

A Conversation with Ruth Stovall, Ph.D.
RCRI's new Senior Principal Advisor

Dr. Steve Norsted, President & CEO

Ruth, welcome to RCRI. We are very pleased and proud that you have joined us in the capacity of Senior Principal Advisor. While we are very familiar with your long and successful career at 3M Company, we thought it would be helpful to have you share a little more about your background and your perspectives on medical product clinical research.

Your doctorate degree is in Pharmacology. How did you become interested in this field?

As an undergraduate, I was interested in both medicine and basic science. My undergraduate degree was in chemistry. Pharmacology provided an opportunity to combine both of my interests.

How did your Pharmacology program evolve into post-doctoral work in the area of electro-physiology?

My doctoral work focused on mechanism of action of inhibitory neurotransmitters involved in intention tremor in the mammalian cerebral cortex. It was a logical extension of this work to do further investigation on transmitter substances in giant axon and single muscle fibers, both classic electro-physiology models.

You have held very senior positions in clinical research. What do you see as the biggest challenges facing professionals in medical device clinical research today?

I think one of the biggest challenges facing clinical research professionals (CRP) is to develop trial designs that not only meet rigorous scientific standards, but are also practical to conduct in the clinical setting, are affordable to the sponsor and generate information that provides a marketing advantage. In order to do this effectively, the CRP needs to be part of the product development team, working with development, marketing, regulatory and reimbursement team members from the beginning of the product development effort. This early and integral involvement provides the background the CRP needs to design a study that best meets the needs of all functions.



Another challenge is conducting a clinical trial within the evolving constraints of the product development timeline. We have all experienced the impact of product development delays on clinical study initiations. One approach to minimize this impact is to start pre-study activities as soon as possible and significantly ahead of the targeted study start date. For example, qualifying and selecting investigators can begin with a study protocol summary rather than a completed, detailed protocol and case report forms.

As part of this activity, the ability of potential investigators to generate the desired patient population can be quantified since patient enrollment can frequently prolong the duration of a study.

Continued on page 2

IN THIS ISSUE...	page
A Conversation with Ruth Stovall, Ph.D.	1
Interim Analyses: Planning Ahead	3
Common Deficiencies of Nonclinical Studies	4
New RCRI Employees	5
Events	6

A Conversation with Ruth Stovall, continued from page 1

This may require funding the investigator to conduct a review of their case load in light of the study inclusion/exclusion criteria to assure that subjects will be available. Finally, use of electronic data capture technology can pay dividends in compressing time on the back end of the study.

Similarly, what are the largest issues facing administrators of medical device clinical research programs?

I think the largest issues facing clinical program administrators are accurately forecasting financial and human resources required for clinical studies and effectively justifying study needs to business management. Typically this information is requested very early in the product development cycle before study design and mechanics has been finalized. This requires an ongoing dialogue with business decision makers as the study design evolves. It's also critical to involve investigators in the process early on so as to develop the most realistic picture of what the study will cost. It also requires that the study costs be re-evaluated periodically as details of the study design become firm, and particularly if significant time has elapsed from the first estimates.

For many devices the cost to conduct the desired study may become prohibitive when factored into the product P&L. Cross-training in a CR department will optimize human resource utilization. For example a CRA may serve as a project leader on one study and support another study as a monitor. If internal resources are limited, the services of a CRO may be an effective means to implement study activities.

It can often be a challenge to satisfy potential conflicting approaches to clinical trial design between the sponsor, FDA, and CMS. What advice do you have for sponsors when preparing for pre-IDE or IDE submissions?

In preparing for a pre-IDE or IDE submission, I recommend that sponsors research prior FDA guidance and decisions, published clinical studies on a device type, and the possible ramifications this information may have on their particular study design. A sponsor can use the pre-IDE submission to obtain FDA feedback on specific study design concerns. In preparation, it is wise to strategize about alternative design elements and their impact on financial expectations, internal regulatory strategy and business objectives: does the contemplated change affect the intended use statement, does it impact the marketing strategy, does it increase study

cost, etc.? It is wise to do this ahead of time in the event that it is necessary to make changes based on FDA feedback, so the regulatory review process can continue with minimal delay.

You have been very successful in designing clinical studies departments and their respective standard operating procedures. What are the key elements to a smooth operating department?

I have found that key elements to a smooth operating department include:

- *setting clear objectives*
- *keeping everyone involved and informed*
- *respecting individual's expertise and ability*
- *and just having fun.*

There is no question that smooth operation depends on SOPs which clearly define study conduct requirements, user-friendly templates and processes that optimize clinical personnel time, and a quality system capable of measuring performance and facilitating performance improvement.

But, even with that, there are challenges that can pop up on a daily basis: studies are delayed, timelines are compressed, investigational devices don't always perform as expected, patients are enrolling too slowly, and unexpected study costs arise. But what makes our work worthwhile, is working on a daily basis with clinical research colleagues that you respect for their expertise and integrity and flexibility, and making a contribution that in the end will provide improvements for patients' health and well-being. That is why I have enjoyed clinical research so much for the past 30 years.

Thank you Ruth. In closing, how may readers who have questions about clinical trial design or operations contact you?

The most efficient way to reach me is via e-mail at rstovall@rcri-inc.com.

Dr. Steve Nosted, Ph.D., MPH (snorsted@rcri-inc.com) is a founder of RCRI, Inc. and a Principal Advisor in worldwide regulatory and clinical affairs. He has been responsible for the design, conduct and analysis of preclinical and clinical studies since 1980. Steve served as an epidemiologist for the Washington State Health Department, and has lectured on preclinical and clinical studies, as well as clinical research methods and regulatory affairs. He joined the medical device industry in 1988 and has held senior-level positions in Regulatory Affairs/Clinical Studies.

Interim Analyses: Planning Ahead

Chris Lyle, Director of Health Economics and Biostatistics

The majority of medical device clinical trials allow for a single statistical “look” at the data when enough patients have been followed to satisfy the primary endpoints. This is often a source of frustration to management and investors alike who would like more “real-time” evidence of the likelihood of trial success. The FDA guidance, *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006), provides a good basis for a discussion of what is “allowed”. It states: “Sponsor exposure to unblinded interim data,...,can present substantial risk to the integrity of the trial. One concern is that unblinding of the sponsor increases the risk of further unblinding, e.g., of participants, potential participants, or investigators, thereby potentially compromising objective safety monitoring, equipoise, recruitment, administration of the intervention, or other aspects of the trial”. Some thoughts on managing multiple looks are included below.

The single greatest argument against multiple interim looks is that the statistical interpretability of the trial is compromised. In short, a set significance level of 0.05 means that the FDA is willing to tolerate a 5% chance that a device is improperly approved. If multiple interim analyses are conducted, that 5% increases with every look, so that at the completion of the trial the 0.05 is no longer valid. This may be enough to invalidate the entire trial in the FDA’s eyes.

A second argument against multiple looks is that the results could bias the trial making the final outcomes difficult to interpret. If investigators see that certain subgroups have worse outcomes, they may change recruitment or treatment patterns to help “adjust” the final results. This would also be cause for a great deal of concern for the FDA.

There are, however, several reasons why interim looks may be required. Examples include a demand for statistical stopping rules by the data safety monitoring board (DSMB), a desire to verify that the assumptions used in the sample size calculations are relevant to the current study, the need to provide potential investors with evidence of probable trial outcomes in order to obtain the funding necessary to finish the trial, and for preparation of reimbursement dossiers to payers.

There may also be a belief that the new therapy will markedly outperform the control arm, in which case it makes a lot of sense to see if stopping the trial early is possible. All of these cases can be accommodated by careful planning, open dialogue with the FDA, statistical adjustment, and pre-determined rules on the dissemination of interim analysis results.

Unplanned (Ad Hoc) Looks

Smaller companies often run a risk of running out of funding before a trial comes to a close, and investors are used to seeing objective data to help support their decision to invest.

Larger companies may want to report up through management how a particular trial is progressing. In these types of circumstances, one can usually summarize the data with point estimates (means, proportions, etc.) and confidence intervals without generating any p-values (i.e., formal tests of statistical significance). This allows decision makers to form an opinion about the current status of the trial without infringing upon the significance level of 0.05. Be careful, however, about how these results are communicated; one can still bias participating physicians even in the absence of formal statistical testing.

Planned Looks

There are times when formal statistical tests are required. Perhaps the DSMB or the FDA would like to have formal rules to stop a study for either poor safety results, or the lack of a therapeutic effect, thereby proactively protecting patients from unnecessary risks. A variety of tools, including sequential trial design and Bayesian statistical methods can be employed to accommodate such requests, while preserving the overall level of significance of 0.05.

Alternatively, there may be evidence that the experimental arm of the study will outperform the study requirements for success. In these instances, the same tools employed above to protect patients can also be configured to accelerate study completion. In both cases, the level of 0.05 is “spread around” the multiple looks to preserve the integrity of the study to the end. There are literally an infinite number of ways to configure these stopping boundaries to conform to any set of risk preferences.

In either case, the rule with these planned looks for early trial termination is that each plan should be submitted to and discussed with the FDA prior to study initiation to obtain their consent.

Chris Lyle (clyle@rcri-inc.com) is a Principal Advisor and Director of Biostatistics and Health Economics at RCRI. He assists clients in the design, analysis, and interpretation of clinical, preclinical, and health economics studies. With over 10 years experience in the pharmaceutical and medical device industries, Chris has extensive knowledge of cardiovascular, wound healing, urology, neurology, and IVD devices.



Common Deficiencies of Nonclinical Studies

Jill Cernohous, Principal Advisor
Carole Stamp, Director of Corporate Quality

The FDA's Bioresearch Monitoring Program includes inspections to verify compliance with *21 CFR Part 58 Good Laboratory Practice (GLP) Regulations* (Sept. 4, 1987). These regulations apply to nonclinical laboratory studies that support, or are intended to support, applications for research or marketing permits for products regulated by FDA. A nonclinical study is defined as any *in vivo* or *in vitro* experiment in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. It does not encompass basic exploratory studies conducted to evaluate the feasibility or characteristics of a product providing safety is not assessed as part of the study.

If the FDA identifies nonconformances to GLP regulations during an inspection, a Form FDA-483 will be presented to the laboratory at the close of the inspection. An FDA Warning Letter may subsequently be issued. The most common nonconformances noted are listed below.

Section 58.31, Test Facility Management – Management failed to:

- designate a Study Director prior to the initiation of a study.
- assure the establishment of an adequate QAU.
- assure personnel understood their job functions.

Section 58.33 Study Director – Study Director failed to:

- document all changes to the approved protocol including reasons for the changes.
- ensure GLPs were followed.
- ensure proper archiving of study documents once the study was complete.
- ensure study data was accurately recorded and verified.

Section 58.35 Quality Assurance Unit (QAU) –

The QAU did not:

- maintain current master schedule and copies of the approved study protocols and amendments.
- maintain QAU staff separate from the study staff.
- inspect the study at adequate intervals and document results.
- sign a QA statement in the final report regarding inspections conducted.
- document and bring issues to the attention of management.
- document deviations to the protocol.
- inspect a contract lab used to analyze samples required by the study protocol.
- review the final report to assure the reported results accurately reflected the study.

Section 58.63 Maintenance and Calibration of Equipment

- Records were inadequate.
- Daily quality controls were not performed as required by product insert.
- Appropriate calibrations were not performed.

Section 58.81 Standard Operating Procedures (SOP)

- Changes to SOPs were not authorized by management.
- Deviations from SOPs were not authorized by the Study Director and not documented in the raw data.
- Inadequate SOPs for QAU activities; lab tests required by the protocol, equipment operation, testing and maintenance; and tracking and handling of test articles.
- No historical file of all revisions and dates of SOPs was maintained.

Section 58.120 Protocol – Protocol did not:

- include approvals before study activities started.
- define the number, age, weight range, sex, source of supply, procedure for identification, diet, species, strain, and sub-strain of animals.
- identify automated systems to be used for data collection.
- identify the type and frequency of the monitoring, analysis, and measurements of test animals.

Section 58.130 Conduct of a Nonclinical Laboratory Study

- Study was not conducted in compliance with the protocol.
- Poor documentation practices such as: reasons for changes to raw data not stated; data generated during the study not recorded; entries for data not signed and dated; corrections to data not made appropriately; person inputting automated data was not identified; specimens were not appropriately identified.
- Postmortem observations and gross findings for specimens were not available to the pathologist.

Section 58.185 Reporting of Nonclinical Lab Study Results –

Final report did not:

- indicate the date the study was initiated.
- describe all circumstances that may have affected the quality or integrity of the study.
- identify all changes to the protocol.
- identify the location where all specimens, reserve samples, raw data and final report are to be stored.
- contain the names of scientists, professionals and supervisory personnel involved in the study.

Continued on page 5

Common Deficiencies, continued from page 4

- contain the signed and dated reports of each scientist professional.
- describe characteristics of the test articles.

Nonconformances to these regulations can easily be avoided by having the appropriate SOPs established and implemented including training to ensure adherence by all employees at the laboratory. RCRI has qualified resources available to help implement, update, and train personnel, as well as audit your SOPs, protocols, records and final reports to ensure FDA inspections do not result in a Form-483 or Warning Letter.

Warning Letters issued to a laboratory in regards to a specific study may potentially affect the credibility of the data for the Sponsor to use in support of applications for research or marketing permits. RCRI also has qualified resources who can conduct GLP audits to assist in determining the most appropriate laboratory to conduct a particular study.

In addition, RCRI can provide assistance with protocol development and study management in collaboration with the laboratory to minimize the potential for nonconformances to the regulation.

Jill Cernohous (jcernohous@rcri-inc.com) is a Principal Advisor, Clinical Affairs at RCRI. Jill's technical skills are especially strong in the areas of clinical trial design and management, auditing, data management, and compliance. She is experienced in medical device and pharmaceutical studies, as well as combination products. Additionally, she has experience in conducting nonclinical studies (in vitro and in vivo), and clinical and field trials in animals. Jill has spent a significant amount of time conducting audits of nonclinical studies for compliance with GLPs.

Carole Stamp (cstamp@rcri-inc.com) is a Principal Regulatory and Quality Advisor at RCRI, Inc. She has 23 years of experience in the medical device, diagnostics, and biologics industries. With her industry and third party experience, Carole has acquired a thorough understanding of product design/development, process validation, manufacturing, quality systems and regulatory requirements. Carol is well skilled in auditing nonclinical studies for compliance with GLPs.

New RCRI Employees

RCRI is very pleased to announce the addition of several new staff members.

Jane Cleary, *Senior Regulatory and Quality Specialist*

With 17 years of relevant experience, Jane has acquired a thorough understanding of validation, quality systems, and regulatory requirements. She specializes in design and implementation of quality systems, as well as compliance audits of national and international bio/pharmaceutical and medical device facilities. Jane has also set-up QA and QC Microbiology departments at multiple firms. Her education includes a BS in microbiology with additional training in the areas of validation and quality system auditing.

Kaisa Kivilaid, *Biostatistician*

Kaisa, a native of Estonia, earned a BA in mathematics from Augsburg College and a MS in statistics from University of Minnesota - Twin Cities. During her graduate studies, she acquired indispensable experience as a consultant while working at the statistical clinic assisting other graduate students and faculty members with their research.

Lisa Erickson, *Clinical Research Associate*

Lisa holds a BA from the University of Minnesota - Morris in biology. While obtaining her Master of Public Health degree in epidemiology, Lisa gained valuable experience as a clinical research coordinator and scientist at the University of Minnesota - Twin Cities.

Sonia Diaz de Leon, *Assistant Clinical Research Associate*

Sonia graduated from Iowa State University with a degree in biology, where she performed research on allergic reactions in rat mucosal mast cells. Sonia also recently obtained her

professional certificate in clinical research at Anoka Ramsey Community College.

Angela Leitner, *Senior Clinical Research Associate*

Angela's experience includes several clinical research positions at successful medical device firms. Her expertise is highlighted by clinical study management for both the US and EU, Clinical Events Committee and adverse event management, as well as monitor training with subsequent monitoring. Angela holds a BS from the University of Minnesota and an MA from the College of St. Scholastica.

Shelly Paipal-Umland, *Business Development Specialist*

Shelly's background includes project management and GMP-compliant chemical analysis of pharmaceutical, medical device, and combo products. In addition to her R&D experience, Shelly has held multiple positions in sales, marketing, business development, and management. She graduated from the University of Wisconsin - River Falls with a BS in chemistry and holds an MBA in marketing from the University of St. Thomas.

Susan Strobel, *Clinical Research Associate*

Susan started her career at The Children's Hospital in Boston, where she volunteered her research skills for numerous studies. She graduated with degrees in nursing and chemistry from the College of St. Scholastica. Susan also holds Masters in Public Health in epidemiology and environmental health from the University of Minnesota. Her breadth of experience includes coordinating drug and disease research efforts in the Ethics department at the University of Minnesota, teaching Public Health Nursing, and writing diagnosis based position papers for a private health care company.

EVENTS

Visit us at the following conferences to discover how RCRI can assist you with your next project.

- Manufacturers Alliance Educational Program
Supporting Monitoring for Clinical Trial Success
August 17, 2006
Medtronic, Inc. Headquarters
Minneapolis, MN
www.mfrall.com
- 17th Annual LifeScience Alley Golf Tournament
August 21, 2006
Minneapolis, MN
- RAPS Annual Conference
October 15-18, 2006
Baltimore, MD
- 5th Annual LifeScience Alley Conference & Expo
December 6, 2006
St. Paul, MN

Knowledge, Integrity, and Ingenuity

Our mission is to serve our clients with knowledge, integrity, and ingenuity. At RCRI, we are proud of our successful record in providing integrated CRO services to the medical device, IVD, and combination product industries.

Since our inception in 1999, RCRI has helped more than 180 companies worldwide - development stage start-ups as well as Fortune 500 companies – translate their product plans into successful revenue generating businesses.

Whether it is a single task or a complex multi-faceted project, you can count on the experienced professionals at RCRI.

Contact us today to discuss how we can assist you with your next project.

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