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What do source documents have to do with Real Estate?

When you buy real estate, the agent's mantra is "location, location, location." For those of us in clinical research, the mantra is "documentation, documentation, documentation." In the current clinical research climate, it is more important than ever that our data is above reproach. One of the ways to ensure this is to document all data points. Our data points also need to be easily retrievable for review. In this article I will outline the use of source documents.

A source document is the initial record of a data point. Types of source documents may include: medical records, data tools, and notes to file. Data is transcribed from the source document to the case report form (CRF) which contains each protocol-specific data point. Every CRF will have a source document file referencing each data point. The source document file should include enough information to completely reconstruct the case report form if it were lost.

If a data point comes from the medical record, a copy of the pertinent page(s) will be placed in the source document file. Be sure to copy the full medical record document including the signature



RITA GERARD, CCRP
PECARN Site Monitor

and date by appropriate personnel.

If the data point is not recorded in the medical chart or is difficult to retrieve, a data tool may be developed by the site or CDMCC (e.g. the Bronchiolitis clinical worksheet).

A data tool is a form that is developed for the purpose of recording protocol-specific information, both subjective and objective, to ensure that all research required information is collected. Data points on the tool must be signed and dated by appropriate personnel. The completed data tool must include a subject and protocol identifier.

Another source document is the note to file. This note includes information that cannot be recorded elsewhere, it is not a data point per se, and usually requires a narra-

tive. If the note to file documents a mistake made in the course of the study, it requires an explanation of the event along with a plan of action to make sure it doesn't happen again. As with any source document, the note to file needs to be signed and dated by appropriate personnel and reference the subject (if applicable) and protocol.

The note to file will be stored based on the event being documented. For instance, if the note to file is subject specific, it will be stored in the subject's source document file. Submission to your IRB depends on local IRB requirements. In general however, if the note to file documents an event relating to patient safety or informed consent, the IRB should be notified. If the event is a protocol deviation, the note to file can be incorporated in the CDMCC protocol deviation form (bottom of the form) and submitted to the CDMCC.

In summary, all source documents need to be signed and dated by appropriate personnel, all data points in the CRF require a source, and the source document file should include enough information to reconstruct the CRF.

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upcoming meetings

The PECARN Steering Committee Meeting is scheduled for Tuesday, January 25 and Wednesday, January 26, 2004 in San Francisco, CA. The PECARN meeting will begin at 8:00 AM on Tuesday and will adjourn at 6:00 PM. On Wednesday the meeting will be from 8:00 AM to 5:15 PM. It is recommended that those outside of the San Francisco area arrive on Monday, January 24, in the afternoon or evening.

The PECARN Steering Committee Meeting will be combined with two study training sessions. On Monday, January 24 from 1:00 PM to 6:00 PM the Diagnosis Grouping System for Child ED Visits meeting will take place. On Thursday, January 27 and Friday, January 28 from 9:00 AM to 5:00 PM the Seizure Project Training Sessions will take place.

The PECARN Steering Committee Meeting and the study training sessions will be held at the Westin, St. Francis Hotel, San Francisco.

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Phone: (415) 397-7000
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In Memory



STEVEN MILLER, MD
1958-2004

Dr. Steve Miller died in a aviation accident October 19th, 2004. Among his countless teaching and clinical responsibilities, Steve served as a traveling Fellow for the Arnold P. Gold Foundation and at the time of his death was traveling to the Kirksville College of Osteopathic Medicine in Missouri to conduct a workshop on Humanism in Medicine. The Gold Foundation strives to nurture and preserve the tradition of the caring physician. Steve's legacy to medicine is fostering empathy, respect, caring, integrity and service, not just among medical students, but everyone he met. Steve's care and attention in teaching medical students compassionate and ethical medicine cannot easily be rep-

licated or replaced.

A native New Yorker, Steve did his undergraduate work at Columbia College with a major in English (1980), and later completed medical school at CU's College of Physicians and Surgeons (1984). He completed his Pediatrics residency at Montefiore Medical Center, and was chief pediatric resident at Bronx Lebanon Hospital Center/Albert Einstein College of Medicine. Steve later served as Co-Coordinator of Resident Education, as well as Director of Education and Pediatric Emergency Service at Bronx Lebanon Hospital.

In 1993, Steve came to Columbia University Babies and Children's Hospital-New York Presbyterian Hospital where he served as the founding Director of Pediatric Emergency Medicine. Steve was the Director of Medical Student Education in Pediatrics and the Arnold P. Gold Associate Professor of Clinical Pediatrics. As the director of pediatric medical student education, Dr. Miller was honored with numerous prestigious awards for his exceptional teaching skills, including the Columbia University Presidential Award for Outstanding Teaching. His students at Columbia University, College of Physicians and Surgeons, named him Teacher of the Year on numerous occasions. Additionally, he served as President of the Council of Medical Student Education in Pediatrics.

In November of 2003, Steve assumed the role of PEDNET Nodal PI. Under his leadership PEDNET made great strides meeting its goals and developing new

ones, in particular developing and achieving a nodal pre-hospital research initiative. At the December 2004 PEDNET meeting, that group had its first meeting.

Steve served as PI and Work Group leader for two projects; the Psych Working Group and "Promoting Quality Improvement in the Treatment of Pediatric Sepsis." He served as site PI for the "Biosurveillance Grant" and "Disparities" projects. Additionally, Steve led the Nominal Group Process forum to develop the PECARN Research Priorities, and was the lead writer on the manuscript.

Steve is survived by Dr. Dodi Meyer, a native of Argentina and Assistant Clinical Professor of Pediatrics and Director of the Dyson Initiative at the Children's Hospital of New York. They have three children Jesse, age 12, Maya age 10, and Nico age 6.

PECARN has lost a good friend in Steve. He entertained us with his quick wit, and warmed us with his engaging personality. He had an intense commitment to everything important in his life and balanced his love of life and family with his involvement in PECARN and other professional projects. His casual style, and warm approach put people at ease. He enjoyed people and had a unique way of engaging others; he had a gift for conversation and a good sense of humor. His sensitive nature and positive approach put people at ease. He will be sadly missed by all those who worked with him.

A Special Message from our Friend, Steven Z. Miller, President (2004)

(Web editor's note – this column is adapted from the Summer 2004 issue of the Pediatric Educator. It describes an ambitious agenda for Dr. Miller's Presidency, unfortunately cut short by the tragedy. Please see <http://www.comsep.org/PresidentLoss/> for a tribute to Steve and our other friend and Past President Richard Sarkin).

It has been four months since we were all together in Florida – and I miss you all – a lot. COMSEP is special for the great work that gets done by the vibrant membership and for the great attachments and friendships we make with each other (Kumbaya).

I'm happy to say that COMSEP has been extremely busy and productive these past four

months. We have committed ourselves to three things. These are:

- Making pediatric medical student education an outstanding experience for every student in the country – and thereby improving the care of children and families
- Creating new collaborations between those who teach students, resident, fellows and faculty
- Inspiring and supporting the personal and professional growth of each and every member of COMSEP

I'd like to ask that you make note of the following things that are going on to support these efforts.

1. We are designing a survey of COMSEP members, designed to define who we are, what we believe is critical to outstanding medical student education and most important-

ly, to define the value of COMSEP to promoting education and educators. I believe it is everyone's responsibility to fill out this survey carefully, if we are to meet our goals.

2. The Curriculum and Evaluation Task Forces have been working to create a core competency document and begin to develop evaluation methods to match. This will be a unique contribution to the field of clinical teaching.

3. The Learning Technology Task Force has been working to revitalize our web site and create more dynamic dialogue among all of us. This will be a great opportunity for scholarship for our members as well.

4. The Faculty Development Task Force has been working to solidify our mentoring program. They have also reached out to the APA Faculty Development Special Interest Group for col-

laboration.

I have asked the new members to form a COMSEP Young Executive Group. Bill Wilson will be helping coordinate the new members by working with Aleca Clark.

Finally, the planning for the meeting in April 2005 has been exploding with creativity. There is no doubt that we will be better teachers after those fateful four days. We will be exploring ways to expand our imaginations and creativity to enhance our work with students. The sky is the limit on this. Mike Lawless describes this further in this issue.

So, I hope you enjoy this issue (including the Journal Review) as a way of touching base about our continued hard work. And so – everyone – hold hands and sing "Kumbaya."

Source: <http://www.comsep.org/AboutUs/WelcomeToCOMSEP.htm>

Learning Curves

A learning curve is the progression in skills, technique, or implementation over time. For example, in a trial of hypothermia in cardiac arrest patients an investigator may become more familiar with the protocol decision or more proficient at the intervention (such as pulmonary artery catheterization) as they enroll more patients. We often think of learning curves in clinical trials that involve new procedures or surgical techniques and not in terms of the implementation of a new protocol. However, in a recent clinical drug trial, the PROWESS trial, a learning curve was found related to adherence to study protocol (Source of variability on the estimate of treatment effect in PROWESS trial: Implications for the design and conduct of future studies in severe sepsis. Macias, WL; Vallet, B; Bernard, GR; et al. Crit Care Med. 32(12); 2385-2391). The PROWESS trial was a double-blinded placebo-controlled, phase 3 trial evaluating the efficacy of drotrecogin alfa in adult patients with severe sepsis. The primary outcome measurement



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was mortality at 28 days (yes/no). There were a total of 164 sites involved in the study and a total of 1690 patients were enrolled. The study found an overall decrease in mortality with the administration of drotrecogin alfa. But the really interesting result came with further analysis based on protocol adherence. Patients with protocol violations did not have a decrease in mortality with administration of the drug, and the protocol violations were associated with the sequence of enrollment at each site. Furthermore, the treatment effect varied with the sequence of enrollment when protocol violations were included in the analysis.

This was not the case if protocol violations were removed from the analysis. These results present evidence that a learning curve was taking place in administering the study per protocol. This learning curve affected the mortality outcome. Why are these findings important to PECARN investigators? First, this was not an extremely complicated protocol. In fact, most protocol violations were associated with failures to administer the appropriate dose or duration for the study drug, as well as violations relating to the enrollment criteria. While PECARN moves towards more protocol-driven studies, even seemingly simple protocols, it will become crucial that a learning curve be taken into consideration. Investigators may want to consider giving time for protocol-specific experience, such as a run-in period. Prospectively defining analyses to examine such learning effects and to control or adjust for them should be undertaken. In fact, determining the amount of time for the learning curve to dissipate may also be an important finding of a study.

TBI Corner: Recent Bits of Information

Reporting Positive CTs

On page 1 of CRF 4 the first question asks about the initial CT. A positive CT (of any type – either from trauma or an incidental non-traumatic finding) should be marked as ABNORMAL on question 1b even if it is a non-traumatic finding.

- 1c. Is the question pertaining to any traumatic findings.
- 1d. Is the question pertaining to any non-traumatic findings.

For example, if there was a non-traumatic abnormality such as a brain cyst, and no traumatic findings.

1b. (Any findings at all?) should be marked abnormal, 1c. (Any traumatic findings?) should then be marked NO and question 1d. (Any-non traumatic findings?) should be marked yes- with a description of the cyst.

Remember, that scalp hematomas and fluid in the sinuses are NOT considered to be abnormal findings. If you have not been recording non-traumatic findings on CT as indicated above, please go back to the CT reports and fix this.

Reporting Protocol Deviations



Sites are not being asked to do anything extra that your IRBs are not already asking for in this minimal risk study. We are asking that you check with your IRB to make sure that you are doing what they call for, and determine whether or not they require you to report even minimal risk protocol deviations. The most frequent and typical Protocol deviations for this study are:

- 1) forgetting to hand out information sheet,
- 2) misclassifying ineligible patient as eligible or vice versa.

nodalnews

ACORN

- ACORN has had two promotions with Mike Shults taking a supervising position and Emily Kim taking on the role of Nodal Administrator. We have hired a new RA, Marlena Kittick, to take over for Emily at CHOP and look forward to Emily's high energy participation as the Nodal Administrator.
- ACORN has hired Shari Nichols to run the UC Davis Seizure efforts and

work with us in managing the Head Trauma Grant.

GREAT LAKES

- Here we grow! We are currently in the process of adding Children's Memorial Hospital in Chicago to the Great Lakes Node. The only freestanding children's hospital in Illinois, CMH is consistently ranked as one of the top children's hospitals in the U.S. We are

very excited to have them! The investigators bring to PECARN extensive experience in EMS-C research as well as some great new ideas. Besides, they're on a Great Lake!!

CDMCC

- The CDMCC would like to welcome Rita Gerard as the new PECARN site monitor. We are very happy to have Rita with us and know that she will be an asset to the Network.

PCDP Abstracts

Four manuscripts based on the PCDP data are currently in preparation. In addition, six abstracts were recently submitted for presentation to the Pediatric Academic Society and/or the Society for Academic Emergency Medicine meetings. Below is a brief synopsis of the abstracts.

Abstract	Objective	Conclusions	Author
1. Epidemiology of Pediatric Emergency Department Recurrent Visits	To describe the epidemiology of pediatric patients with recurrent ED visits.	A large number of pediatric ED visits are accounted for by a minority of patients with recurrent ED visits. Young children, those with public insurance, and some minority populations who visit the ED are at an increased risk for recurrent visits. Future evaluation of how these factors influence high ED utilization may improve patient care.	Elizabeth Alpern
2. Use of Geographic Information Systems (GIS) to Locate High Risk Areas for Injury Prevention	To determine whether there are high-risk census tracts for injuries requiring ED visits.	GIS mapping of readily available electronic data from hospital computer systems can be used to identify high-risk census tracts for community injury prevention efforts.	Jim Chamberlain
3. Disagreement in Pediatric Emergency Visit Diagnosis Information From Administrative and Clinical Data Sources	To determine the agreement on final diagnoses between two sources, electronic administrative sources and manually abstracted medical records, for ED visits in the nationwide Pediatric Emergency Care Applied Research Network (PECARN).	ED diagnoses retrieved from electronic administrative sources and manual chart review frequently disagree, even if similar diagnosis codes are grouped together. Agreement varies by institution and by diagnosis. Further work is needed to improve the accuracy of diagnosis coding; development of an EMSC-specific grouping system may be beneficial.	Marc Gorelick
4. Descriptive Analysis of Psychiatric Related Illnesses in PECARN	To describe emergency department visits for psychiatric related illness (PRI) in PECARN.	The PECARN data is consistent with national data indicating that PRI visits account for a significant proportion of ED visits and adversely impact resource utilization.	Prashant Mahajan
5. Variations in Diagnostic Testing in the ED for Pediatric Non-urgent Illnesses	To demonstrate variations in diagnostic testing in ED patients with non-urgent diagnoses.	Institutional practices may be more important than provider training, staffing models or hospital characteristics in determining diagnostic testing rates in children with non-urgent illnesses. Potential areas for future research include benchmarking diagnostic testing in well-defined risk groups and adherence to accepted testing guidelines.	Rachel Stanley
6. The Epidemiology of Children With and Without Health Insurance Seeking Emergency Care in the Pediatric Emergency Care Applied Research Network	To describe and compare the subset of patients identified as lacking health insurance to insured children in the PCDP.	Uninsured children were more likely to use the ED for non-urgent problems and to have ED diagnoses related to lack of access to non-ED care. Children with chronic diseases presenting to EDs were more likely to be insured. Further study of uninsured children seeking care in EDs may provide additional information and insight into this vulnerable population of children.	James Tsung

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. The group has been working on cleaning data and obtaining missing data elements from all five sites, as well as drafting the first set of abstracts for submission in the Spring of 2005.

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 sent it to HEDA sites for completion. Additionally, the C-spine proposal previously submitted to PCRADS is submitted an EMSC targeted issues grant. 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: At the beginning of year 2005 we crossed the 10,000 patient mark! RAs have worked hard to get caught up with data entry and reporting, which has allowed us to perform another interim quality control data analysis in January. We are currently capturing 80% of eligible patients. All sites are currently being monitored/ audited. The site visits will be completed by February, at which point we will re-assess the accuracy of capture rates. We are currently planning our first CQI/Trauma Registry/Morgue checks on patients who left the ED and were unable to be contacted. We continue to ask each site to reinforce the importance

of complete data forms. We also urge each site to remember to motivate all those involved in carrying out the Head Trauma Study. Due to everyone's great work and collaboration we continue to see great success with this study.

Bronchiolitis Study: The Bronchiolitis season has officially started across the country. All 16 sites are busy screening and enrolling patients. We have already enrolled 60 patients of the 300 patients we anticipate enrolling this season. On January 1st we received a notice of grant award from The Health Resources and Services Administration to fund the Bronchiolitis Study for two years.

Hypothermia Study: The eligibility period for Hypothermia ended December 31st, and we are now focused on data submission and cleaning. As of the first week in January, almost 300 records have been entered into the database. The first round of data queries went out in December and the sites have been quickly resolving them. The goal is to have all eligible patients captured in the database by the end of March. Once all of the data is in, a second round of queries will be sent. Kudos to the Hypothermia Investigators and Abstractors - the end is in sight!

PECARN Core Data Project: The ongoing annual collection (2003-2007) of PCDP electronic data is now in progress. Sites should have already submitted IRB renewals or addendums in this regard. The deadline for the initial submission of 2003 electronic data to the CDMCC is March 15, 2005. Please direct any questions regarding this process to Libby Alpern at alpern@email.chop.edu.

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: Use of Lorazepam for Pediatric Status Epilepticus: A Double-blinded Randomized Diazepam Controlled Clinical Trial: The NIH issued a request for proposals (RFP NICHHD-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 is the first in a series of RFPs that will be issued by NICHHD under the BPCA. The contract was funded September 30, 2004 and has 11 participating PECARN sites.

The contract is divided into a pharmacokinetic (PK) study and a efficacy study comparing Lorazepam and Diazepam. The efficacy study will be awarded after successful completion of the PK study. Thus far, progress has included submission of an Investigational New Drug (IND) application to the FDA, formation of the Pediatric Off Patent Drug Study (PODS) steering committee, and submission of the protocol at all 11 IRBs. An investigator meeting will be held in conjunction with the PECARN steering committee meeting in January 2005.



eRoom

PECARN Core Data Project: <https://www.nedarcssl.org/eRoom/nddp/PECARNCoreDataProject>
 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 Controlled Trial
 Clinical Decision Rules for Identifying Children at Low and High Risk for Traumatic Brain Injury

newfaces

Vijay Verma, RA



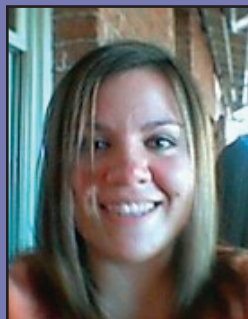
Vijay Verma currently serves as the Project Research Assistant for the Center for Pediatric Emergency Medicine, assigned to the Bellevue Hospital HEDA of PEDNET. He graduated from Binghamton University with a Bachelor of Science degree with a concentration in Finance. His previous experience includes working with Goldman Sachs where he was a Analyst with the Information Security group working in New York and London. Vijay returned to school and worked on his Post Bacc requirements at NYU to prepare for a career in Medicine. He is also a Bellevue PAVERS volunteer and begins his EMT coursework in January.

Cicely J. Augustine, RA



Cicely J. Augustine, a native of New Orleans, LA, has recently relocated to join CARN in Washington, DC as a research assistant. Cicely graduated from Xavier University of Louisiana with a Bachelor of Science in Psychology. She recently earned a Master's of Public Health from Tulane University School of Public Health and Tropical Medicine. She is dedicated to improving the health of children and adolescents through advocacy, education, and research. She aspires to return to graduate school to obtain at Doctorate of Public Health. Although this young lady is very focused on her work don't let her fool you. She can cut a rug when it comes to dancing. We've heard she's quite an actress too. She'll be performing in a major stage play this spring.

Marlena Kittick, RC



Marlena Kittick is the new Research Coordinator for the Division of Emergency Medicine at CHOP/PECARN RA. She recently relocated to Philadelphia from Tucson, where she spent the last five years. Born and raised in NY; attended college at Cornell University and received her MPH from the University of Arizona. Loves to travel (has been to Europe twice), and enjoys museums, plays and wine tasting.

Katie Whorf, RA



Katie Whorf graduated this past May from Bates College in Lewiston, Maine with a BS in Biology. She is currently a full time Masters in Public Health student at the George Washington University. Her concentration is Maternal and Child health. Katie is originally from Bloomfield Hills, Michigan. She enjoys working for CARN and plans to attend medical school within the next few years.

Rita Gerard, PECARN Site Monitor



I am thrilled to have landed the job as PECARN site monitor. When I was a site coordinator, my favorite projects were always investigator initiated studies, so I am happy I now get to monitor that type of study. Another benefit of my job is sky miles! I have a personal goal to step foot on each of the seven continents. I have three more to go, and with the sky miles I will earn visiting you all, I hope to attain my goal in short order. I think Antarctica will be the

toughest. I hope you will feel free to use me as a resource for your compliance and data collection questions. I can be reached the following ways: email rita.gerard@hsc.utah.edu or phone-801-587-7550. I look forward to meeting you at my site visits!

Good Clinical Practice Tip

Q) Given the importance of raw data and text as an original records, can clinicians make corrections to, or insertions in, raw data or text?

A) Yes. Source data, however, must be relatively permanent and be protected from unauthorized changes. When changes to raw data are necessary, they must not obscure the original values. Whiteouts, redactions, and similar attempts to obliterate the original data are unacceptable. Although the clinician's intent in making the changes may be benign, an FDA inspector could view such alterations as an attempt to obscure the real data, and might

even suspect fraud. Four elements must be visible each time a raw data value is changed:

- the old value
 - the new value
 - the date and time of the change; and
 - an identification (e.g., initials) of the person making the change.
- In making a change, a clinician should simply draw a single line through the original value, record the new value and the date, and initial the change."

Reference: Good Clinical Practice: A Question and Answer Reference Guide. June 2003. Douglas Mackintosh, Dr.PH, MBA, MS Hyg, GCPA, Inc. Vernetta J. Molloy, MBA, RN, GCPA, Inc. and Mark P. Mathieu.

Assessing Diagnostic Accuracy when no Gold Standard is Available



CLAY MANN, PhD, MS
Research Director

In the process of conducting research, investigators often rely upon professional judgment when determining how well a novel intervention detects physiologic anomalies or some type of lesion. For example, a study may utilize radiologist's impressions (as the "gold standard") to determine if a novel CT enhancement increases diagnostic accuracy. An obvious problem with this approach is the known variability in professional judgment. Nevertheless, a true gold standard (such as surgical results) may not be available or impossible to obtain.

In the absence of a true gold standard, a variety of techniques have been suggested to increase the accuracy of professional judgment. Most of these techniques employ some method of aggregating the opinion of several experts. For example, a majority opinion among a group of experts may be assigned to a particular CT scan, in essence creating a standard by fiat. Although an interactive process may lead to classifications that are more accurate than those of an individual, interactive techniques are not optimal, because responses are not independent and may be influenced by interpersonal dynamics.

The simple aggregation (or a

majority rule) of independent responses has been advocated as a means to combine the opinions of several experts. Advocates continue to publish research suggesting that the accuracy of independent assessments is a function of the number of raters and the level of agreement between them. This relationship was formally described almost a century ago and is known as the Spearman-Brown Prophecy Formula.(1,2)

Probably the most appropriate and established statistical model for combining several independent dichotomous ratings for a single case is a restricted two-class latent structure model.(2) This model utilizes a maximum likelihood algorithm to evaluate patterns of agreement among raters to accurately predict the correct diagnosis for each case. An obstacle to utilizing latent structure models is the large number of cases that must be assessed by even a few raters to statistically test the resulting model. For example, a two-class latent structure model generates $2N$ possible response patterns where N represents the number of raters. The sample of test cases must be large enough to compare estimated frequencies of each possible response pattern to observed frequencies using a likelihood Chi-square statistic. Other candidate statistical procedures such as multiple discriminant analysis, mixture distribution models and neural networks also require large samples of test cases.

Consensus theory is an attractive alternative model for predicting the correct diagnosis of test cases from the independent opinion of raters when no adequate standard is available.(3) Consensus theory approximates findings based on a

restricted two-class latent structure model, but may be applied when a much smaller sample of cases is available. In essence, consensus theory provides a method of pooling information provided by raters to select the most likely "correct" diagnosis and assess the degree of confidence in that selection. To accomplish this, for each case assessed, the consensus model estimates the competency of each rater by comparing each rater's response to the responses of all other raters. A rater is considered more "competent" if his or her answers are more often in agreement with those of the majority. The model then uses estimates of rater competency to weight each rater's responses. Using Bayes' theorem, the model uses weighted responses to estimate the most likely correct diagnosis for each case. Published simulations indicate that consensus model estimates of rater competency and case classification vary by less than 10% when simulated raters express extreme bias in their responses.(3)

In sum, even when no real gold standard exists, robust statistical techniques are available to optimally aggregate clinical impressions provided by experts to precisely diagnose test cases or assess research findings.

References:

1. Spearman C. Correlation calculated from faulty data. *Br J Psychol.* 1910;3:271-295.
2. Brown W. Some experimental results in the correlation of mental abilities. *Br J Psychol.* 1910;3:296-322.
3. Uebersax JS., Grove WM. Latent class analysis of diagnostic agreement. *Statistics In Medicine*, 1990;9:559-572.
4. Weller SC and Mann NC. Assessing rater performance without a standard using consensus theory. *J Med Decision Making*, 1997;17:71-79.

Exception from Informed Consent for Emergency Research

As described in our last PECARN newsletter, 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).

There are instances in which research involves greater than minimal risk and offers the prospect of direct benefit to the individual, the second category listed above. What happens when it is impossible to obtain consent because the parents or guardians are simply not available, and the therapy is of an emergent nature?

A PECARN study concerning hypothermia after cardiac arrest is one example. If it will be generally infeasible to communicate with parents and obtain their permission before a therapeutic intervention in a critical emergency, then the hypothermia investigators would have to obtain an exception from informed consent for emergency research (21 CFR §50.24). There are seven requirements that must be documented by any IRB that grants such an exception: (1) the human subject must be in a life threatening situation, available treatments are unproven, and the study is needed to determine safety and effectiveness of the intervention under study; (2) informed consent is not feasible; (3) participation offers potential direct benefit to the human subject; (4) the study is not practical without the exception; (5) the length of the therapeutic window is based on scientific evidence and the researcher will attempt to obtain parental permission during that window, if possible; (6) informed consent procedures and documents are available when their use is feasible; (7) additional protections will be provided, including community consultation,

public disclosure, and establishment of a DSMB. We discuss an approach to community consultation and public disclosure, the most unique aspects of this regulation, toward the end of this article.

The application of 21 CFR §50.24 in children poses interesting problems, as the regulations do not mention the age of research subjects, and concepts of parental permission and child assent are not considered. This probably was important in the somewhat difficult confusion concerning the seizure study being directed by Dr. Chamberlain for a subset of PECARN sites.

To facilitate community consultation, each clinical site mails letters to community leaders, provides newspaper and radio advertisements, and conducts formal public meetings in the community. The letters and advertisements indicate the purpose of the trial, the need for waiver of informed consent, and include an invitation to the public meetings. Specifically invited participants might include community members with medical conditions most likely to be affected by the trial (e.g., persons with families affected by cardiac arrest). Meetings will include a brief presentation by study investigators, followed by open forum discussion (community consultation). Content for the community presentation may include 1) background information on cardiac arrest; 2) current lack of effective treatment; 3) profile of the typical study patient; 4) description of the protocol; 5) rationale for hypothermia; 6) what randomization means; 7) potential study risks; 8) potential study benefits; 9) differences between research and treatment; 10) why waiver of informed consent is needed for this study; and 11) ethical constructs of waiver of consent. Minutes of the meeting will be transcribed and the meeting may be video taped for later review. The meeting participants will be asked if the meeting represents adequate community consultation. If not, additional public meetings will be scheduled.

To address public disclosure issues, investigators at each clinical site will



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Principal Investigator

formulate a local steering committee to oversee the process of public disclosure before and after the study is completed. That committee is selected to fit the demographic profile of the community and families of potential study subjects, and includes community members, scientists, representatives from local organizations and others to represent the broad interests of the community. The committee will determine methods for public disclosure of the study, such as public service ads in the local and community newspapers prior to study initiation, and audio and video announcements to local radio and television stations. Each clinical site provides assistance to the local committee to coordinate these public disclosure activities. The local medical community will be informed of the research study using Grand Rounds, medical conference presentations, and publications. Each site must provide a 24-hour telephone number to facilitate communication between community members and lead investigators.

It is obvious that this is a difficult process, and in our experience with the Public Access Defibrillation (PAD) trial (Clay Mann was PI), conducting community consultation and public disclosure, and subsequently obtaining IRB approval, will require at least one year. In the PECARN network, a decision to seek an exception from informed consent should require approval at several levels, including the Steering Committee, the DSMB of the study, and the MCHB and other funding agencies. As part of the process, we would propose that the Steering Committee and the protocol working group involve nationally recognized bioethicists with expertise in pediatric clinical research, as suggested in a recent IOM report entitled "Ethical Conduct of Clinical Research Involving Children."

Federal Corner

Welcome to the Federal Corner! This new feature will provide the PECARN community with federal resource information, tips & updates about the federal EMSC program which are pertinent to the successful functioning of the PECARN. This inaugural edition introduces the EMSC program in the context of the federal government, including a very brief overview of the federal support for PECARN's infrastructure, followed by some resources to assist you with research and funding opportunities. Remember, with a little help, it is possible to successfully navigate the labyrinth of our federal bureaucracy!

EMSC Program "in a Nutshell"

The EMSC Program was created in 1984 by authorizing legislation sponsored by Senator Daniel Inouye, D-HI (co-sponsored by Senator Orrin Hatch R-UT and then Senator Lowell P. Weicker, Jr. R-CT). The following year, the EMSC Program received its first federal funding appropriation of \$2 million. The FY 2004 appropriation is \$19.8 million. The EMSC Program was conceived as a national initiative designed to reduce child and youth disability and death due to severe illness or injury; and to ensure that all ill and injured children and adolescents receive state-of-the-art emergency medical care. The Program defines "children" as ages 0-21 years. The focus of the program is extensive and called the EMSC "Continuum of Care." Topic areas include:

- Injury and Illness Prevention
- Bystander Care
- Dispatch
- Prehospital EMS
- Hospital care
- Rehabilitation
- Community

Alphabet Soup of Agencies & Acronyms

Many of you may wonder where the EMSC Program belongs in the great wide world of the government? We'll take it from the top: at the Presidential Cabinet level (headed by a presidential appointee, whose title is "Secretary") you will find the Department of Health and Human Services (DHHS). Some of the many agencies administered by DHHS include the National Institutes of Health, the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), the Food and Drug Administration (FDA) and Center for Medicare and Medicaid Services (CMS). The Health Resources and Services Administration (HRSA), led by Elizabeth Duke, PhD, is also one of these DHHS agencies. Under HRSA you will find the Maternal and Child Health Bureau (MCHB), led by Peter Van Dyck, MS, MD, MPH. Within MCHB is the Division of Child, Adolescent, and Family Health (DCAFH) directed by David Heppel, MD. The EMSC Program is located within this Division and is staffed by Dan Kavanaugh, MSW, LCSW-C and Tina Turgel, BSN, RN-C. Ivy Vedamuthu, MPH is a Dr. Vince L. Hutchins Public Health Fellow detailed to the EMSC Program through June of 2005.

The EMSC program works collaboratively with the Department of Transportation's (DOT) National Highway Traf-

fic Safety Administration (NHTSA), EMS Division. This Division is headed by a long-time friend of the EMSC program, Mr. Drew Dawson (formerly the State EMS Director of Montana). Another NHTSA EMS staff member you all should know is Ms. Susan McHenry, the project officer on the NEMSIS (www.nemsis.org), the National EMS Research Agenda (www.researchagenda.org), and other very important current and former EMS/EMSC research projects. Drew and Sue are at all the EMSC grantee meetings and other EMS/EMSC research venues as well (e.g., NAEMSP, ACEP, etc.).

The cooperative agreements that form PECARN are jointly administered at HRSA/MCHB by the EMSC Program and by MCHB's Division of Research, Training and Education (DRTE), headed by Dr. Ann Drum, DDS, MPH. The Maternal and Child Health Research Program (MCHR), within DRTE is directed by Dr. Stella Yu, Ph.D. Ms. Hae Young Park, MPH, is the public health analyst within MCHR who works closely with the EMSC Program in managing PECARN.

So, What about the PECARN?

The Regional Node Centers which make up the PECARN are supported by the Network Demonstration Development Project (NDDP) grants, awarded by the EMSC program in 2001. PECARN was "born" as a Network at the first steering committee meeting in Washington D.C. in January 2002. The Central Data Management and Coordinating Center (CDMCC) cooperative agreement was awarded to the University of Utah in 2002. Now for posters and presentations, PECARN members are asked to acknowledge funding for the network with:

The PECARN is supported by HRSA/MCHB/EMSC Program grants numbered: U03MC00001, U03MC00007, U03MC00006, U03MC00003, U03MC00008.

In 2005, the EMSC-NDDP cooperative agreements will be recompeted. The grant guidance for this competition is scheduled to be released February 1, 2005. Look for it on the HRSA funding opportunities website (<http://mchb.hrsa.gov/grants/default.htm>) and on the EMSC Research listserv (see EMSC Technical Assistance, below).

EMSC PROGRAM RESOURCES AND TECHNICAL ASSISTANCE: Research & Funding Resources

One group important to the PECARN which is coordinated by the EMSC program is called the federal Interagency Committee on EMSC Research (ICER). These Committee members are federal agency staff from AHRQ, CDC, FDA, HRSA, NIH and other agencies who are interested in EMSC-related research issues. Several of them are strongly committed to the cause and facilitate RFAs and PAs which are very relevant to the PECARN community. Many ICER members have presented at EMSC meetings on workshops and panels, and at the PECARN meetings as well. For example, Dr. Bill Rodriguez presented in September at PECARN, and in the past other ICER members have presented at PECARN discussing research funding opportunities at their agencies. The ICER meets about three times a year in Washington D.C.

spotlights

KATHLEEN LILLIS, MD (PED-NET)



Kathleen A. Lillis is a Clinical Associate Professor of Pediatrics and Emergency Medicine at the Children's Hospital of Buffalo. She works in the Pediatric Emergency Department at the Women and Children's Hospital of Buffalo, where she has served as Chief of the Division of Emergency Medicine for nine years. In July 2003, she stepped down as chief to pursue her research interests, and has numerous publications and presentations in the areas of childhood injuries, emergency medical services and asthma management. Kathy holds a Medical degree from the State University of New York (SUNY) at Buffalo School of Medicine and Biomedical Sciences. She completed a Pediatric Residency at Rainbow Babies and Children's Hospital and a fellowship in Pediatric Emergency Medicine at St Louis Children's Hospital. Kathy's husband Mike has a Ph.D. in Organizational Behavior and is an Associate Professor at Medaille College. They have five children ages 11, 9, 7, 4 and 3 months.

EMILY KIM, MPH (ACORN)



I have really enjoyed the past 1 1/2 years working for PECARN at CHOP, and am looking forward to learning and growing within the network as ACORN's new nodal administrator. I just moved from Philadelphia to Davis, and believe it or not, I'm still cold all the time! I am a University of California junkie; I earned my BA in Ethnic Studies at UCSD, and then my MPH in Community Health Sciences at UCLA. I am in the process of formulating my research interests, but have dabbled in Minority Health and Gerontology (am I in the right network?). I've been married for about 2 years.

Investigator Responsibilities

The following tips were adapted for PECARN from "A Guide to Good Clinical Practice," Vol. 12 #4 Jan 2005. This list comes from a former FDA inspector and summarizes the most important Dos and Don'ts for clinical investigators who want to stay in compliance with FDA and Good Clinical Practice (GCP) regulations. Following these guidelines will also help prepare you for a PECARN or other type of site monitoring visit. Although these items were described as a "to do" list for investigators, many of the tips are appropriate for RAs as well.

What Clinical Investigators Should Do:

1. Be qualified - be able to provide details of education, training and experience that qualifies the investigator to conduct the study. For PECARN this means on site training as well as what is provided at the training meetings.
2. Provide adequate training for staff and determine whether staff is overworked or under-trained. Provide remedial training as necessary.
3. Have knowledge of your responsibilities in conducting a clinical trial. Know the consequences of failing to fulfill those responsibilities.
4. Adhere to responsibilities set forth in the Investigator Responsibility form or in the 1572.
5. Personally conduct and supervise the study.
6. Maintain documentation of specific study related tasks that are delegated to others (Staff responsibilities list in the MOO). This should be up to date and accurate.
7. Submit progress reports to the IRB at specific intervals per your local IRB.
8. Document that all serious adverse events (SAE) were appropriately reported to the sponsor per the study proto-

col. Follow your local IRB rules for reporting.

9. Retain all records pertinent to the study including electronic records.
10. Maintain accurate records to document study drug accountability.
11. Record clinical data using the ALCOA principle-Attributable, Legible, Contemporaneous, Original and Accurate. Data must be "attributable" meaning it is clear who first recorded it; "contemporaneous"- meaning that information is being recorded as it is being observed; and "original" meaning it is clear where the original information located. (medical record, etc)
12. Maintain and audit trail created in real time to document the rationale for the changes to the original data. This means that changes to original data must be timed and dated clearly and legibly so there is no suspicion that changes were fraudulent. Sometimes sloppy corrections can be interpreted as fraudulent data in FDA inspections.

What Clinical Investigators Should Not Do:

1. Over-delegate responsibilities to non-physicians. For ex: relatedness of AE or decisions about subject eligibility
2. Erase, white-out or obliterate and original data entry either in case report forms or source documents.
3. Accept suggested changes from monitors to study data without checking source documents or without justifying such changes.
4. Blame anyone for inaccuracies in the CRFs
5. Forget to obtain IRB approval of informed consent revisions
6. Destroy any required study records

PECARN on the Road...

With several studies in progress, site monitoring is in full swing. The following sites have been visited over the past several months.

CDMCC Visits

John Hopkins
Children's Hospital of New York
Children's Hospital of Philadelphia
Children's of Michigan
Children's National Medical Center
Primary Children's Medical Center
Washington University / St. Louis Children's

Nodal Administrator Visits

John Hopkins
Howard County
Children's of Michigan
Children's Hospital of Buffalo
Upstate Medical University
Children's National Medical Center
St. Barnabas Health Care System
Bellevue Hospital Center
Morristown Memorial Hospital

Study Monitoring

Study Monitors are employed by the research study sponsor (in this case PECARN) to help assure adequate protection of human subjects and quality of the data being submitted. Study monitoring needs increase based on the risk to the subject, study complexity, number of sites, and amount of data to be collected.

A number of sites have asked what I will be looking at when I come to visit.

As much as possible, I will outline what I will be reviewing in my monitoring announcement letter. However, I will not be limited to the outline in the announcement letter. On some visits I might interview the RA or PI regarding study processes. I may request a site tour. I will usually request that the following documents be available:

1. Essential Document Binder including:

- Curriculum Vitae Medical License (s)
- Documentation of GCP training (Participating Physician Agreements)
- IRB Approval Letter (s)

- IRB Correspondence
- IRB Membership Roster & FWA # (Available through your IRB Office)
- 2. Case Report Forms & Source document files
- 3. Complete Patient Medical Records
- 4. Study Drug records
- 5. Manual of Operation

I will consider the following scenario when monitoring a site: Let's say that the data or compliance at a particular site is questioned by the Federal Government at some point after the study has been completed. Let's also say that the site staff members that performed the study have relocated to a remote tropical island and are now SCUBA guides. In that case, I would want to feel comfortable that an auditor from the Federal Government would go to the site and have enough documentation to endorse our data and compliance practices. I would also want to visit that remote tropical island...

by Rita Gerard

Federal Corner Continued...

Isabelle regularly posts to the Grant Resources e-room updates received from the ICER group, including ICER members' contact information. The new Program Announcement on EMSC Research (the original one expired recently) completed by several ICER members is scheduled for release to the NIH Guide to Grants and Contracts. When this occurs, Isabelle will post it to the e-room and send it out on EMSC Research Listserv.

Remember there are several valuable federal research resources available at AHRQ, CDC, FDA, HRSA/MCHB, the NIH and the Office of Human Research Protection (OHRP):

- AHRQ (www.ahrq.gov)
- CDC (www.cdc.gov)
- FDA (<http://www.fda.gov/>)
- HRSA/MCHB (<http://mchb.hrsa.gov/research/>)
- NIH (<http://www.nih.gov/science/>)
- OHRP (<http://www.hhs.gov/ohrp/children/>)

EMSC Technical Assistance

The Federal EMSC Program
(<http://mchb.hrsa.gov/programs/emsc/>)

- Dan Kavanaugh, MSW, LCSW-C, Director
(301) 443-1321 or dkavanaugh@hrsa.gov
- Tina Turgel, BSN, RN-C, Nurse Consultant
(301) 443-5599 or cturgel@hrsa.gov

The EMSC National Resource Center (NRC) – Contract with federal EMSC Program (www.ems-c.org)

- Isabelle Melese-d'Hospital, Ph.D., Research & Program Analyst,
(202) 884-6861 or imelese@emscnrc.com
- Send a message with your Name, Title, Institution and phone number to emscresearch@emscnrc.com to join the EMSC Research Listserv
- Michael Tunik, MD, mt12@nyu.edu, (Center for Pediatric Emergency Medicine (CPEM) www.cpem.org)

The National EMSC Data Analysis Resource Center (NE-DARC) – Cooperative agreement with federal EMSC Program.
www.nedarc.org

- Michael Ely, MHRM, Director
(801) 585-9761 or michael.ely@hsc.utah.edu