currently under development by the Human Subjects Working Group.

Documenting Consent

NETT monitors documentation of the consent process for all studies. The consent can be included in the patient record or a separate note to file, depending on your IRB's requirement.

What and who is the Legally Authorized Representative?

Michelle Biros, MD, MS, Minnesota NETT Hub PI

A Legally Authorized Representative (LAR) is an individual or legally appointed agent who, under applicable law, is authorized to consent on behalf of a prospective patient-subject for enrollment into research studies or procedures. Federal regulations require that investigators obtain and document informed consent from research subjects or their LAR prior to enrollment into a research trial, unless the IRB has waived the requirement for informed consent (i.e. in studies using waiver of consent or exception from informed consent).

When it comes to surrogates who can speak on behalf of research subjects, state law mandates the hierarchy of Legally Authorized Representatives (LARs). State law supersedes federal guidance on this, if such state law exists. The rationale for this is that state law provides extra protection for its own patient-subjects that may be unique to the state population, and that cannot be anticipated in federal guidance. However, federal regulations require that the designation of a state's hierarchy provides a "reasonable basis" for allowing that person to provide surrogate consent for a research subject.

This becomes relevant in NETT research studies if a subject is not able to speak on their own behalf and prospective consent from a surrogate (the LAR) is required. Examples are SHINE (Stroke Hyperglycemia Insulin Network Effort), which is ongoing, and ALIAS (High Dose Albumin Therapy for Neuro-protection in Ischemic Stroke), which was recently halted. In these studies, the patient-subjects are victims of ischemic stroke. While some stroke patients may have the cognitive ability to be decision-makers, the assessment of capacity in the immediate aftermath of a potentially life- threatening disease in other patients is difficult if not impossible. Most stroke patients are identified by the time they reach the ED and the enrollment window of these studies allows the LAR to be present before the intervention is started. Since the LAR is likely upset but not as distraught as those whose loved ones have sustained horrendous trauma, a meaningful consent process is felt to be possible. Therefore in SHINE and ALIAS, if the subject cannot speak on their own behalf, informed consent is obtained from the LAR.

When a number of family members and friends are present, the research team must determine who among these is the LAR who can provide consent for study enrollment of the patient-subject. This may be a tricky question, since often the calmest, most organized, most attentive, or most vocal family member is easiest to approach, but may not actually be the surrogate decision-maker. This person may be outspoken enough to sway the true LAR' s decision; it is up to the research team to be sure the true LAR's decision is informed and well thought out.

The University of Minnesota IRB has provided some guidance for the hierarchy of LARs. Their standard operating procedures state the following:

"Under Minnesota law, an incapacitated adult who has a court appointed guardian or conservator might not receive experimental treatment of any kind without a court order. Except for this requirement, Minnesota law does not address the issue of research participation by incapacitated adults. Based on legal advice and established practice, the research community follows the rules that apply to surrogate consent for treatment. Legally authorized representatives of incompetent or incapacitated adults are determined in the following order of priority: healthcare agent previously appointed by the individual through a health care power of attorney; spouse; parents; adult children; and finally, adult siblings. (Minnesota Statute 524.5-313, 144.291, 13.384)."

The operating procedures of the Mayo IRB also state that the "nearest" adult family member is the LAR when there is no court appointed LAR. They also state that if there is more than one person with the same kinship status, they should serve jointly to represent the patient-subject.

A final issue that has not yet been studied or considered in the regulations is the difference between the Legally Authorized Representative and ethical representative. Is the LAR always the best person to speak on behalf of the individual patient who is being considered for trial enrollment? Does the LAR really know what the patient might want in this circumstance or is there a better representative for that individual patient? These are fascinating questions and from the ethical perspective, if not necessarily the legal perspective, warrant study.

ProTECT

Progesterone for the **T**reatment of Traumatic Brain Injury

We continue to be successful in enrolling subjects in this study locally. A new challenge for the sponsor is verifying daily transgressions. They released new guidelines for completing Case Report Forms (CRF) in January 2013. We will learn more this week when we have a monitor visit for HCMC enrollments. In early March, the ProTECT team will send out 3 monitors for Regions as they go over data with a fine tooth comb to ensure that all sites are meeting the new CRF guidelines. We will share what we learn immediately with spokes. If you need help with resolving CRF issues in the meantime, please let us know how we can help.

ProTECT Minnesota Spokes Enrollment Summary

Spoke	Active	Enrollment
Hennepin County Medical Center	09/03/2010	14
Regions Hospital	11/04/2010	47
North Memorial Medical Center	09/02/2011	6

ProTECT National Hub Enrollment Ranking

Total Enrollment Nationwide:	**705**	**Enrollment Goal:**	**1140**
Rank	**Hub**	**Enrollment**	
1	Cincinnati	73	
2	Emory	72	
3	Arizona	70	
4	**Minnesota**	**67**	
4	Stanford	67	
5	Texas	66	

Expiring Regulatory Documents

PIs, investigators and coordinators need to complete trainings and maintain their certifications with studies. Expect us to notify you or your site coordinator about 30 days before the expiration date. We **promise** to send you more frequent and urgent notices as the expiration date approaches. When a certification is expired, you cannot perform that assessment for a subject without incurring an **unwanted and unnecessary** protocol violation. **Send completed certificates to: blan0181@umn.edu**

Spoke Codes

(For entry next to the Subject Number on each CRF)

Hennepin County Medical Center	1105
Regions Hospital	1106
North Memorial Medical Center	1107
Abbott Northwestern Hospital	1109
Ridgeview Medical Center	1110
UMMC - Fairview	1121
Fairview Southdale Hospital	1232
Two Twelve Medical Center	1432
United Hospital	1457
Essentia Health - Duluth	1493

POINT

Platelet-**O**riented **I**nhibition in **N**ew **T**IA
and minor ischemic stroke Trial

Most of our sites are currently or soon to be working under the Version 4 protocol. This version added one phone call at 30 days for the purpose of keeping tabs on the patient (but no data is collected) and added an optional Ancillary DNA/Biomarker study.

Study Coordinator Mindy Rumbolz, RN, has been working with us since mid-December and is now fully immersed in the details of this study including helping sites get their labs set up to process DNA/Biomarker samples. If sites have questions, Mindy is our local expert! She is also responsible for subject follow up for POINT at the sites where our Hub team enrolls patients.

At the ISC meeting earlier this month, Dr. Biros and Kathleen Miller had the opportunity to speak with Dr. Easton and Mary Farrant, UCSF Project Manager. They are very grateful for our Hub's performance in this study.

iPAD Update: If sites are interested in using iPAD videos to **supplement** the consent process at your site, please let us know. Currently the NETT plans to send them to the top performing hubs first to pilot test them. We have IRB approval to use the iPADs at HCMC, UMMC, Fairview Southdale, Ridgeview Medical Center and 212 in Chaska and Regions Hospital. Unfortunately, UCSF is still working through technical issues with the iPADs and no firm shipping date has been set. Once the pilot program is completed, they will be distributed to all active enrolling spokes.

To view the iPad video, go to the POINT Toolbox at nett.umich.edu.

POINT Minnesota Spoke Enrollment Summary

Spoke	Active	Enrollment
Hennepin County Medical Center	June 2010	17
UMMC - Fairview	November 2010	10
Fairview Southdale Hospital	July 2010	7
Regions Hospital	January 2012	23
Ridgeview Medical Center	February 2012	1

POINT National Hub Enrollment Ranking

Total Enrollments Nationwide: 1308 **Total Enrollment Goal: 4150**

Rank	Hub	Enrollment
1	UPenn	117
2	Wayne State	72
3	**Minnesota**	**58**
4	Cincinnati	54
5	Texas	41

SHINE

Stroke **H**yperglycemia **I**nsulin **N**etwork **E**ffort

Version 2 protocol was released January 30, 2013. It removed the **requirement** for subjects to be enrolled within 3 hours of ED arrival. It is now a **recommendation** only. Patients must still be within the 12-hour window from time of stroke onset or last known well.

We had our first monitor visit at the end of January following our first enrollment at UMMC. We were pleased with the positive feedback and tips for managing future subjects. Nursing staff were very receptive to the technology involved with the study and to study coordinator assistance.

The protocol amendment adds an optional ancillary study called I-SPOT. A baseline and 48 hour blood sample will be assayed for coagulation factors. This study hopes to better understand relationships between ischemic stroke, hyperglycemia and hypercoagulability.

We look forward to adding sites to this study in the Twin Cities. The EPIC order set build process has caused substantial delays in activating sites. We expect HCMC to be ready to enroll by March 1, 2013.

SHINE Minnesota Spoke Enrollment Summary

Spoke	Active	Enrollment
UMMC - Fairview	December 2012	2

SHINE National Hub Enrollment Ranking

Total Enrollment Nationwide: 83 **Total Enrollment Goal: 1400**

Rank	Hub	Enrollment
1	Emory	13
2	NYP	8
3	Temple, Kentucky	7
5	Texas	5
6	Cincinnati	4
7	Ohio	3
8	**Minnesota**	**2**
9	Stanford, Pittsburgh, Maryland, UCSF, UPenn, & Wisconsin	1

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Eric Irwin, MD	Patty Reicks, RN	North Memorial Medical Center

POINT

Principal Investigator	Primary Study Coordinator	Spoke
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David Larson, MD		Ridgeview Medical Center
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SHINE

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