PECARN
Pediatric Emergency Care Applied Research Network

PECARN In a nutshell

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Adverse Event Reporting in Clinical Trials

Sally Jo Zuspan, RN, MSN
CDMCC Program Manager

You have heard about Fen-Phen, the diet drug that lead to reports of problems in women taking it for weight loss. So what does this have to do with PECARN studies? The Fen Phen experience has some important lessons that serve to educate everyone conducting clinical trials.

What is fen-phen?

Fen-phen refers to the combined use of fenfluramine and phentermine, prescription medications that have been approved by the FDA for many years as appetite suppressants for the short-term management of obesity. Phentermine was approved in 1959 and fenfluramine in 1973. In 1992, a series of studies reported that the combination of these two drugs, dubbed Fen-Phen, reduced certain side effects while maintaining weight loss in patients. Despite the fact that these drugs were approved for "short term use", another physician studying the same drugs reasoned that since both drugs were being taken at lower doses, patients could take the combination drug for many months instead of a few weeks. This type of drug use is called "off-label use" meaning that the drug is used in ways other than described in the FDA-approved label. At the time of these decisions, no studies were presented to the FDA to demonstrate either the effectiveness or safety of these drugs taken in combination. Furthermore, the safety of fenfluramine use beyond one year had not been established.

Problems Emerge

On July 8, 1997, the Mayo Clinic reported that 24 patients developed heart valve disease after taking fen-phen. The cluster of these unusual cases suggested that there might be an association between fen-phen use and valve disease. Further study reported that 1/3 of patients who had taken the combined drug had leaky heart valves and abnormal EKGs. Five patients in this study underwent valve replacement surgery. On the same day that this report was released, the FDA issued a Public Health Advisory that described the Mayo findings. The Mayo findings were reported in the August 28 issue of the New England Journal of Medicine, along with an FDA letter to the editor describing additional cases. Since then, the FDA has received over 100 reports (including the original 24 Mayo cases) of heart valve disease associated with fen-phen. Based on these data, the FDA asked manufacturers to voluntarily withdraw these drugs from the market and recommended to the public that patients stop taking them. The Fen-Phen lesson is clear: Nearly forty years after phentermine received FDA approval, the combined use of this drug and another drug resulted in a previously undocumented and unexpected physical finding: leaky heart valves. The Fen-Phen experience teaches us that even well established, seemingly "safe" drugs can cause unexpected results, resulting in death or disability for patients.

How did this happen?

How does such a problem with a known, effective drug develop? Some say it happened because "off label" use was initiated without adequate study. Lack of appropriate reporting was also a contributing factor. FDA approval for fenfluramine was granted for use alone and not in combination with another drug. In addition, earlier trials did not study long term use for either drug. Furthermore, there was evidence that the drug might have adverse effects on the heart. A Belgian study in 1994 had shown leaky heart valves associated with fenfluramine use but this information did not get passed along to the FDA. It is for these reasons that the FDA requires all drug companies to report any serious or unexpected adverse events regardless of their apparent relationship to the study drug.

PECARN Clinical Trials

Reporting of Adverse Events (AE) and Serious Adverse Events (SAE) is required during a clinical trial. Failure to report an adverse event is a violation of federal regulations and good clinical practice. The Fen-Phen story teaches us that even "safe" drugs can have unexpected effects. Because PECARN investigations by definition involve children, who are known in research as a "vulnerable population," we must be extra cautious with reporting adverse events.

Dexamethasone was approved by the FDA on October 30, 1958. Since that time, labeling for the drug has

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upcomingmeetings

The PECARN Steering Committee Meeting is scheduled for Tuesday, September 21 through Thursday, September 23, 2004 in Chicago, IL. The PECARN meeting will begin at 2:30 PM on Tuesday and will adjourn at 6:30 PM. On Wednesday the meeting will be from 8:30 AM to 6:00 PM and on Thursday the meeting will begin at 8:30 AM and adjourn at 12:00 PM. It is recommended that those outside of the Chicago metropolitan area arrive on Monday, September 20th, in the afternoon or evening.

The PECARN Steering Committee Meeting will be combined with four study training sessions. On Tuesday from 8:00 AM to 2:00 PM the Hypothermia Planning Grant Training meeting and the Seizure Principal Investigator Training meetings will take place. On Thursday from 12:00 PM to 5:00 PM the Bronchiolitis RA Training meeting and the Diagnostic Grouping Systems Investigator Meeting will take place.

The PECARN Steering Committee Meeting and the study training sessions will be held at the Swissotel Chicago. For more information regarding the logistics for this meeting please refer to the IQ Solutions eRoom.
https://www.nedarcssl.org/eRoom/nddp/IQSolutions

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Adverse Event Reporting in Clinical Trials Continued

been changed thirteen times, most recently on May 17, 2004. This most recent label revision provides new information concerning drug interactions with dexamethasone.

Although it is a seemingly safe, well established drug that has been used successfully in children, dexamethasone is a drug that may yet demonstrate unexpected side effects. We are using only a single dose in our Bronchiolitis study. So why report seemingly benign events such as admission, vomiting, rash, or even relatively expected events like intubation? The answer is clear: no matter how safe an approved medication appears, there is ALWAYS the possibility of a previously unknown effect. Seemingly insignificant or isolated events may be viewed as a "cluster of cases" when they are analyzed together. It may be hard to appreciate why it is necessary to report events that appear to be completely unrelated to the study drug, or are more likely related to the disease itself. However, we must remember, it is impossible to determine if an event is drug-related in a single patient. These events must be evaluated in the context of the entire study population in order to determine relatedness.

A Primer for AE Reporting

The International Council on Harmonization, (ICH) Guidelines on Good Clinical GCP guidelines (E6) define an adverse event (AE) as: "An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

The same guidance defines a serious adverse event (SAE) as "Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant dis ability/incapacity
- Is a congenital anomaly/birth defect"

An unexpected SAE is defined by the guidelines as "An adverse reaction, the nature or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan".

Finally, the guidance requires SAE reporting as follows: "All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority (ies) and the Institutional Review Board (IRB)."

Can you translate that?

An AE is an experience that takes place after the investigational drug is given that is "untoward," harmful, or increases the risk of harm to the patient. Say your cute, squalling infant, affectionately known as study subject number one, suddenly sprouts horns after administration of the study drug. This is an adverse event (AE). Since this was not listed in the consent form or the drug information, as a known side effect of the drug, it is an "unexpected AE." I am sure the parents would agree! If the development of horns requires admission to the hospital, or surgery to remove them so the child does not suffer psychological torment, then it becomes a Serious Adverse Event (SAE). Is this interesting finding related to the study drug? Maybe, maybe not. Perhaps it was related to the combination of the study drug and the stress of spending 4 hours in a busy ED. Maybe you have just discovered an alien life form. It doesn't matter which; you must report this event even if it does not seem to be caused by the study drug. Reporting the event is the first step. The AE report will also ask the investigator to determine the causal relationship of the horns to the study drug. The choices are:

- Definitely related
- Possibly related
- Probably related
- Unlikely to be related
- Unrelated

These choices require the investigator to make an assessment regarding the causal relationship between a drug or intervention and the AE. Reporting the AE is not an option; categorizing it in terms of relatedness relies on the opinion of the investigator on site. If horns have been sprouting in babies who are not in the study, then a relationship is unlikely. This is an important distinction and helps the Data Safety Monitoring Board (DSMB) or IRB determine the action to be taken as a result of your findings.

Another Example:

Suppose an investigator studied head injured patients' response to a study drug. One site reported that 4 out of 10 subjects vomited after receiving the study drug. Since vomiting could be related to the underlying head trauma, the event may seem insignificant. However, it is possible that oral administration caused vomiting in numerous of patients across multiple sites. This would not be revealed unless all investigators reported the vomiting events. The conclusion of the study may be that the drug, while effective, caused vomiting frequently enough that its use is not justified. This is precisely why all adverse events must be reported without investigator bias.

The protocol can define reporting requirements for AEs and expected SAEs, but unexpected SAEs are required by regulations to be reported immediately. The Bronchiolitis study will detail specific requirements for immediately reporting all unexpected SAEs.

We are studying vulnerable populations in PECARN (and the current bronchiolitis RCT) and it is important to adequately report Adverse Events. The updated Manual of Operations (MOO) and study guidance will clearly specify how AEs and SAEs should be reported. If you are unclear at anytime about how to report AEs, please contact the study PI or the CDMCC.

The most important things to remember are:

- Reporting: You are required to report all AEs and SAEs to your IRB and to the CDMCC as specified by the study protocol and MOO.
- IRB requirements: Each IRB has specific requirements about AE reporting and often has special forms on which to report AE. It is the responsibility of the Investigator at each site to report AE as required by the individual hospital.
- Forms: Complete all information on the AE form.
- Site Monitoring: Site monitors will evaluate how well a site has reported AE by completing chart abstractions.

AE reporting is much like a puzzle; you cannot make sense of it until you have all the pieces. Reporting promptly and accurately is one of the keys to conducting a safe, ethical and responsible clinical trial. To report AEs accurately, you must approach the process with no pre-conceived notions about the symptoms or events that occur. Reporting ALL adverse events is akin to dumping all the pieces of the puzzle on the table and putting them together to form a complete picture. This process will help ensure that all the information is available to assess the safety of the study drug.

From Initiating to Regulating

Throughout the months of May and June every site involved in the Head Trauma Study received a "site initiation visit." The main purpose of this visit was to review study materials, educate research personnel about compliance to Good Clinical Practice, and to review study procedures to assure compliance to the protocol. A visit at this stage of the study was intended to clarify confusing issues and assure that the study would proceed in the appropriate manner. Now that sites are familiar with study implementation and have been instructed on how to maintain an Essential Documents Binder as well as how to report clean data, a "Standard Operating Policy and Procedure for Ongoing Site Monitoring" will be implemented.

The site monitoring policy for the TBI study states that "visits are to be conducted during the study to assure regulatory compliance, sufficient patient entry, (and) data quality..." The policy also states that there are "triggers" which would initiate investigation of site performance. Several performance indicators will be measured to evaluate the need for a site monitoring visit. These performance indicators may include everything from enrollment rate (below 70 % of eligible patients for a 4 week period), to poor data quality, to unexpectedly high numbers of patients who meet exclusion criteria, to low total numbers in any category (missed eligibles, patients who meet exclusion criteria, and enrolled).

Brooke Millar, BS
Head Injury Study Coordinator

As mentioned, these triggers initiate a site investigation. A phone call, email, or letter will be sent to the site prior to the monitor showing up to conduct a formal site visit. If the issues are unresolved after the inquiry then a Site Monitoring Visit will be scheduled. This process is intended to provide a means to identify systematic problems so that a resolution can be instituted at the site and therefore increase data quality.

Welcome Back Isabelle!

We are pleased to see our former colleague, Dr. Isabelle Melese-d'Hospital has returned to the EMSC National Resource Center (NRC) with a new title, "EMSC Research & Program Analyst." Previously a "Social Scientist" at the Office of Strategic and Program Planning at NHTSA (USDOT) from 2003-2004, Isabelle worked closely with the Administrator's office in international health, traffic safety policy and strategic planning, earning both agency recognition and a Secretarial award from the DOT. Prior to her four years as the NRC's Research Specialist from 1999-2003, Isabelle earned her Medical Sociology Ph.D. in 1993 in at UC San Francisco, where her dissertation on adolescents' perceptions of HIV prevention education earned her the first Anselm Strauss Qualitative Dissertation Award. After graduation she held a 2-year Hewlett post-doctoral fellowship in reproductive health policy research at UCSF's Institute for Health Policy Studies, after which she moved to the East Coast. She is the proud mother of 3 children. Now that she is back at the EMSC NRC, Isabelle will again assist MCHB staff to promote and support the PECARN. She will also resume providing research advice to state grantees along with NEDARC and CPEM. She will resume coordination of the federal Interagency Committee on EMSC Research, renewing contacts with federal and non-federal research entities of relevance to EMSC. The EMSC Researcher Listserv will be revived as well; send your email address to emscresearch@emscnrc.com to join!

You'll see Isabelle at PECARN meetings, EMSC Grantee meetings and at some research conferences. You can also contact her directly at imelese@emscnrc.com or 202-884-6861.

Evie Alessandrini, MD, MSCE
Investigator

Creating a Diagnosis Grouping System for Child ED Visits

Since ED's provide care to patients with a full spectrum of illnesses and injuries, it is important to have a taxonomy system and severity scale that are applicable to all pediatric emergency patients.

The specific aims of this EMSC funded project are:

1) Create a Diagnosis Grouping System (DGS), driven by clinical sensibility, by grouping ICD-9-CM diagnoses given to children during ED visits. The goal is to create a system, using expert consensus and clinical judgment, in order to comprehensively, sensibly and parsimoniously describe ED diagnoses.

2) Create a Severity of Illness Classification System (SCS), by stratifying ICD-9 diagnoses within each Diagnosis Group into four mutually exclusive categories of illness severity and to examine the relationship between diagnosis severity and measures of EMSC resource utilization.

3) Evaluate the Diagnosis Grouping System and Severity of Illness Classification System by applying them to external data sets. The goal is to ensure that the systems created as part of this project may be applicable to data sets routinely used by EMSC researcher, clinicians, policy makers and administrators.

Methods used for this research include both Nominal Group and Delphi Process consensus techniques and will draw on the expertise of a panel of pediatric and general emergency medicine physicians led by an experienced facilitator. Both the DGS and SCS will be derived from the PECARN Core Data Project. This proposal advances Objective C-4 of the EMSC Five Year Plan that requires research about the quality and effectiveness of the EMS system's services for children. The first consensus meeting will convene in Chicago on September 23rd.

Evaline A. Alessandrini, MD, MSCE; Elizabeth R. Alpern, MD, MSCE; James M. Chamberlain, MD; Marc H. Gorelick, MD, MSCE

nodalnews

ACORN

• ACORN welcomes the following research assistants: Virginia Koors at St. Louis Children's Hospital, Kateland Webber at Cincinnati Children's Hospital, Kammy Jacobsen at Primary Childrens Medical Center in Utah, and Duke Wagner at Medical College of Wisconsin.

CARN

• CARN welcomes Kate Barcomb as a new research assistant and Bobbe Thomas as a new nodal project assistant.

GREAT LAKES

• Please join us in congratulating Mary Ann Gregor, DrPH on a new position she will soon be taking. Effective September 7, 2004, Dr. Gregor will be the Director of the Urban Health and Wellness Center at the School of Health Professions, University of Michigan-Flint, and Assistant Professor in the Department of Health Sciences and Administration. We wish her the best of luck in all her future endeavors!

PED-NET

• Births: to Lynn Cimpello, Site PI at University of Rochester, Abigail and Luke born on July 26th; to Neil Schamban, Site PI of Newark Beth Israel, Alexander born on April 15th; to Michael Bachman, Co-Investigator at Newark Beth Israel Alice Maya born on August 28th.

• The Department of Emergency Medicine at SUNY – Upstate Medical University in Syracuse, NY has received approval from the Residency Review Committee on Emergency Medicine for a Fellowship Program in Pediatric Emergency Medicine. The first fellow in this re-established Fellowship program is Dr. Jennifer Mackey, a 2004 graduate of the Pediatric Residency Program at SUNY – Upstate. James Callahan, MD, FAAP, FACEP, Associate Professor of Emergency Medicine and Pediatrics has been named the director of the Fellowship Program.

• Peter Dayan of Children's Hospital of New York has been awarded a K12 grant for the period 8/1/04-7/30/06. The project title is: Multicenter Emergency Department Study to Assess the Risk of Intracranial Abnormalities, Interrater Reliability of Clinical Findings, and Management Patterns for Children with First, Apparently Unprovoked Seizures.

Intention to Treat

Rich Holubkov, PhD
Biostatistician

Many study protocols say that the data analysis will be done by "intention to treat". What does this expression mean, and why is this done? "Intention to treat" analysis is usually used in the setting of randomized trials. It means that patients assigned to a treatment are counted as being in that treatment group for the analysis, even if they wind up discontinuing the treatment, and even if they wind up changing over to the other treatment arm in the study!

Why would you want to look at a study in this way? Early on, when a drug or device is being developed using animal models or even in early, small-scale research in human volunteers, the major interest is if the agent works in a controlled "lab setting". For example, studies are done to see if there is a dose-response curve for a drug, and what the maximum tolerable dose is. For these early studies, crunching the data using only animals or subjects who received the drug according to protocol often makes sense.

By the time a drug is being studied in our network, we want to know if the drug is effective in the "real-world setting". Let's say a powerful new drug is very effective in reducing admissions in kids who receive a full dose, but also has strong side effects that lead to its withdrawal in a large proportion of kids, before they can get the beneficial effect. This drug is being compared to an older, less effective agent, which is tolerated by most kids. Among kids receiving a full regimen of either drug, those getting the new agent would show a better treatment effect. When all randomized kids are compared, though, those assigned to the older drug may have lower overall admission rates, because so many kids assigned to the new drug had side effects preventing its full delivery.

Hopefully, it's clear that the old drug would be preferred for use in the above example, because for a child walking into the ER, his/her overall chance of admission would be lower if the older drug were given. From a pharmaceutical point of view, the new drug is better than the old drug when both are given in a "lab setting" without regard to potential side effects. But, the STRATEGY, or regimen, of using the old drug is superior (in the "real world" ER setting) to a STRATEGY of giving the newer drug. I always look at "intention to treat" as a comparison of strategies rather than drugs or devices themselves, since all consequences of first trying a particular treatment are counted in favor of, or against, that treatment regardless of what the patient undergoes after that. In our example, so-called "secondary" analyses would look at if the new drug is in fact better among kids receiving a full dose of each, and whether well-defined subgroups of kids can be found at very low risk of side effects from the new drug; such kids might be the focus of a subsequent study.

One question that is often debated is whether "intention to treat" extends to study entry criteria as well. For example, if our study had an upper age limit of 9 years, but due to a birth-year mix up, a 10-year-old was in "good faith" entered into the study, should that subject be counted in the final analysis? I do not believe there is a "right answer" here; I might lean towards excluding that subject from the main analysis because a "hard" study entry criterion was violated and because the study results will be represented as applying to children up to age 9, but one could argue in the other direction just as well. Perhaps more important is that all enrolled subjects are accounted for in the final report (see this author's earlier article on CONSORT, which you have no doubt cut out, framed, and put on your office wall) and that the effects of any enrolled subject exclusions on the study results are described.

pecarnupdate

Psych Working Group: Data collection for the PWG Pilot Project, "Referral Patterns and Resource Utilization for Pediatric Emergency Department Patients Presenting with a Psychiatric or Mental Health Problem: The PECARN Psych/Mental Health Working Group Pilot Study" is almost concluded. Data abstraction and entry is completed at all but two participating sites. Derivative projects and grant development are planned for fall 2004, including submission of abstracts in December 2004 - January 2005. A second project is near completion: a PECARN-wide survey of Psych/Mental Health issues in the ED. The survey will be presented to PECARN subcommittees for approval and prioritization in the coming months. A survey of ED physician perception of Psych/Mental Health training is next in line for development.

Prehospital Working Group: Prehospital Working Group: The working group Submitted a survey to PCRADS at the February meeting which received conditional endorsement. The survey is designed to catalogue the EMS systems that serve PECARN HEDA's to be able to meaningfully prepare to conduct EMS research within PECARN. We hope to finalize the survey soon and send it to HEDA sites for completion. Additionally, the C-spine proposal previously submitted to PCRADS is forming a working group. If you would like to be a part of the Prehospital or C-spine Working Group, please contact Tasmeen Singh at tsingh@cnmc.org.

Head Injury Study: Since the last PECARN Newsletter was published, we have seen a lot of progress with this study. The Head Injury Study continues to move along and gather enrollment momentum. Our overall percentage of enrollment has gone from 74 percent in June, to 80 percent at the end of August. Almost 5000 patients have been enrolled thus far. Enrollment reports are sent out each week. We have had several conference calls, email discussions, and even a PECARN wide meeting (Washington DC) since the last PECARN Newsletter publication. The working group will begin to have their conference calls every third week from now on. RAs had a conference call in July to discuss common issues and questions. Efforts are being made to regulate site performance. A new site monitoring policy has been developed. PIs and RAs are being contacted regularly. The study continues to go very well due to the great collaboration of the Site PIs, the Site RAs and the CDMCC.

Hypothermia Study: As of August 11, the study database contains 110 abstracted records from 15 sites. Site investigators and abstractors will meet in Chicago before the regular PECARN meeting. The application for the R34 clinical trial planning grant is under development. This grant will provide $100,000 over 1 year to write the protocol and manual of operations for the randomized controlled trial. Mary Ann Gregor is leaving the project to take a new position as the director of Urban Health and Wellness Center at the School of Health Professions, University of Michigan-Flint, and Assistant Professor in the Department of Health Sciences and Administration. Jenn Suhajda will act as the coordinator for the project.

PECARN Core Data Project: Phase I electronic data are complete and analyses are ongoing. Phase II data (electronic and chart review) are being finalized. Four manuscripts are currently in preparation based on the six abstracts presented at the Pediatric Academic Society and Society for Academic Emergency Medicine meetings earlier this year. Targeted submission of manuscripts is fall 2004. The proposal for ongoing annual collection (2003-2007) of the electronic data was reviewed by PCRADS in June with approval to move forward. Templates for IRB modification have been provided by the PCDP Working Group. Sites should be in the process of submitting IRB renewals or addendums to reflect a change in protocol that allows annual submission of data for a five-year period.

Bioterrorism Surveillance: Bioterrorism Surveillance: Historical data has been sent to Children's Hospital of Boston from Children's National Medical Center and real time data transfer has begun. Additional PECARN sites are getting IRB approval or are in the early planning phases.

Use of Lorazepam for Pediatric Status Epilepticus: A Double-blinded Randomized Diazepam Controlled Clinical Trial: The NIH issued a request for proposals (RFP NICHD-2003-10) under the Better Pharmaceuticals for Children Act (BPCA) for a contract to study the pharmacokinetics and efficacy of lorazepam for the treatment of pediatric status epilepticus. Lorazepam is a commonly used drug for pediatric seizures but is not FDA-approved for children under 18 years of age. The BPCA has a congressionally mandated list of such drugs that require pediatric study. The objective of this contract is to determine the pharmacokinetics and optimal dosing of lorazepam for pediatric use and to conduct a randomized controlled trial of lorazepam with a diazepam control arm for the treatment of status epilepticus. The lorazepam study was the first in a series of RFPs that will be issued by NICHD under the BPCA. Since status epilepticus is an emergency condition and informed consent is not feasible in the 5-min. therapeutic window, this protocol was submitted under an exception from informed consent using the community consent process. Five PECARN sites were originally submitted with a budget of $2.9 million. The NIH responded in Dec. 2003 informing CNMC that we were in competitive range for the contract and requested the addition of 6 sites. All of the PECARN nodes responded and a total of 11 sites were resubmitted in Dec. 2003 with a total budget of $4.6 million. Since that time, we have been negotiating with the NIH regarding the exception from informed consent process. The NIH has a unique relationship with the FDA under the BPCA and has been working with CNMC to conduct this study without an exception from informed consent, which is a long and labor intensive process. The NIH recently asked for a revised submission to begin the contract by conducting the pharmacokinetic portion of the study using pre-consented neurology patients and those with seizure disorders who would volunteer for elective Lorazepam therapy. This proposal was submitted with a budget of $1.9M for the Pk study and $5M for the 3-year randomized trial using 11 PECARN sites for both parts. Although a final award has not been determined for this contract, the intensity of ongoing negotiations and the official response from the NIH indicate a competitive proposal. If funded, this will be the largest external grant received by PECARN and begin October 1, 2004.

eRoom

PECARN Core Data Project: https://www.nedarcssl.org/eRoom/nddp/PECARNCoreDataProje
Hypothermia: https://www.nedarcssl.org/eRoom/nddp/Study-HypothermiaPlanningGrant
Bioterrorism Surveillance: https://www.nedarcssl.org/eRoom/nddp/Biosurveillance
Effectiveness of Oral Dexamethasone in Acute Bronchiolitis: A Multicenter Randomized Contro
Clinical Decision Rules for Identifying Children at Low and High Risk for Traumatic Brain Injurie

newfaces

Kammy Jacobsen, RA

I am so excited to be working with the PECARN network! I have worked with some of the CDMCC staff on the Public Access Defibrillation Trial and it is great to be involved with them again. I am a certified EMT-Intermediate and in my "spare time", I run a BLS training company. I am also an EMT instructor and I am loving this opportunity to expand my Medical vocabulary with words like "opacification". I am the only girl in my family with two adorable boys and a wonderful husband that keep me active and enjoying life!

Christy Hansen, Executive Secretary

Christy is the new Executive Secretary for Pediatric Emergency Care Applied Research Network (PECARN) at the Intermountain Injury Control Research Center. She has attended BYU for 3 years and was majoring in Marriage, Family, Human Development and Pre-Med. She is currently working on completing her associated degree in Executive Administration and would like to continue her Bachelors at the University of Utah. With 5 years secretarial experience she is working to be a helpful addition to PECARN. Christy is busy with her 2 little boys and keeping up with her husband's school schedule. She is very thrilled to be working with Sally Jo, Brooke and Kym at the CDMCC.

Neysha Fletcher, RA

A member of the five-time Grammy Award winning Brooklyn Tabernacle Choir and Globe trekker, Neysha is the new Research Coordinator at Harlem Hospital Center. She did her undergraduate work at The University of Pittsburgh and at The City University of New York – Sophie Davis Bio-Medical Program. Her ultimate goal is to continue Globe trekking with her 18 month old son until they have conquered every country / island, while completing her education to become the next CEO of Harlem Hospital Center.

Duke Wagner, RA

I have a diverse background and really enjoy being a part of the research team here at the Medical college of Wisconsin in Milwaukee, WI. I have degree's in Chemistry, Human Biology and a Doctorate in Chiropractic. I was in practice for 12 years in a suburb of Milwaukee and finally decided to become a part of a bigger medical facility. Chiropractic practice is not out of the realm of future possibilities again, but research is engaging and important (I remember this even when entering data), and I hope for a future in it with this excellent facility. My wife Carlyn and I have two children and a new home in Waukesha county west of Milwaukee.

Margaret Boyle, BS, EMT-D

Margaret Boyle received her BS in Biology from Syracuse University in 2001. After graduation, Margaret began working at Upstate Medical University for the Advanced Life Support Training Center. She is planning to attend graduate school in the fall of 2005 to pursue a Masters' Degree in Nursing. Margaret is very excited to be part of the PECARN team and is enjoying her first clinical research experience.

Virginia Koors, RA

I am very pleased to start my third career at Washington University School Medicine. Since graduating from University of North Carolina – Chapel Hill with a degree in Biostatistics, I spent over 17 years conducting qualitative and quantitative marketing research at a local telephone company. When my position was moved out of state, I decided to change careers and focused on being a mom and volunteering at my children's school. I also became an Adjunct Faculty member at Webster University teaching marketing research and marketing statistics. As my children grew, I decided that it was time to pursue a full-time position. Here at Washington University I am the Research Coordinator for the TBI and the Bronchiolitis studies, as well as being Program Coordinator for the Pediatrics Emergency Medicine Research Associates Program (PEMRAP). (By the way, my boys are now 13 and 16 years old.)

Kate Barcomb, RA

My name is Kate Barcomb, everyone calls me KB, 'cause it's easier. I went to Hopkins for undergraduate and received my BA in Public Health. I played Lacrosse for Hopkins and was an academic all-American in 2004. I am from a family of 6, of which I am the youngest and the only girl, besides my wonderful mother. My life long goal is to start a Lupus treatment center in my mother and father's name. I am excited to be a part of PECARN and to be working with a great group of people.

Good Clinical Practice Tip

Section 4.9.4 of Good Clinical Practice states - "The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents."

If you keep trial documents in your e-mail system make sure you talk to your IT department about archiving/saving your e-mail messages.

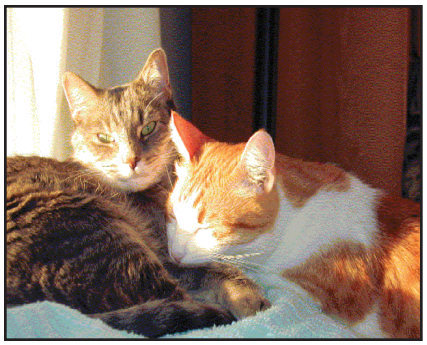
Bottom line, you should be able to retrieve trial documents until CDMCC informs you in writing when the trial-related records are no longer needed (GCS section 4.9.5).

ct

lled Trial: https://www.nedarcssl.org/eRoom/nddp/BronchiolitisRCTProject

es after Mild Blunt Head Trauma: https://www.nedarcssl.org/eRoom/nddp/HeadTraumaStudy

Sepsis

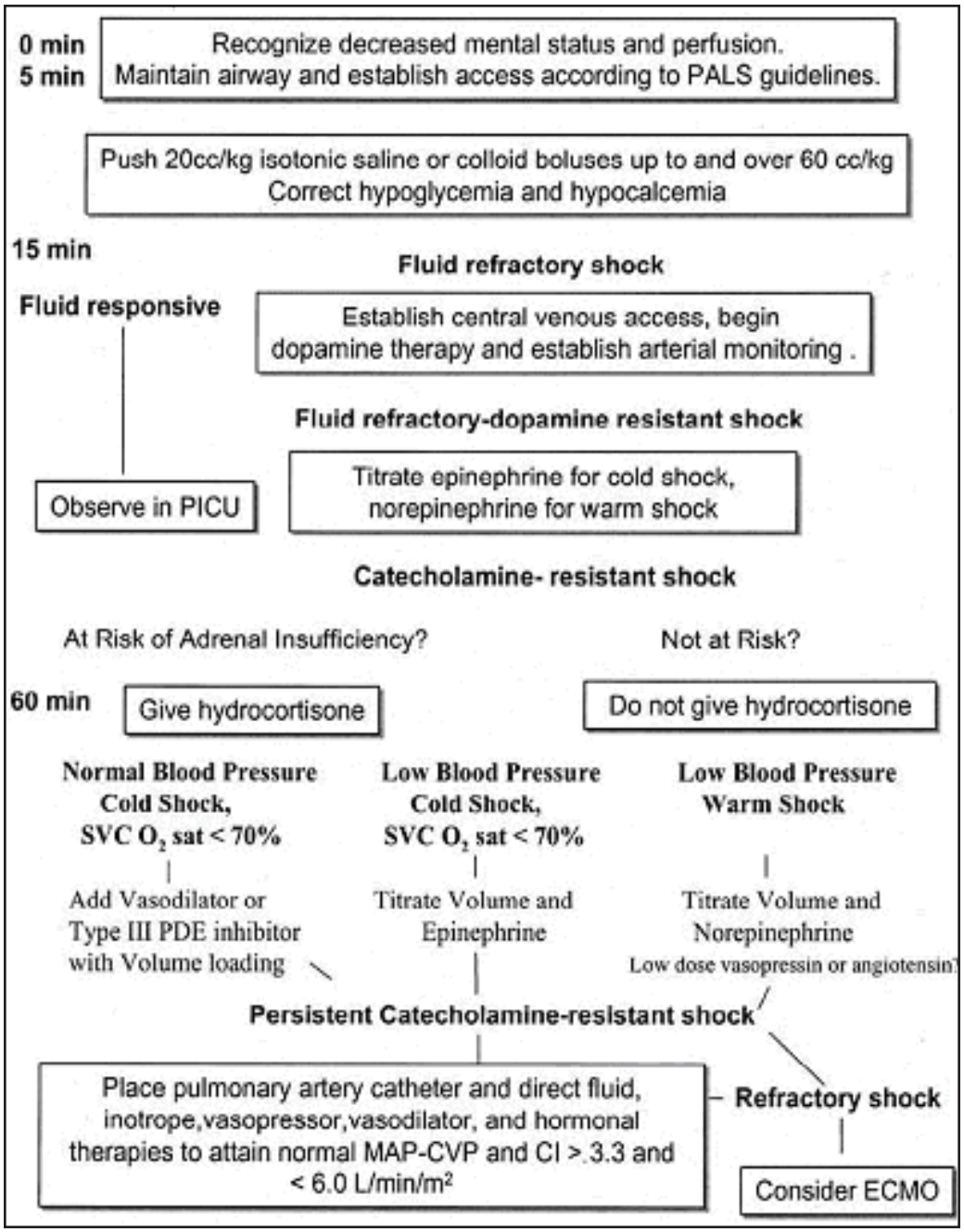


Helena Rincon
PED-NET Nodal Administrator

Mortality rates due to sepsis in children have decreased from as much as 97% to as little as 9% over the past 25 years. Different practices may affect outcomes, and variations in practice persist. Sepsis still accounts for 4,400 pediatric deaths in the United States each year. Standardized early aggressive therapy in the emergency department for adults with sepsis has been shown to decrease mortality. Studies in children with sepsis have also suggested that early aggressive fluid resuscitation and treatment in specialized centers may decrease mortality. These observations, among others, led to the delineation of a practice guideline published in June 2002 by the American College of Critical Care Medicine, endorsed by American Heart Association/Pediatric Advanced Life Support (ACCM-PALS) recommending standardized early aggressive therapy for pediatric sepsis. Research has demonstrated that adherence to this guideline may decrease mortality, yet adherence remains variable. Additionally, the importance of the ACCM-PALS guideline for the management of pediatric sepsis in the emergency department and the commitment of individual ED practitioners to the guideline remain to be confirmed. The evidence for the recommendations, the ability of the guideline to alter outcome and the feasibility of the suggested approach are not definitive. The guideline includes three major recommendations; aggressive fluid management with the administration of up to 60 cc/kg of fluid within 15 minutes of presentation, use of pressors if initial fluid management fails to restore perfusion, and the use of steroids in patients who are resistant to catecholamines and suspected to be adrenally insufficient.

The Sepsis Project Working Group, led by Dr. Steve Miller, has developed a physician survey to determine current variation in practice for pediatric septic shock and to determine acceptance of the guideline by practitioners. The Working Group includes the following members: Kathleen Brown, MD (CNMC-CARN), Peter Dayan, MD and Dale Hesdorffer, PhD (CHONY/CUMC-PEDNET), Rene Enriquez (CDMCC), Stephanie Kennebeck, MD (CCMC-ACORN), Clay Mann, PhD (CDMCC), and Rachel Stanley, MD (UM-GLRN),

Figure 1. Recommendations for stepwise management of hemodynamic support in infants and children with goals of normal perfusion and perfusion pressure (mean arterial pressure - central venous pressure [MAP - CVP]). Proceed to next step if shock persists. PALS, pediatric advanced life support;PICU, pediatric intensive care unit;SVC O2, superior vena cava oxygen;PDE, phosphodiesterase;CI, cardiac index;ECMO, extracorporeal membrane oxygenation. From Carcillo, et al 2002 (CCM 30:6, pp 1365 – 1378).



Protocol Deviations

A just-in-time-refresher...

Protocol Deviations-the term strikes a familiar chord in your brain. Of course! The Bronchiolitis study last year; it is all coming back now…

PECARN learned some important lessons about protocol deviation reporting during the Bronchiolitis study, our first PECARN randomized controlled trial. Gathering protocol deviation reports early in the study helped us correct confusion regarding specific procedures, identify site specific medication administration issues, and re-think patient communication. Proactive reporting by the HEDA allowed Dr. Corneli, Stacey Townsend, and the CDMCC to make clarifications so that the study would run more smoothly. When we noted confusion among parents about steroid use in their infants, an updated list of steroids with common names and descriptors was circulated to help increase parent accuracy in identifying whether their baby had taken steroids before. This is just one reason why understanding Protocol Deviations (PD) is so important.

Just in case you are a little rusty, here is a quick primer on PD.

Q: What is a Protocol Deviation?
A: A Protocol Deviation is any departure from the defined procedures and treatment plans as outlined in the protocol that was approved by the IRB. Failure to follow GCP may also represent a deviation.

So far, the concept is simple: if the protocol states that a procedure, exam or clinical event should be done a certain way, and it was not, then you have a deviation.

Q: Why is protocol deviation reporting so important in a clinical trial?
A: Protocol deviations must be reported for several reasons:

- Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research.
- Consistent patterns of a particular deviation at multiple sites may reveal the need to amend the protocol, or may impact analysis of the study data. Consistent reporting helps the PI recognize and correct study or clarify the protocol as needed. For example, let's say an investigator studying the use of XYZ drug decides that an additional dose of the study drug is better for the patient than the dose specified in the protocol. Will this have an effect on the data? And could this cause a problem in the study participant? Is it a protocol deviation? The correct answer is yes to all three questions.

Q: Is there a regulatory requirement to report PD?
A: Of course! Good Clinical Practice (GCP) requires reporting of PD: ICH GCP 4.5.3 states that the investigator or person designated by the investigator should document and explain any deviation from the approved protocol.

Q: What types of protocol deviations should be reported for Bronchiolitis?
A: Each HEDA IRB will have a defined list of reportable protocol deviations that must be reported by the site personnel to the local IRB. You must contact your IRB to see what they require, and how you must report deviations. For Bronchiolitis, the CDMCC requires the following to be reported to even if they are not reportable by local IRB standards. Standard PD and an example of each deviation is listed below:

- Enrolling subjects who do not fulfill inclusion/exclusion criteria
  ex: A site that unknowingly enrolls a baby with a previous history of wheezing because the mother states child has never wheezed
- Subjects receiving any study related activity such as treatment, procedures, or drug administration prior to obtaining documented IRB approved Informed Consent
  ex: Study drug is administered prior to consent being signed
- Variations in drug dosing/dispensing/storage
  ex: A drug dose is intentionally increased above what the protocol specifies.
- Medication errors (wrong pt, wrong time, wrong dose, wrong med)
  ex: The RN erroneously gives the patient 2x the dose of the study drug.
- Use of prohibited medications
- Incorrectly performed or missing protocol required procedures
  ex: The 1 or 4 hour RDAI is done late, or is not done at all. The RDAI is done with the baby (not the RA) laying down and on Oxygen

Sally Jo Zuspan, RN, MSN
CDMCC Program Manager

- AE or SAE not reported according to guidelines
  ex: The patient had a seizure and the site did not report it as an AE
- Premature "unblinding" of research treatment or data
- Loss or corruption of study data or study files
  ex. The patient record was left in the ED lobby
- Other deviations as identified by the site personnel or site monitor

Q. Does a protocol deviation mean a site made an error?
A. Not necessarily. Deviations may result from problems on the part of the study participant, parent, investigator or site staff. If the mother states the baby has never wheezed, then it may not be avoidable. On the other hand, maybe the error points to a need to further describe "wheezing" when speaking to parents. Furthermore, deviations may not be attributable to any one error, and identifying them should not be a punitive process. Rather a deviation is simply an event that does not comply with the protocol.

Q: How do I report PD to the CDMCC in the Bronchiolitis study?
A: PD reports will be reported by fax to the CDMCC. More details will be available when the study starts.

Q: Will the CDMCC track and report PD?
A: Since the CDMCC is a data center, we track everything! However the focus of these reports is to improve the quality of the study and the more consistent the reporting of PD, the better the study will be.

We all need to keep on top of reporting of protocol deviations. Your diligence and timely reporting will make a big difference in the safety and quality of study. You will be hearing more about protocol deviations in the coming weeks.

Research in Children

J. Michael Dean, MD, MBA
Principal Investigator

PECARN research often involves human subjects. The subjects are children, a vulnerable population, and the diseases and therapies under study have significant mortality and morbidity. We consider it imperative to approach the privilege of conducting human subjects research with a prospective, thoughtful, rigorous and ethical framework. This framework recognizes that human subjects protection is not "IRB approval", but rather, involves a complex interaction of organizations (e.g., sponsors, funding agencies, academic institutions), organizational entities (e.g., Institutional Review Board, Office for Human Research Protections), and individuals (e.g., children, families, investigators). In the multi-institutional setting of a research network such as PECARN, the human subjects protection system involves multiple research institutions with their local IRBs, potentially multiple sponsors and funding agencies, the MCHB, NICHD and FDA, the DSMB, the PECARN Steering Committee, different state laws governing informed consent by minors, different community standards and interpretations of risk, and different community cultures and ethical norms [1]. The network itself is an important component of the human subjects protection system, and PECARN Principal Investigators and CDMCC must assure that all participants in network research are fully compliant with all regulatory and ethical requirements, MCHB policies, and policies and procedures that have been defined by the Steering Committee.

This article will concentrate on two subjects that are relevant to pediatric research: informed consent, and definition of risk. Problems with informed consent have been important in other research networks. The definition of risk in pediatric research has been a topic of controversy and a recent IOM report has significantly altered the landscape of debate. Both topics are of importance to us as PECARN researchers.

Informed Consent

Most research subjects in encountered in PECARN projects will be children who are not legally able to provide informed consent. Thus, informed consent is more complicated for the our network than for research networks dealing with adults. There are two issues worthy of discussion here: (1) parental permission and child assent; (2) informed consent by minor (under age) research subjects.

Parents cannot provide informed consent on behalf of their children. Rather, parents (or guardians) provide permission for their children to participate, and when appropriate, children provide assent for their own participation, in research studies [2]. In the pediatric emergency setting, we anticipate that most patients will not be able to provide assent because of their acute illness. However, during follow up research after discharge from the ED or hospital, issues about assent become applicable. In most jurisdictions, the standard is that when a child is believed to be cognitively able to understand, then assent should be sought. This is often translated into an "age of assent" of 7 years, but this age criterion differs between communities.

Research suggests parents may have a therapeutic misconception that the purpose of research is treatment [3] or that allowing their child to enter a clinical trial is an avenue to obtaining "cutting edge therapy [4]". It is important that the parents understand that while there may be potential benefits to their child participating in a PECARN trial, our basic premise is equipoise – that is, the clinical community truly does not know if there is benefit from the treatment under study. The situation is worse for parents when the child has a serious illness such as cancer, and studies suggest that parents often do not perceive a real choice or do not understand the difference between research and treatment [5-7]. In desperate situations, stressed parents may perceive that study participation is part of "trying everything" to save their child [8]. In a study of neonatal clinical research, parents who consented were more likely than decliners to believe that the research would probably benefit their infant [9].

We raise these issues about parental understanding because "…the conditions for informed and reasoned choice are threatened when parents are confronting a new diagnosis of a life-threatening medical condition and a crisis situation in which immediate decisions are sought [1]." Our network is likely to be dealing with parents in such a stressful situation. It is crucial that the processes used for informing parents and obtaining their permission for research participation of their child are on-going and thorough, as instances of misunderstanding can have serious ramifications for the function and even the on-going existence of the research network (in addition to the obvious ethical imperative to effectively inform the parents). We believe that thorough understanding of these issues, on the part of the PECARN investigators and CDMCC staff, is absolutely critical.

If genetic material is obtained from a PECARN research subject and banked for future analyses, then the standards for assent and consent may change as the child becomes older. We do not have easy solutions but it will be necessary to decide if a child's assent will become necessary in later years, and it is probable that complete informed consent will be needed from a research subject when the age of majority is reached. Unlike the situation with adult research subjects, who may provide informed consent for the future use of their genetic material, our consent process will have to adapt to the changing ages of our subject population.

Our proposal for this problem (genetic material) is that parental permission must be obtained for sampling and storing the material for specific or non-specific purposes, and that if the child is able to provide assent, that should be obtained. At the time of specific analyses of the genetic material, the current age of the subjects should be checked, and if the developmental status of the subject has changed to permit assent for the research, this should be obtained. If the subject has reached the age of majority, then the parental permission is no longer applicable, and the subject should be approached for informed consent.

It is likely that the Steering-Committee may approve a PECARN project or topic involving emergency illness in adolescents. In some instances, adolescents may be emancipated and legally enabled to provide informed consent on their own behalf. However, variable state regulations will be faced. State statutes have been summarized in the Appendix of the Institute of Medicine publication "Ethical Conduct of Clinical Research Involving Children" [1] but the state statutes do not deal with research consent. The network will need to consider these issues if we undertake a trial likely to involve emancipated adolescent populations.

What Is Risk?

All research projects carried out by the PECARN involve children (infancy through 21 years) almost exclusively. Research in children involves special protections under 45 CFR §46 Subpart D "Additional DSSH protections for children involved as subjects in research" and 21 CFR §50 and §56. To simplify this discussion, we will only refer to

Continued on Page 12

spotlights

DOMINIC BORGIALLI, MD (GR LAKES)

I am an Emergency Physician and the new HEDA Director at Hurley Medical Center. I graduated from the Emergency Medicine residency at Michigan State University-Lansing in June, 2003. Prior to medical school, I completed a Masters in Public Health (Epidemiology) at San Diego State University. I have worked as a wine maker, EMT, infectious disease epidemiologist, and researcher on injury-related studies. My research interest is the impact of injury on our society. I am married to Michele, and have 2 young children-Cypress and Bryce. Activities for fun are mountain biking and sailing.

JULIE LEONARD, MD (ACORN)

July 2004 marked the end of my training and I joined the faculty of the Washington University School of Medicine Department of Pediatrics. When I am not manning the St. Louis Children's Hospital ED or working on a variety of cervical spine injury projects, I am "Soccer-Tennis-Basketball-Skating-Piano-Tap-Baseball" mom to Jake and Jordan, wife to Jeff, and dog owner of Hank and Lina (a Labrador and Chihuahua). We are originally from Washington State (Go Dawgs!), so most of our vacation time is spent in the Pacific Northwest where we enjoy cruising the sound, fishing the ocean and streams, and skiing the lakes and mountains.

HAIPING QIAO, MS (PED-NET)

Haiping Qiao currently serves as the Research Assistant for the EMSC-NDDP project in the Department of Pediatric Emergency Medicine at the Women and Children's Hospital of Buffalo (WCHOB). She graduated from the Capital University of Medicine, Beijing, China with a MD degree in Pediatrics. She expects to get her Master's degree in Epidemiology from the State University of New York at Buffalo in December 2004; her thesis examines the role of probiotics in preventing antibiotic-associated diarrhea. Her previous experience includes working as a research associate in Beijing Pediatric Research Institute, Beijing, China, and in the Infectious Disease Department at the WCHOB. In both institutions, she served as a microbiologist and conducted microbiology and immunology research. Haiping enjoys classical music and her son's funny stories. Haiping and her family are happily living in Canada.

BOBBE THOMAS, Nodal Assistant

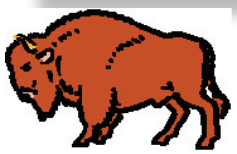
Tonetta Thomas - always referred to as Bobbe - is the new nodal project assistant for CARN. She was recruited for the nodal project assistant position after working in the Emergency Dept. for only 4 months - thanks Dr. Atabaki! So, PECARN being all the buzz in the ED, she immediately seized the opportunity. A North Carolinian, Bobbe is a graduate of the Univ. of MD with a BA in Communications. With a yearning to pursue pediatric advocacy and health care, she is starting a nursing program at Howard University this fall. Her future goal is to pursue clinical nursing and research. FYI, her favorite movie obsession is the Sound of Music.

Informed Consent Checklist

FDA regulations require that informed consent be obtained before a human subject may participate in any clinical investigations. (21 CFR Part 50). The required elements that must be present in an informed consent form are as follows:

- Statement that study involves research
- Explanation of purpose of the research
- Description of the procedures to be followed
- Expected duration of the subject's participation
- Identification of any procedures which are experimental
- Description of any reasonably foreseeable risks or discomforts of the subject
- Statement that there are risks that are currently unforeseeable
- Description of any benefits to the subject or others reasonably expected
- Disclosure of appropriate alternative procedures or treatment advantageous to the subject
- Statement that notes the possibility of FDA inspecting medical records
- Statement informing the subject that their medical records may be examined by the sponsor and if so, the extent to which those records will be kept confidential
- Statement as to whether compensation is available if injury occurs
- Explanation as to whether any medical treatments are available if injury occurs
- Information on whom to contact for answers to pertinent questions about research, research subjects' rights, and in the event of a research related injury.
- Statement that participation is voluntary
- Statement that if they decide not to participate there will be no penalty or loss of benefits to which the subject is otherwise entitled
- Statement that the subject may discontinue participation at any time without penalty or loss of benefits.
- Statement of anticipated circumstances under which the subject's participation may be terminated by the investigator without the subject's consent
- Statement regarding any additional costs to the subject that may result from participation in the study
- Statement that significant new findings developed during the course of the research which may affect the subject's willingness to continue participation will be provided.
- Statement concerning the approximate number of subjects.
- HIPAA language
- Any other elements that are specific to the protocol or required by the institution's IRB.

Many IRBs approve informed consent forms that are missing some of these required elements. Therefore, we recommend that you review your informed consents to ensure that all of the above elements are included.



CDMCC on the Road...

A CDMCC visit was a great excuse to travel to Buffalo this July. Sally Jo visited the Children's Hospital of Buffalo (CHOB) and welcomed Haiping Qiao, Research Associate, to PECARN. Haiping has been a whirlwind of activity in the few short months she has been involved in the network. She jumped right into the TBI project and has already set up a very detailed highly organized filing system for the TBI project. She and Kathy Lillis MD, familiar faces in the ED; were warmly welcomed every time they walked through. This might have something to do with the fact that Haiping and Kathy have been providing "sweet rewards" to staff who have been actively enrolling and identifying TBI patients. Haiping and Kathy have developed several strategies to improve enrollment including: providing direct feedback on enrollment numbers to ED staff, developing a specific training program to teach residents to complete the forms, training medical students to cover RA shift hours, and instituting an incentive program for attending and residents. The Hypothermia project is also up and running in the PICU. Donna Kielma RN, and Brad Fuhrman, MD have identified appropriate patients and have completed several charts for data entry. Donna has extensive PICU experience and is doing a great job on this project.

Research In Children Continued...

45 CFR §46 because the FDA regulations (21 CFR §50 and §56) are sufficiently identical for this discussion. However, the PECARN needs to adhere to all applicable regulations in any particular study.

Children are defined as persons who have not reached the legal age for consent, and we point out that this definition will vary by state laws. Research in children may only be approved if the research falls within one of the following categories:

- Research not involving greater than minimal risk (45 CFR §46.404).
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR §46.405).
- Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR §46.406).
- Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR §46.407).

Approval of pediatric research under the first and third categories listed above requires that the child be subjected to "minimal risk" and a "minor increase above minimal risk", respectively. The precise meanings of minimal risk and minor increase above minimal risk have been subject to detailed ethical analyses, and in July 2004, the Institute of Medicine released "Ethical Conduct of Clinical Research Involving Children" [1]. This publication will have significant impact on pediatric research approved under these categories of risk, and alters the interpretations of minimal risk and minor increase over minimal risk.

Minimal risk compared to what? This interpretive problem has sometimes led to comparison of the risk of participation in research to the risk of the individual subject, given his or her conditions of living or presence of disease. This "relativistic approach" might have led to approval of research that involves risk considered minimal to a child in the intensive care unit, for example, but not considered minimal if compared to the healthy child who is at home or at school. Similarly, a minor increase above minimal risk as sometimes been interpreted as "compared to the baseline risks of the specific research subject". Under these relativistic interpretations, a child with intracranial pressure monitoring, ventilatory support, and requirement of PA catheter monitoring, might be permitted to be subjected to a different minimal risk or minor increase above minimal risk than would be permitted for a healthy child.

The relativistic interpretation of minimal risk has been resoundingly rejected by the IOM report [1]. This has implications for all PECARN studies that do not present the prospect of direct benefit to the child. Our PCDP database does not offer the prospect of direct benefit to the child, but can easily be approved (under §46.404) because it involves minimal risk. But consider a project to study the metabolism of a drug in an acutely ill child. If the drug administration presents no possible direct benefit to the specific child, then the study (which might be a simple pharmacokinetics study of a relatively benign, commonly used drug) can only be approved if the risk of drug administration presents only a minor increase above minimal risk compared to the average healthy child who is not in the emergency department or ICU. For most drugs, this is unlikely to be the judgment for most IRB members, since the non-zero risk of a serious drug reaction is not a "minor increase above minimal risk". For another example, consider isotopic studies of metabolism in acutely ill children. Again, the relativistic interpretation might have led to approval of such studies, since the risk of isotope administration is minimal in comparison with the baseline risks of critically ill children in the ED or the PICU. But if reviewers conclude that administration of isotope presents more than a minor increase above minimal risk, compared to the average healthy child who is not ill, then this research cannot legally be approved.

Clinical trials are likely to hold out prospect of direct benefit, and in such instances, the research may involve significantly greater than a minor increase above minimal risk (the second category listed above). We believe that all interventional studies in the network will fall in this category, in which case the judgment about whether the research may be carried out relies on a risk to benefit analysis by the Steering Committee, the PCRADS, the MCHB and other funding agencies, the DSMB, and each of the HEDA IRBs. If the risk to benefit ratio is considered reasonable by these reviewers, the research is approvable under §46.405.

Studies that are likely to be implemented by our network will fall under the first three categories; the last category (§46.407) requires approval "...by...the Secretary..." (of Health) and the associated 407 review process remains very unsettled [10]. We would not recommend attempting to obtain approval under §46.407 until the process is clarified and our network has successfully implemented other complex studies.

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