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ILLU *clinical trials*

Growing Together

Contributed by Linda Wu, Director — Clinical Trial Center

As we reflect on 2011, we are pleased to report that it was a year full of many highlights, including an increase in the number of contracted clinical trials, improved processing times, a campus-wide research billing workshop, more vibrant Coordinator Networking Group meetings, and a successful billing audit.

The CTC continues to build a partnership with research coordinators across the institution and functions as a resource center to serve their needs. In addition to this ongoing support, the CTC is prepared to support the professionalization of our clinical research sites by hosting clinical trial toolbox courses for study coordinators and supportive research staff this year. The first hands-on workshop will be held on February 24, 2012, and is further detailed in this issue. Furthermore, regular meetings with research departments, including principal investigators and coordinators, to brainstorm solutions for quality research activities are being conducted. We are pleased to observe improved subject enrollment and study monitoring reports as the result of this effort.

Looking toward the future, there is a more rigorous qualification demand on study personnel for new drug and device approvals, which is tied to an increasing complexity of study design. These changes bring us to the realization that the need for committed investigators and qualified research coordinators is more critical now than ever before. Thus, CTC's main focus this year is upon professionalizing the clinical research site. Only when we conduct quality clinical trials which meet enrollment goals and maintain a strict adherence to the study protocol, then trust can be built and the institution's reputation can be established for future trials with the sponsor.

In addition to the development of industry sponsored clinical trials, the CTC is entering our third year projected development milestone and will begin building expertise to assist with investigator initiated clinical trials. The downturn of the economy is making research grants more difficult to obtain so all avenues of grant sources (government, foundation, and industry) will need to be explored. Our goal is to grow our expertise in this area in the next five years by partnering with interested investigators in obtaining funding support and by providing assistance and/or facili-



tation in protocol development, project management, regulatory submission, FDA application and data management. We encourage clinical investigators who are interested to begin your own clinical trials to contact us.

For 2012, we look forward to embracing another year of growth with our investigators and coordinators. We look forward to building professional clinical research sites on campus that meet enrollment goals and maintain accurate and complete study data with no protocol violations. We also hope by partnering with committed clinical investigators, more quality investigator-initiated clinical trials will be conducted on campus.

As always, we are here to serve you. If you have any questions, comments, or suggestions, please do not hesitate to contact our office.



TRIAL TRIVIA

Q: What if a potential subject, that is not currently a Loma Linda patient comes in for a screening visit?

A: When a new patient is present for a screening visit for a clinical trial, they must be registered as a patient to complete the required research documentation.

Q: Who do I contact for ancillary support pricing requests?

A: Contact the CTC at extension 15002 or clinicaltrials@llu.edu.

Coming soon!



The CTC is proud to announce that a clinical trial coordinator toolbox workshop will be offered on Friday, February 24, 2012 from 8:00 a.m.-2:00 p.m. in Mountain View Plaza. The clinical trial coordinator

toolbox is a class designed with a focus on theoretical and practical knowledge of patient management in clinical trial studies. The participants will receive lecture as well as hands-on instruction, which will provide information highlighting regulatory document management, study subject management, study advertising guidelines, patient recruitment guidelines, and retention strategies. The explanation of clinical trial study forms, samples of forms, and managing your study files will be included with the class. Any clinical research coordinator or medical office that is involved in clinical studies interested in enhancing their clinical trial study management skills and learning useful tools should attend this class. Four CEU credits will be offered for this course.

To register for this course, visit the [Owl Portal](#) and self-register using the keyword “toolbox.” The course fee is complimentary to LLUHS employees, \$60.00 for LLU students and faculty, \$80.00 for AHS members and \$120.00 for all other participants. [CITI GCP training](#) is an encouraged pre-requisite for the course.

Speakers will include:

Lila Dalton, RN, BSN, CCRP -- Associate Director, Clinical Trial Center

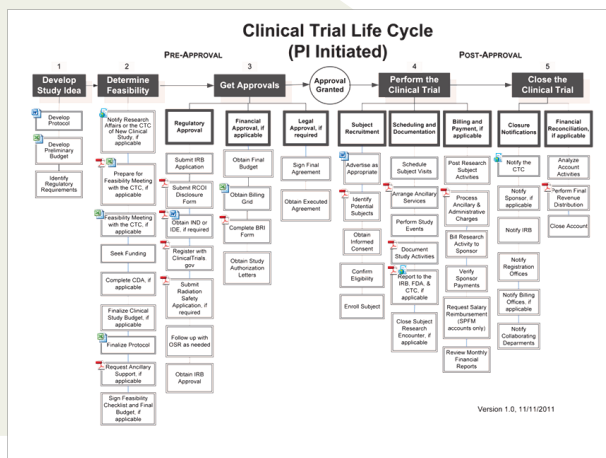
Mary Ann Nyc, BS, MPH(c) -- Regulatory Affairs Coordinator, Clinical Trial Center

Objectives:

- Understand the required elements of regulatory documents for a patient under a clinical study.
- Describe study subject management techniques and how they contribute to a smooth-running and compliant research study.
- Identify effective subject recruitment and marketing strategies that meet required standards.
- Assemble a regulatory binder to serve as a sample of the maintenance of regulatory documents.

ctc website updates

- Regulatory Management
 - [Regulatory Management](#) has been added to “Our Services”
- PI-Initiated Clinical Studies
 - An interactive [PI-Initiated Clinical Study Life Cycle](#) has been added to “Manage Your Trial”



Clinical Trial / For Clinical Researchers / Manage Your Trial

Processing a clinical study from onset to completion is a complex project. Careful planning is crucial in order to avoid any delays. This section acts as a hub for clinical study processing, and is designed to provide investigators and their staff with a comprehensive outline and detailed steps of the required processes in order to achieve the successful and efficient conduct of clinical studies.

The CTC provides information for two types of clinical studies: Industry-Sponsored and PI-Initiated. There are differences and similarities in processing these types of studies.

To start a new clinical study or manage an ongoing study, please select the appropriate study type:

Industry Sponsored Clinical Studies

PI-Initiated Clinical Studies

investigator zone

Contributed by Emmanuel Katsaros, D.O. — Physician, Rheumatology

A tropical breeze hits me as we walk with our tour group down a long narrow path in a remote area of Viti Levu, Fiji. Yes Fiji. It was a great adventure, which my wife won after buying an opportunity ticket for a community-based volunteer organization. I loved this trip, and not just because it was free. Viti Levu, is a serene lush island, that is easy to travel to and a real pleasure for the senses at every turn of the road, vistas to admire and secluded beaches to uncover. The path leading down to the river was the start of a kayak tour, which was filled with various bird calls, the sounds of rustling leaves and palms, the deep greens of the landscape, and the smell of flowers. Upon arrival at the riverbank we were met by our guides, with helmets in their hands. Yes, helmets. Now, I have gone kayaking before, but never on any body of water that required protection for my cranium. What happened to serenity?

As we got on our way after a brief safety training overview, we proceeded through a lovely grotto and then the wild rapids. We had expert guides leading us through crops of jagged rocks, yet many in our party lost their oars and or capsized. Luckily, no one got injured and everyone enjoyed the day.

I tell this story because my experience as a researcher involved in my first investigator-initiated study is similar to this kayak trip. Both adventures require an expert guide to navigate sometimes treacherous waters, but overall they are very enjoyable experiences.

My research project started with an idea to see whether a drug intervention can improve fatigue and quality of life in lupus patients, even though the literature tells us that immune-altering medications have not made such improvements despite disease control. I took this concept to the American College of Rheumatology national meeting and looked for possible funding from pharmaceutical companies. One company was interested, and I pitched the idea to their representative, not unlike a screen writer may interact with a producer. I wrote a proposal which was approved, and then I was asked for a more formal and detailed proposal. It was a lengthy process.

It was not the literature review, nor the statistical methodology development that was daunting; it was designing a study that could answer the research question in a *practical* manner. One suggestion to accomplish this is to develop a timeline that would be sensible for yourself, ancillary staff and most of all the patients that you hope to recruit. The patient must feel comfortable with the time commitments you are requiring. Questionnaires must not be too long, and intervals between appointments should be appropriate for their condition. I did not want patients coming into clinic more frequently than what was normally required to monitor their disease. The study timeline should also not drag on too long, which makes recruitment easier.

As the principal investigator, one feels the responsibility of designing a successful study, which depends heavily on well designed and *practical* inclusion and exclusion criteria. The inclusions and exclusions must not be too liberal or restrictive. The researcher has a responsibility to successfully recruit patients, which provides a temptation to be too liberal, yet at the same time being a patients' advocate may make the exclusions too restrictive. The researcher must make exclusions that respect patient safety, and not allow for uncontrolled medical conditions or concomitant medications that could confound the variables you are studying. This is a delicate balancing act that is best managed by discussions with your colleagues to assess the practicality of this important part of your project.

When I received the "letter of congratulations" stating that I was awarded the grant, I felt both the serenity of the grotto I kayaked as well as the thrill of the rapids I managed to navigate. Of course, I was guided through my experiences, and my guide through my first research adventure was the Clinical Trials Center. The first tool I was given to launch the study was the "Clinical Trial Feasibility Checklist," which analyzed the protocol and the Rheumatology Division's infrastructure to determine if my research project could be successful. The many questions that needed to be answered

included: Did I have the right study population? Did I expect significant adverse events? How was I assessing compliance? Are the dosing regimens too complex? Etc. This process transformed the protocol into a practical document and allowed me to organize the staff, equipment, schedules and medical services to carry out the protocol.

The guided tour continued with budget development. Inclusions in the budget consist of start-up fees and adequate reimbursements for the time of physicians, research assistants, nurses, ancillary medical services and patient travel/time. Is the sponsor paying for the monitor? You will likely have to hire a monitor to assess the compliance with your own protocol, and this monitor cannot be a colleague within your division. Behind the scenes supporting your adventure is the budget negotiation with the sponsor. I was grateful not be directly involved in this task. For me, negotiations simultaneously takes patience and the ability to be good at poker, neither of which is my forte.

The tedious parts of my research trip included developing my own source documents, and applying for an Investigational New Drug Application number (which definitely needs our friendly CTC guides). Another less interesting task was entering the project into the clinicaltrials.gov website. This is basically an advertisement on the web, but when you update your study's webpage to say that the project is "currently enrolling," there is a sense of satisfaction.

Once the study is underway, be certain to talk nonstop about the study and annoy your colleagues, fellows and residents on rotation, which is critical to successfully recruit patients. People must get sick about hearing of your project. I knew I was successfully irritating others when my fellow proposed that I wear a T-shirt to clinic featuring the inclusions in the front and the exclusions on the back.

The sometimes unpleasant job of promoting the study was offset by the gratitude of the research patients. The many touching comments by study participants include: "I want to find out why I have so much fatigue," or "If I can help others, I will always be glad to volunteer," as well as "Being part of research is why I came to a university for treatment." Finally, another participant was so happy to be involved in a study that she made a cash donation to the Rheumatology fellowship endowment fund.

In summary, the research adventure has been exhilarating and satisfying, much like the twists and turns of a Fijian river. However, a pleasant journey takes much preparation and an experienced guide like the Clinical Trial Center's staff.



Department Highlights

Research Integrity

Contributed by the Department of Research Integrity

Research Integrity is a primary source of support to LLU researchers, staff, and faculty and the various research regulatory committees in identifying, understanding and complying with federal and state statutes, regulations and guidance from an array of agencies as well as institutional policies and procedures. We provide surveillance of the legal and regulatory environment potentially impacting research. We conduct audits to diagnose compliance risk areas, and design and foster corrective actions for issues that are found. This audit process is integral to Loma Linda University's delivery on its promise to conduct all facets of research in accord with the highest ethical standards, in keeping with core values.

Specific services include:

- Conduct routine research compliance audits. The results empower researchers with the knowledge and tools necessary to promote compliance and effectuate continuous quality improvement.
- Investigate and discern the facts when allegations of research misconduct, patient complaints, or noncompliance surface. This allows the institution to respond appropriately, effectively and lawfully.
- Support registration of clinical trials into the clinicaltrials.gov registry, to protect the ability for study publication in prominent journals, and to avoid high fines for non-compliance for studies with registration mandated by law.
- For investigator-initiated studies and in conjunction with the Clinical Trial Center, assure that IND or IDE submissions to FDA and associated reporting requirements are met; and train investigators regarding the expanded obligations they assume when performing as a "sponsor-investigator"
- Assist principal investigator and study staff in conducting self-assessments
- Assist in preparing sites for external audits, such as FDA audits
- Assist with investigator questions on responsibilities under the NIH Guidelines for recombinant DNA research
- Assist researchers with the regulatory aspects of international collaborations and transfer of materials. We screen

identified export issues to see if a license is required. If an export license is required we submit those license requests to the Bureau of Industry and Security and/or the Office of Foreign Assets Control. Special concerns are in place if investigators are going to be working in areas that are under an embargo or other strict export controls such as North Korea, Iran, Syria, Cuba or Sudan or with students or collaborators from these countries.

- Serve as regulatory consultants for the development of policies and procedures that incorporate compliance mandates and institutional ethical values.

Education and Training in Research (other than scientific methodology) is another "service line" of Research Integrity. Education provides:

- Development, maintenance, and tracking of training that is prerequisite for participation in Human Subjects Research
- Curriculum and training development, emphasizing online education
- Represents and coordinates research education through "OWL" Council (the LLUAHSC coordinating entity for all staff education).
- Consult with other education initiatives such as CTC, Clinical Research Coordinator Network and volunteer services.
- Technical liaison with Information Technology, Staff Services, and outside vendors for platform development supporting research education objectives.

The Research Integrity Staff is available at the listed extensions during regular business hours Monday thru Friday.

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Research Education Coordinator



irb corner

Contributed by Anu Diekmann, Sponsored Research Analyst at Sponsored Research

Linda Halstead, Director of Sponsored Research

JR Krausz, Research Education Coordinator at Research Integrity

Ask the IRB

In accord with important changes made by the Federal government over the last couple of years, Loma Linda University has re-examined and substantially overhauled its policy on reporting Adverse Events (AEs). The regulatory changes have generally moved in the direction of *less* reporting, rather than more, so that the reports are more meaningful to the IRB and the local investigator.

Accordingly, the updated AE reporting system at LLU has been modified to be as streamlined as possible for the coordinator and the investigator.

Key features are:

- At time of IRB approval, each study will be provided with an AE reporting matrix: what to report, when to report, and to whom.
- The current, on-line AE Tool on the Research website will still be used, with minor edits to reflect current regulations.

LLU's new AE policy (H-43) has just been approved and should be accessible at http://www.llu.edu/pages/handbook/lluahsc_policies/index.php?dir=H-Research%20Affairs soon.

Research Affairs will provide further guidance and info sessions as part of the roll-out of the revised AE reporting requirements.

Stay tuned for information on upcoming training sessions!

Feel free to e-mail us at IRB@llu.edu if you have any other questions.

announcements

Training must be completed prior to study start-up. Please begin all sponsor-required study training as early as possible to avoid potential start-up delays.



Did you know...

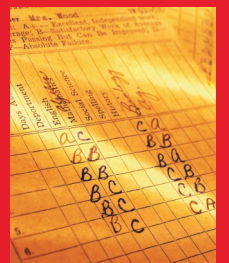
A research contract is between the Institution and the sponsor.

Therefore, all clinical trial agreements, confidential disclosure agreements, and contract amendments must be signed by the Institutional Official in order to be valid.



CEUs will now be offered for every possible CRC

Networking Group Meeting. Be sure to sign in and complete an evaluation at every CRC Networking Group Meeting this year in order to earn nursing CEU credits.



policy particulars

Policy & Procedure Updates

Contributed by Lorraine Sarmiento, Accreditation Coordinator at Research Affairs

The following policies, procedures, and guidelines were recently approved:

Authorship Criteria (Guidance)

This document was primarily based on the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. This identifies the criteria for authorship as well as those who do not qualify to be listed as author. Primarily, the individual has to substantially contribute to the conception and design, acquisition of data, analysis or interpretation of data, or the individual has drafted the article or revised it critically for significant intellectual content. One author must assume responsibility for managing and developing the manuscript. The co-authors' responsibilities are outlined. There is no specific order of authorship, but should be described. Contributors should be acknowledged. Authorship disputes should be referred to the chair or head of the administrative unit most directly involved; further mediation may be required by the school dean or designee, Faculty of Graduate Studies, Provost or designee.

Adverse Event / Unanticipated Problem Reporting & Reviewing (policy/procedure)

Examples of Unanticipated Problems (guidance)

Federal regulations require the reporting of adverse events and unanticipated problems that occur during a research study. The distinction between adverse events and unanticipated problems is important. Adverse events may be unanticipated problems, but not all unanticipated problems are adverse events. To help the research community better understand the subset of unanticipated problems that do not overlap into an adverse event category, a guidance document has been drafted. The IRB will send out the protocol specific reporting requirements with the IRB approval. The IRB will review all reported events and make recommendations, as appropriate.

*Training on the reporting requirements of unanticipated problems and adverse events will be provided at the February 21st CRC Networking Meeting. Investigators and Coordinators are strongly encouraged to attend this training to learn about these requirements and obtain guidance on how to report these events.

Training related questions should be directed to the Research Education Coordinator, JR Krausz at x87463 or jrkrausz@llu.edu.

Use of Devices in Human Subject Research (policy)

Significant Risk (SR) / Non Significant Risk (NSR) Device Determination (procedure)

Loma Linda University Device Study Worksheet

The IRB must review the proposed use of the device in the context of the research study, its associated risk and benefits, whether such use is investigational, and whether it is FDA-approved. Investigational devices must be used in accord with the IRB approved protocol, under the direction of approved investigators, in compliance with FDA and institutional requirements, and must be appropriately labeled, stored, and controlled. The IRB must determine the appropriate device category. In certain cases, an Investigational Device Exemption is required, and unless exempt by IDE regulations, the investigational device must be categorized as either a significant risk (SR) or non-significant risk (NSR) device.

These documents will be available online shortly. Requests for an electronic copy may be made to: Lorraine Sarmiento at ext. 49478 or lsarmiento@llu.edu.

regulatory management

Regulating Multicenter Clinical Trials

Contributed by Mary Ann Nyc, Regulatory Affairs Coordinator at the Clinical Trial Center

In the November issue of *JAMA*, a commentary by Bernard Lo was published in response to the Advance Notice of Proposed Rulemaking ([ANPRM](#)) announced by the Department of Health and Human Services (HHS) in the *Federal Register*. The debate at hand concerns the need to amend regulations for protecting human subjects who participate in research given the modernized climate, wherein clinical trials have become much more complex and large in scope and practice. Proponents like [Dr. Lo](#) vehemently believe that reducing regulatory burdens would result in potentially increased risks to subjects. However, other clinician scientists believe regulatory rigidity of clinical trials creates delays in the development of effective therapies, resulting in potential life-years lost. Before you pick a side on the matter of clinical trial regulations, consider how clinical trials are designed, organized, conducted and to what end?

At its nascence, clinical trials were based within single-entity sites: universities or medical centers. They followed the scientific method and posited singular hypotheses about the use of drugs; their findings came from a small sample size of human subjects but were extrapolated to the population at large. Over time, questions of validity arose, leading to various revisions including the demarcation of clinical trial phases as well as standardized, unbiased study designs.

Clinical trials now test drugs in four phases: Phase I, includes a small group of subjects to test whether a drug can be safely delivered. Phase II includes a slightly larger group of subjects to test the effectiveness of a drug on the disease/disorder in question. Phase III involves an even larger group of subjects and incorporates the use of a placebo to compare with the study drug, and Phase IV refers to study drug use after it has been licensed and marketed.

Along with streamlining drug trial phases, researchers have increasingly been concerned about maintaining clinical equipoise and in that vein have arrived at the gold standard: double-

blind, randomized clinical trials. Double-blindedness ensures that neither patients nor doctors know which treatment has been given. Randomization assigns subjects to a treatment or control group with some measure of equality.

While clinical trial logistics have changed, the overall purpose of trials has remained steadfast. The underlying objective of clinical trials is to give clinicians a background of information on a disease and/or treatment based on good quantitative information. Therefore, clinical trials that are too small fail to give reliable information, and for this reason they have grown to accommodate enormous sample sizes. In fact, since the 1980's, pharmaceutical companies began to outsource clinical trials to larger, private networks called contract research organizations (CROs) so that they could manage multicenter projects. While the trend continues, it has now shifted overseas and out of the U.S. This is somewhat due to diseases becoming global in nature, but also due to market interests—pharmaceuticals want to sell their products in other countries and want to cut costs by conducting trials abroad. However, moving out of the U.S. also allows companies to overcome regulations on compliance, documentation and training that have become burdensome.

Current regulatory approaches to multi-center trials are a drain on local research resources and discourage research participation by both clinician investigators and subject participants. While revisions to the guidelines established in the 1990's that govern human subject protections are long overdue, the proposed rules described in the ANPRM are a step in the right direction. Multi-center trials are sure to be a mainstay in clinical research, but updated regulations are on the horizon.



Congratulations!

The Clinical Trial Center would like to extend an enthusiastic congratulations to the Cardiology Research Division. They have met a major milestone of their recruitment goal. On 12/31/2011, Dr. Hilliard and his study team enrolled their 45th patient to their Translate-ACS study.

This represents the 75% mark of their enrollment goal of 60 subjects. These enrollments occurred within the first 4 months of their enrollment period. Congratulations!

Thank you for your continued dedication to transform lives through clinical research.

Researcher's Resources

Your toolbox is only useful if you fill it with the right things. Here are some ideas...



**MAGI's Clinical Research
Conference
2012 East**

**May 20-23, 2012
Arlington, VA**

www.magiworld.org



ACRP Global Conference

**April 14-17
Houston, TX**

www.acrpnet.org



**MAGI's
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