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DATA BASICS

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Promoting Clinical Data Management Excellence

A NEWSLETTER SUPPORTED BY AND FOR THE MEMBERS OF THE **SOCIETY FOR CLINICAL DATA MANAGEMENT, INC.**

Letter from the Editors

Dear SCDM Members,

Welcome to the Spring issue of Data Basics. In this issue we focus on a topic that, perhaps more than any other, inspires passion, confusion and questions! It is, of course, clinical laboratory data. We have invited a number of authors to submit articles clarifying various aspects of lab data. These articles are not exhaustive, but we hope they will help to provide some insight into the world of lab data.

The next issue will center on data quality. This is the theme for the SCDM Spring Forum, and we expect some lively discussions! Topics include data quality as defined in the GCDMP, regulatory requirements for data quality, assessing and ensuring database quality, and software validation and quality. The issue is not limited to those participating in the forum, nor to those specific topics. If you have ideas about data quality, please consider submitting an article. Check the Spring Forum brochure for ideas – you can find it at www.scdm.org/events.

Investigation on the feasibility of the Journal of Clinical Data Management is proceeding. Later in this issue you will find the results of the survey that was distributed late last year. Thanks to those of you who responded – your input was extremely valuable in helping us move forward. Most of the work done to date has been exploratory in nature, but in the near future we expect there to be more tasks that will lend themselves to broader participation. If you have contacted us expressing an interest in being involved, you should be hearing from us in the reasonably near future.

Finally, in the spirit of April 1st, there is a spoof hidden somewhere in this issue. See if you can find it!

Best regards,
Kit and Lynda ■

Introduction to Clinical Laboratory Data

By: Kit Howard (Kestrel Consultants)

Clinical laboratory data are a frequently misunderstood and underestimated aspect of clinical trials. While considered simplistic by many, the subtleties are considerable, and can make or break a study. This article will provide a very brief overview of several aspects of clinical lab data, and the remainder of this publication will examine many of them in more detail.

Clinical laboratory data are generally defined as the results obtained by analyzing samples of human tissue (e.g., blood, urine) for specific substances. These substances can be naturally occurring, such as white blood cell counts in blood analysis, or foreign substances, such as illicit or study drug levels in urine. Lab data are an excellent source of clues to help scientists understand what may be happening in the body long before any obvious symptoms can be observed.

Clinical lab samples are collected during clinical trials for several reasons, and the data they generate can serve many purposes. The vast majority of clinical lab data collected is designed to monitor the health of the patient, i.e., 'safety data'. This usually involves conducting a standard basic panel of tests on the blood and urine of patients at baseline and then at intervals during the study. The baseline measure serves as the 'yardstick' against which later samples are compared, as variations in measures over time may be significant. Lab data can also be used to assess efficacy, such as monitoring the levels

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This Issue

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Submission Deadlines (Articles and Advertising Art Work)

Our quarterly publication schedule for the next three issues requires the following input deadlines:

Volume 10, #1 (Spring)	27 February 2004
Volume 10, #2 (Summer)	26 April 2004
Volume 10, #3 (Fall)	27 July 2004
Volume 10, #4 (Winter)	25 October 2004

Publication Policy

We welcome submission of previously unpublished materials for publication in *Data Basics*. Materials should preferably be submitted in electronic form (MS Word). Acceptance of materials for publication will be at the sole discretion of the Editorial Board. The decision will be based primarily upon professional merit and suitability (i.e. publication may be edited at the discretion of the Editorial Board.

Niether SCDM nor the Data Basics Editorial Board endorses any commercial vendors or systems mentioned or discussed in any materials published in *Data Basics*.

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Letter from the Chair of the Society for Clinical Data Management

Marianne Plaunt, Ph.D. (STATPROBE, Inc.) Chair

The responsibility of the Board of Trustees (BoT) is to manage the property, affairs and business of the Society, to establish policies, and to manage the organization of its administration and its expenditures. In January, the BoT held our annual planning meeting. We spent two plus days reviewing, brainstorming, organizing and prioritizing the many ideas and suggestions that have come to us from our membership. While doing so, we continually kept in mind the mission of the Society - Promoting Data Management Excellence, and the main purposes of the Society as outlined in our Bylaws. These include:

- to advance the discipline of Clinical Data Management as a profession;
- to support educational opportunities and to improve skills and specialized knowledge for the discipline of Clinical Data Management;
- to advance professionalism within the discipline of Clinical Data Management by providing an environment for exchange of information and experience;
- to enhance communication between professional groups involved with Clinical Data Management;
- to promote standards of good practice within Clinical Data Management.

Throughout our discussions we sought to create a balance between the desire to work on a particular initiative with the time availability of our many volunteers and our budgetary constraints.

Our active committees within the Society include Certification, Effective use of Technology, Good Clinical Data Management Practices, Membership, Publications, and Website. Each trustee/committee liaison presented the goals and wish lists of their committee for the year. The challenge of the BoT was to prioritize these goals and work within the constraints of time (both of our administrative staff and of our volunteers) and our annual budget. The committee initiatives were evaluated by the following criteria:

- impact the initiative would have on the Society
- financial impact the initiative would have on the budget
- effort it would take to successfully complete and implement the initiative

Several areas emerged as the priorities for 2004.

Conferences – both our Spring Forum and our Fall Conference provide an excellent opportunity to fulfill many of the purposes of the Society listed above. As you can imagine, they also require a large investment of both time and money. We have determined that some of our energies should be spent on developing a Sponsorship Prospectus to support our conference efforts and that we should more actively market our conferences to stimulate attendance. The prospectus is in its final stages of production and will be available early 2nd quarter of this year.

Certification – We have received sufficient numbers of participants for the Beta version of our Certification Exam. It is our current goal to have the "cut score" determined and approved by early summer. At that time the final version of the Certification Exam will be available and the Society is working on the development of marketing materials as well as developing regional training seminars.

Advertising – One of the sources of revenue for the Society comes from the advertising and job posting opportunities provided in Data Basics, Data Connections and on our website. We are working on developing an Advertising Prospectus which will provide further information about our offerings and their benefits to our potential advertisers.

Website repository – Our Society is predominantly run by a network of volunteers, therefore, it is important for us to utilize advances in technology that enhance our ability to work together across the country. We are investigating the creation and use of a website repository that will allow document sharing and archiving of crucial documents. All committees, and specifically the Good Clinical Data Management Practices and Publication committees, will benefit from this tool.

As you can see, we have our work cut out for us this year and we are all very anxious to move these initiatives forward resulting in more opportunities for our membership. If you have any questions or would like to become involved with any of these items, please contact me or the committee members listed on the website. ■

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Web Sites to Check Out

ACDM - www.acdm.org.uk
CDISC - www.cdisc.org
FDA - www.fda.gov
ICH - www.ich.org

There are more links to be found on our web site!
SCDM - www.scdm.org

Please let the Web site Committee know about any other "hot" web sites that you feel would be of interest to the SCDM membership.

Introduction to Clinical Laboratory Data

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of insulin in a diabetes trial. There are other kinds of analyses as well, such as pharmacokinetic and pharmacodynamic analyses, where the action of the drug on the body and the action of the body on the drug are studied, and biomarker and pharmacogenomic studies, where scientists search for indicators that might help them, for example, identify people who are most likely to respond to the drug.

The protocol should define the samples, tests and timing for the study. Working with representatives from a lab can ensure that the right tests are selected, and that samples are drawn at the right times. For example, there is often more than one way to assess the level of a particular substance in the body, often known as a methodology. Some are more accurate than others, and may cost more or less. If all that is needed is a general safety assessment, a less accurate and less expensive assay may be perfectly adequate. On the other hand, if the test is a key efficacy parameter, a more precise, but more costly, assay may be appropriate. Another example is that the levels of some analytes vary in the body over longer periods of time. If changes can only be seen on a monthly basis, drawing samples every week is useless, invasive and expensive. Understanding this can help a clinical scientist get the most appropriate results in the most economical way possible.

Lab data results by themselves are of little value, and must be analyzed in context. That context can come from other samples taken from the same patient or from normal ranges. Normal ranges are the values for each test that are considered to be unremarkable. They are usually established by analyzing a large number of samples and taking the statistically central range of results. These results can be influenced, among other things, by the age, sex and health of the patients, which is why there are often several ranges established for a given test. Labs can either generate their own set of normal ranges for each test, or they can obtain ranges from published sources. There are advantages and disadvantages to each approach, and which one is appropriate depends upon the sensitivity of the test, the availability of samples, and a number of other factors.

Laboratory testing is generally conducted in one of two settings – local and central. Local labs are those that are used by individual investigators in a study. The investigator chooses a lab to process the samples from his/her patients, and this lab is not used by any other investigator in the study. That lab can be the one associated with the hospital in which the study is conducted, or a clinic, or even the local pharmacy, as is often the case in France. Each lab has its own set of normal ranges, and the data are usually transcribed onto case report forms and handled similarly to other kinds of data. By contrast, a central laboratory is a company that arranges to have all the samples from all patients in a study shipped to their analytical facilities, and all samples are analyzed in the same manner and are associated with the same set of normal ranges. The data are usually saved directly into a database by the machine performing the analyses, and are transmitted electronically to the sponsor.

Regardless of the arrangement, all laboratories doing analyses for clinical trials must be certified with a standard acceptable by the regulatory authorities, and must be compliant with 21 CFR Part 11, the regulations covering the use of electronic data in clinical trials. There are electronic standards emerging that can assist in this compliance. CDISC includes a laboratory data module that defines variable names and descriptors, and lab data are increasingly commonly being encoded using LOINC, which allows for common test identification.

Managing clinical lab data can pose specific challenges for clinical data managers. Lab data are more difficult to interpret if one does not have clinical training, and what is appropriate to query is less clear. Data transmitted electronically are often assumed to be clean, as they are generated by machines and are not manually entered. This may not always be true, however, as some specialty tests may be hand-entered, and systematic problems may occur as a result of faulty programming. Data managers can also use lab data to alert them to possible adverse events that may not be recorded, although it is wise to collaborate with clinical colleagues prior to issuing queries.

Running a study from a clinical laboratory's perspective, particularly a central lab's perspective, is a logistical juggling act. They must supply the investigative site with all the supplies necessary to collect and handle the samples, along with labeling and shipping materials. Samples must be packaged in accordance with applicable regulations, and this may involve dry ice packaging, multiple containers, etc. Ambient samples must reach the analytical lab fast enough that the tests can be performed accurately, and this often requires overnight shipping. This can be challenging when sites are located away from major metropolitan areas in developing countries, and can greatly add to the cost. ■

Lab Data Specialists in Clinical Data Management

By Karen Petrie (Genentech)

The management of lab data has become such a specialized discipline in clinical data management that many companies now designate individuals to work exclusively in this area. These individuals are experts in:

- Interacting with central labs
- Electronic data formatting and loading
- Lab unit conversions
- Local lab ranges
- Lab data checking
- Corporate lab data standards
- Providing advice to study teams

This article will address this discipline and discuss the usefulness of maintaining experts in a clinical data management organization who specialize in the areas listed above.

Interacting with central labs

The importance of creating and maintaining a close relationship with central labs cannot be emphasized enough. The aspect of this relationship that is greatly improved by the appointment of a lab data specialist is the consistency of a single point of contact. Having an individual who is responsible for ensuring that standards are maintained and issues are handled consistently can greatly facilitate this relationship.

A lab data specialist maintains this close relationship, and ensures the maintenance of data standards with respect to data formatting, handling of lab comments, mapping of lab test codes to sponsor lab test names, etc. Issues that arise are tracked centrally, such that each study team learns of issues as they arise, and issues are resolved quickly and efficiently because the lab data specialist, as a single point of contact, is able to provide a single message that is managed consistently across studies and projects.

Electronic data formatting and loading

The formatting of electronic lab data must be extremely precise to ensure that preprocessing and loading into the clinical database occur without errors. Additionally, the interpretation of any errors generated by preprocessors and data loaders is not necessarily an easy task.

A lab data specialist is an expert at specifying a company standard format with central labs. Through performing this task on a regular basis, the lab data specialist understands the pitfalls or integrities of the company standard format and is able to work through these with the central lab through knowledgeable and effective communication.

Interpreting data preprocessing and data load error messages can be difficult, as there is a vast number of errors that can occur, and the errors are not always presented in straightforward language. It takes a clear understanding of both the clinical and lab databases to determine the most effective resolution of a given error. A lab data specialist responsible for interpreting these errors on a regular basis quickly becomes an expert in understanding problems and identifying the most efficient resolution. Furthermore, the communication of electronic file errors, whether to the central lab or to the study team, is handled in a consistent manner when overseen by the single point of contact afforded by the lab data specialist.

Lab unit conversions

Lab data should be presented in study reports and regulatory submissions using a single set of units. Unfortunately, when one considers the global situation, there are two sets of units in general use by laboratories reporting data. Most of the world uses SI units, whereas the US and parts of Canada use a different set. It is generally accepted that sites should use those units with which they are most familiar, in order not to jeopardize the safety of study subjects, so very often the sponsor is presented with data where the units differ from one site to another.

A lab data specialist acts as a situational study team advisor with respect to unit conversions, and has the knowledge to maintain a conversion table either within or outside a clinical database system. Statisticians find these conversion tables useful for standardizing the data for analysis and submission.

For local lab data it is a common practice to preprint standardized units on the CRF. Does preprinting units on the CRF solve the lab unit conversion problem? Experience has shown that in most cases this solution tends to backfire. The disadvantage of this is that the investigational site must now manually perform the data conversions to match the CRF unit. If the site actually remembers to perform the conversion, it is still a process that is highly error prone, and leaves the raw source data and local lab ranges no longer matching the units of the value written on the CRF, and subsequently entered into the clinical database. Clearly, the submission dataset will be more accurate and consistent when unit standardization is performed electronically by the sponsor, rather than manually by the individual investigational sites

Local lab ranges

Hard copy local lab ranges can be extremely difficult to read and interpret. A lab data specialist, being someone who works with large quantities of local lab ranges, acquires a trained eye for deciphering the poor quality copies, non-standard or incomplete units, and synonymous lab test names, not to mention foreign languages. It is critical to have someone trained or experienced in medical technology working with local lab ranges, as there are numerous synonymous lab test names and units. For example, a mature neutrophil can be represented by many synonyms, neuts, segs, polys, PMNs, to name but a few. Similarly, a platelet count unit can be represented by many synonyms, such as x10E3/uL, K/cumm, cells/mm3, etc. While these are all valid synonyms, it is difficult for an untrained person to easily differentiate a valid synonym from an incorrect lab test or an invalid unit.

Some companies choose to create a CRF to collect local lab ranges, in order to enhance the readability and standardization of the synonymous lab test names and units. While this simplifies the data entry of the lab ranges, it adds an error prone transcription step at

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the investigational site or within the clinical operations area. It also puts the investigational site or clinical operations in the position of interpreting the synonyms mentioned above. While this will save time for entering the local lab ranges into the clinical database, it is not a popular choice within the organization that is required to perform the transcription. It also incurs the risk that if a transcription error was made or if a synonym was misinterpreted, the source document for the local lab ranges may not match the ranges entered into the clinical database.

Lab data checking

The rationale for collecting data in a clinical study is either for the safety of a subject, or to prove the efficacy of an investigational drug. One thing to keep in mind about lab data is that results are not based upon a subjective patient response. While some testing is based upon the subjectivity of the technician in the lab, most results are quantitative, based upon calibrated instrumentation, run in an accredited environment.

A lab data specialist ensures that the same quality standards are applied to the verification of all lab data, regardless of whether they are received electronically or via CRF. While each of these types of data brings different challenges, the efficiency of reviewing these data can be substantially increased with the trained eye and consistent procedures offered by a lab data specialist

Local lab data tend to lend themselves to specific types of errors, for example:

- Transcription errors
- Values written on the CRF that are in different units than the range units received from the lab
- Missing or extra decimal points caused by marks on the paper CRF

A trained eye can not only identify these types of errors more quickly, but also generally identify the cause of the problem, thus speeding up the resolution of the error.

Central lab data, on the other hand, tend to lend themselves to errors which can be identified using less subjective review, such as formatting errors, incorrect patient numbers, incorrect demographics, etc. As suggested earlier, the advantage of a single point of contact with the central lab in tracking and resolving these errors can minimize the time required to ensure that the data for each project meet the required quality standards.

Corporate lab data standards

It is important to develop corporate standards for collecting safety and efficacy lab parameters and have the ability to enforce these standards. Having a centralized function to enforce corporate standards ensures that they are consistently governed across projects. A few examples of questions a company might ask in determining standards are:

- Is it acceptable to deviate from the standards, and if so, under what circumstances?
- What documentation is required when deviating from a standard?
- Is the collection of non-protocol lab data in a study-specific database acceptable?
- What types of local lab range documentation is acceptable?
- What data checks are required for local lab data vs. central lab data?

A lab data specialist ensures that consistency is maintained in these types of process standards, so that the content and quality of data are neither determined nor compromised by decisions made by individual study teams or labs.

Providing advice to study teams

A lab data specialist is a good resource for a study team to help ensure that lessons learned are maintained across an organization. Examples of such are:

- Helping to identify successful central lab partners for studies. While the data files are relatively inexpensive, compared to the other costs incurred by the central lab, the final product – the most important central lab product - is the data file. Without a high quality data file, all the shipping, accessioning, testing, etc. becomes meaningless. The lab data specialist has probably worked with, or is currently working with, multiple central labs, and can provide essential feedback to study teams regarding the ability of various central labs to deliver a quality data product.
- Consistency within a project (from study to study) is important. A lab data specialist develops an overview of multiple studies within the same project, and thus is able to advise study teams so that lab standards are maintained across the project.
- Familiarity with each study's lab database structure and 'quirks', making it easy to quickly define or create useful reports. Observing the nuances of each study builds upon the knowledge of the lab data specialist, thus creating a constantly growing repertoire of useful reports and checks.
- Avoidance of the repetition of previous mistakes, and the promotion of efficiencies by sharing good ideas across multiple, unrelated projects.

Conclusion

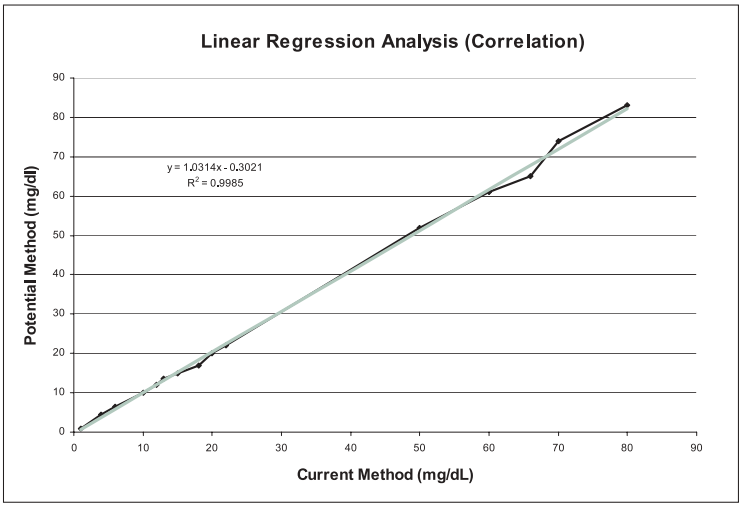
Efficient processes and optimal resource utilization are key to proper study conduct, and eventually to getting products to market sooner. In many studies, the lab data constitute 50%-80% of the data in the clinical database. With this large quantity of data, and with the skills that lab data management demands, it is clear that the consistency a specialist can bring in the management of central labs and lab ranges, units and data handling, is becoming recognized by many companies as a means of optimizing quality and timeliness in their clinical data management organization. ■

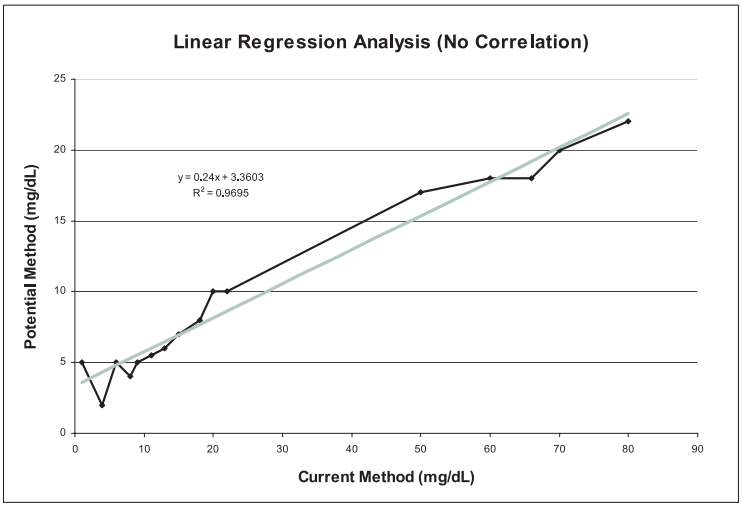
Lab Normals: An Enigma

By Lynda L. Hunter (PRA International)

It is not uncommon for people to think that lab normal ranges are hard and fast identifiers of test results that are problematic. If this were true, then why do different labs have different normal ranges? Shouldn't they be constant regardless of where the test was performed? The truth is that the normal range provided by a laboratory is actually the window of values where 95% of patients without the disease targeted by the test will fall when their samples are measured with that specific machine or methodology. The other five percent of those without the disease are divided into 2.5% outside the normal range, below and above. One exception to the 95% limits would be test results given as positive or negative.

In clinical studies, physicians place subjects in one of two categories, healthy or diseased, based on laboratory results and associated normal ranges. Physicians may order other tests to confirm a diagnosis and eliminate a false positive error. They are aware that the normal range provided by a laboratory usually has 95% limits and that approximately 1 in 20 normal individuals will have a value outside the range. Also, when large groups of tests are run simultaneously on a patient specimen, there is a high probability that at least one test result will be outside the normal range. Most of these physicians, therefore, will consider a result normal if it is within the range limits, suspicious if it is somewhat outside the limits and abnormal if it is considerably outside the range. Data managers may not view the normal ranges similarly. An example is wondering why or querying investigators when an abnormal lab result is evaluated as not clinically significant or taking the range limits too literally.





All measured quantities are either categorical variables or continuous variables. Categorical variables have a known number of possible values, such as 'present' and 'absent'. Continuous variables can have an infinite number of possible values along a continuum. Most laboratory test results are continuous variables that can take on any value within practical limits, although the result is reported in discrete units, such as a blood glucose result. The imprecision of the observed result and of the normal range limits are complicating factors. The precision of a test method has an effect on the discriminatory power of the normal range. Precision is the variation of results obtained when the same sample is assayed repeatedly or the reproducibility of what is observed. Precision is commonly expressed in terms of standard deviation and is determined for every laboratory test. The upper and lower limits of a normal range and the results reported from any specific test all exist within a range created by the precision of the test. The range is expressed as the true value plus and minus the standard deviation of the test. When precision is taken into consideration, a test result close to the limits of a normal range actually may be on the other side of the limit depending on the precision of the test. If the lower limit of normal for a test is 70 mg/dl and the precision is ± 6 mg/dl, then the actual limit is from 64 to 76 mg/dl. Thus, any patient test result between 64 and 69 mg/dl probably is normal even thought it is below the published normal range of the test. In situations where the normal range is narrow and the imprecision is high, the discriminatory power of the test could be compromised. In the case of bilirubin with a normal range of 0.5 to 1.5 mg/dl, if the precision were ± 0.5 mg/dl, it would be difficult to discriminate between a result of 1.0 mg/dl and 1.5 mg/dl. Tests with this issue may be utilized as screening tests to quickly identify specimens requiring further testing by a method with greater precision.

Every laboratory should develop its own normal ranges for tests commonly used. This approach is justified by two reasons:

1. The normal range should represent the population from which patients will be taken, due to the effects of geography, race, etc.
2. The laboratory may have a consistent bias in certain test results produced due to technique in performing the test, minute changes in reagent concentration, etc.

In many cases, this approach is just not practical; therefore many laboratories verify the normal range provided by the manufacturer of

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the test reagents. This verification is accomplished by analyzing specimens simultaneously by the old method and the new method. This data is analyzed with linear regression analysis to determine if the results and therefore the normal ranges are comparable (Tables 1 and 2).

Generally, in the United States, normal ranges are not changed, verified or revised unless a new methodology is adopted, primary reagents are modified or new instrumentation is introduced. Physicians are notified of the change and the effective date. When a central laboratory is used for a protocol or program, the client is notified of the change in normal ranges. However, when local laboratories are used for a study, only the Primary Investigator and site personnel are notified of the change and may not realize the need to communicate this information to the Sponsor or CRO. Minor changes in the normal ranges of an analyte may not be significant due to the issue of precision described above. However, if there is a change in units used for a test or a large shift in the normal ranges, these new ranges should be used for any results after the effective date of the change.

Establishment of normal ranges is further complicated by many variables, including sex, age, race, weight, climate, geography, season, diet, time of day when the specimen was collected, day to day variation, menstrual cycle and whether the patient is fasting or not. It is best to have normal ranges for each subgroup which differs significantly from any other subgroup. This is most commonly seen in normal ranges with significant differences for men and women, such as hemoglobin, and age stratified normals, as alkaline phosphatase. When the ranges are not subdivided into subgroups, this causes a broadening of the normal range. The normal range for hemoglobin in males is generally 14 to 17 g/dl and in females is generally 12 to 15 g/dl. A hemoglobin range for both males and females would be 12 to 17 g/dl and would lose discriminatory power, especially for males with hemoglobins between 12 and 13.9 g/dl.

The preferred method of normal range calculation is a non-parametric estimate of the normal range, because it makes no assumption as to the distribution form of the data. Therefore, this approach is valid whether the distribution is Gaussian, log-Gaussian or neither. For this method, the minimum number of samples needed to calculate the normal range is 120. The samples should be from "normal" people or those who have not been diagnosed with the disease targeted by the test. For example, the serum glucose normal range would be determined from people without diabetes or hypoglycemia. The test results are ranked in order of magnitude and the limits of the range calculated. Although 120 samples are considered minimal, usually a much larger sample is collected. Unless the sample size is large, the normal range estimation may depend on one or two of the lowest or highest values. The problem of outlier values is excerbated when using a minimal number of data points. In non-parametric methods, extreme values play a greater role in the normal range calculation than do intermediate values.

Also, to guard against outliers arising from technical error, it is advisable to repeat the analysis of the three highest and three lowest values. A sufficiently large number of samples will reduce the effect of the outlier problem in normal range calculation considerably.

Biostatisticians view laboratory values as summaries of the data, often comparing the percentage of subjects with out of range values versus the percentage of subjects with normal values for certain analytes. Shift tables are used to present categories of subject results pre- and post-an action according to High-High, High-Normal, High-Low, Low-Normal, Normal-Normal, etc. They also use flags present in the lab data, "H" for an abnormal high value or "C" for a critical value, as cut points to identify out of range values.

Although Data Managers do not need to know the science behind lab normal ranges to perform their tasks, it is always beneficial to know the "why" behind what we do. Data Managers tend to view data as black and white; either a value is within the normal range or it is not. The reality is that data, especially lab data, is not that simple. Realizing that lab normal ranges are rules within a broader context can help clarify the reasons for multiple levels of ranges, including alert values and critical values, and why the same result may be deemed out of range by one lab, but within range by another. Hopefully, the information presented will assist Data Managers in knowledgeable use of laboratory data. ■

Look what they are saying!

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Metrics for Locking EDC Studies

Acceptable Error Rates

Strategies for Handling Missing Data

Validation of Batch-Loaded Data

CDM Software Options

CDISC

Lab Normals Editcheck Ranges

Clinical Trials Cost Metrics

Resolving DCFs Via Email

Managing Laboratory Data

By Wanda Doles (PRA International)

There are many challenges in the Data Management task, but the ultimate challenge is managing the Lab Data. Results of lab samples tell the physician significant information about the body chemicals that are directly related to the safety and well-being of the subject. Reviewing the results of lab samples to a data manager can create havoc in the data manager's world of data unless it is dealt with properly.

The Right Stuff

Review of laboratory data requires the data manager to step into the medical role for just a moment. We are asked to obtain the reference values of "normal" samples of blood tests, urine tests, other body fluids and sometimes even tissue samples to have the necessary information stored in a data table for reference in the clinical study database. Not only are we asked to supply these ranges, we may also be required to understand how to apply them. Often these are simple numerical "range" checks (the high and the low), are complicated by the following factors:

- Units of measure may vary between the supplied normal values and the reported results,
- Normal ranges may not be the same for males and females,
- Normal ranges may not be the same for all ages,
- Changes in the calibration /certification of the instruments or methods cause ranges to change, and
- Language translation for global studies.

Data managers write edits so that we can notify the sites of an out of range value based on the reference tool. Obtaining the correct information is sometimes the most difficult part of the reconciliation process due to the issues listed above. Labs often provide data managers with much more information than is requested! You ask for a reference range of Glucose, but the lab sends you the entire table including every lab test they perform (and a lot of labs have catalog type books to send out). One solution is to ask the lab the right questions "the right stuff". You can accomplish this by sending a spreadsheet that requests only the information specifically needed for a study or send a copy of the CRF lab collection page. The site or lab should complete the page with only the information required for the study. Keep it simple.

How do all of these factors affect data management? First, have you collected the Right Stuff?

Types of lab data collection.

Typically data management is responsible for the validation of data collected in the clinical study database. Collection of the lab data is defined by data management with two terms: local labs and central labs. If the study uses local labs, the results from the lab report are

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directly transcribed onto a CRF page. This data is monitored by the CRA and reviewed by the data manager, just as the other data collected in the CRF. Edits are written and queries applied to data considered being discrepant per the specific processing plan. Data collected by central labs means the results of the lab tests are stored in an external data repository –no CRF pages to enter the lab data and minimal monitoring by the CRA, but there can still be queries written for some of the data items.

Cleaning local lab data:

Data managers create edits to determine if values are out of range by comparing the results to the reference file of the lab normals values. Data managers cannot assess the clinical significance of an out of range value, so we should look for errors in the data item itself. If a lab value is outside of the normal parameters, then the data is evaluated from a ***data perspective:***

- is the value entered for the correct analyte,
- is the value expressed in the correct unit required for the study,
- is there a handwriting error which may have caused an incorrect entry,
- is the data present,
- is the data expressed appropriately according to the required significant digits (i.e. 3.59 mg/dl or 3.6 mg/dl),
- is the value too high or too low per the normal ranges, and
- is the reference tool accurate with the correct information applied to the correct lab?

Cleaning electronically transmitted data:

Most data managers love to hear the terms "central labs". This makes our life easier, because we are removed from the task of obtaining the lab reference range information. On the CRF, the following items are most commonly collected:

- a record of the sample being drawn,
- time/date of collection, and
- a data prompt question to ask if the sample was taken.

The results are electronically transferred from the central lab database to the clinical database and then analyzed for various criteria to ensure compatibility of the data received. Certain identifiers must be common to both the clinical study database (CRF) and the external data results (lab data). Usually these items are patient identifiers, date of birth, sex, plus date and time of lab sample collection.

Central lab data is then assessed as follows:

- Date/time of collection in the clinical database (from CRF data) should match information for the same sample in the external data transfer (from the lab),
- Date/time of collection in the CRF are present, then a corresponding result should be in the external lab database,
- Actual number of samples from the CRF database should match the number of samples in the external lab database, and
- Demographic information should match between the lab data and the CRF data.

So who does the cleaning?

The confusing part of lab reconciliation is actually what role or function is responsible for making the corrections to the data (either the CRF data or the external lab results file data). This is a multifactoral issue. The answer to this is also subject to change for every project. A good communication plan between the data manager, database programmer, CRAs, site coordinator and the external lab contact is imperative for a successful and timely reconciliation. Who should discuss outstanding issues with the laboratory about missing samples or samples in questions should be decided early in the project and issues must be attended to during the study conduct. The timing of the lab transfers must occur so the appropriate reconciliation and resolution can be discussed and evaluated on an ongoing basis.

During the conduct of the study and at the end of the study, the site coordinator should ensure that all lab samples are accounted for and shipped to the appropriate lab for analysis. The Case Report Form entries should be verified by the CRA during monitoring visits to assure the correct sample information is entered. The data manager is responsible for sending queries to assure the lab data is valid per the rules agreed upon at study start-up... The database programmer is responsible for receiving and loading the external lab data and accounting for the correct handling processes of the data. The external lab contact is responsible for any updates necessary to the external lab files.

Managing lab data is challenging because many functions are responsible for the success of this task. It is a team effort to ensure the lab reconciliation is completed successfully. ■

CALENDAR OF EVENTS

October 3-6, 2004	March 13-15, 2005	October 9-12, 2005	October 8-11, 2006	September 16-19, 2007
Fall Conference	2005 Spring Forum	2005 Fall Conference	2006 Fall Conference	2007 Fall Conference
Royal York Hotel	Grand Hyatt Buckhead	Sheraton San Diego Hotel & Marina	Wyndahm Palace Resort & Spa	Hyatt Regency
Toronto, Canada	Atlanta, GA	San Diego, California	Orlando, Florida	Chicago, Illinois

Lab Assays: All Methods are NOT Created Equal

By Lawrence K. Oliver, Ph.D. (Mayo Central Labs for Clinical Trials. Mayo Clinic)

Laboratory scientists as well as data managers are plagued by the multitude of ways of measuring an analyte in human biological fluids. Recent reports document 22 ways to measure cholesterol and 29 ways to measure AST are being used in the US alone. Most data managers have learned the hard way that simply stating that the method is "colorimetric" or that the units are the same does not ensure or even imply that the results will be combinable. Attempts to utilize normal, or reference, ranges, have similarly proven futile, since there is a variety of definitions of "normal" and they are not consistently used amongst labs. Many labs are not sufficiently integrated with a medical facility to perform a thorough clinical assessment of normal or healthy.

In this article, I will provide some background to help not only understand the reasons behind the multitude of analytical procedures available for any one analyte, but also some guidance as to means to objectively evaluate lab-to-lab comparisons and lead eventually to a truly combinable data set.

Method Selection Criteria

The lifecycle of an analytical procedure begins with the identification of the substance to be measured (the analyte) and proceeds through much thought and planning into a development phase. The vital first step of development is to define, that is, *pre-select,* the performance criteria for the assay. The target criteria should include objectives for both analytical performance and clinical performance, and list goals for the various accuracy and precision assessments required. The individual items required are discussed in detail in many other documents, including the regulatory documents governing the operation of laboratories under CLIA, and I will focus on only three – the ones that most strongly affect the proliferation of methods:

- Analytical sensitivity
- Clinical specificity
- Market penetration (no, this is not part of the regulatory documents!)

Analytical sensitivity, represented by the lower limit of quantitation, drives new method development for many substances, both endogenous and xenobiotics. Low natural levels of hormones and the need to reduce sampling volumes (pediatrics, especially) require that increasingly small amounts be quantitated accurately. We have progressed from spectrophotometry to turbidometry to nephelometry to luminescence to mass spectroscopy to immunoassay to tandem MS to nucleic acid probes and Rapid PCR, and won't stop there. They each measure different aspects of the molecule or different signals emanating from the reaction, and are subject therefore to variable and inconsistent interferences and response to analyte and matrix variations.

Clinical specificity is the concept that we are measuring the particular form of the analyte that is responsible for the clinical effect in which we are interested. The converse is also part of the equation: that forms of the analyte which do not contribute to the clinical effect are not part of the measurement. Any method which uses an "analyte-specific reagent", or ASR*, is an attempt to achieve a high degree of specificity. [*ASRs are substances like antibodies, nucleic acid probes, or receptors, which are used as reagents in assays.] The cost of success in *achieving* specificity includes the *loss* of comparability between methods, exactly because we are then measuring different forms of the analyte.

I will use PTH as an example. All proteins (all right, except the circular ones) have an amino terminal and a carboxy terminal, the N- and C-terminals, respectively. If the antibody or antibodies used in the assay recognize only the N-terminal, the results will differ from the assay that recognizes the C-terminal because there are fragments of the parent PTH floating around in the serum, some of which are recognized by one assay and not the other. There are also antibodies directed towards the center of the molecule, leading to another type of analytical specificity, and combination assays using one antibody towards the N-terminal and a second antibody towards the C-terminal. So we have N-terminal assays, C-terminal assays, mid-molecule, whole molecule, and ones now being called "biointact": all of which arise because of different selections of antibodies and assay designs. And all of which are on the market for one of two reasons: 1) to meet different clinical needs, and/or 2) to allow the mfr to capture a portion of a highly competitive field.

Market penetration and the need for product differentiation is the driver for the plethora of methods for cholesterol or AST. Instruments are designed for throughput or convenience or simplicity or low-cost, or all of these factors, and methodologies are modified to work on the resulting instruments. Buffers are changed, enzyme reactions are performed forwards or backwards, substrates are modified to produce light of a particular wavelength, and time and temperature may be changed to facilitate optimum performance on the particular instrument. Unfortunately, standardization of calibrators across instruments, across methods, and across manufacturers is not part of that development process.

Methods, Myths, and Misconceptions

World conferences have been held regularly for decades in attempts to standardize assays, and many improvements have been made. Twenty years ago AST values varied 15-fold between methods, now they vary only three-fold. Cholesterol results differed by 100% lab-to-lab, now its about 25%. The International Federation for Clinical Chemistry and the American Association for Clinical Chemistry continue to work on reducing the variability between methods and promote traceability to common reference materials. It is an optimistic, but fair statement, that within 10 years many of the routine chemistry and hematology assessments will be sufficiently standardized worldwide that method variations may be ignored except for the most precise of assessments.

The optimism does not extend to measurements of specific proteins, however. Accuracy of immunoassays is elusive yet, even though International Reference Preparations (IRP) are available for many

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proteins. The individual assays recognize the IRP differently, and use the IRP to maintain consistency within the assay system over time, rather than attempting true standardization across the various immunoassay systems. All commercial assay systems for insulin, for example, are referenced to the WHO 1st IRP 66/304, but results on split samples demonstrate a range of responses that differ by as much as four-fold in the normal range.

The "FDA-approved" label is misleadingly comforting. The label means that the manufacturer is capable of providing consistent reagents for the performance of the assay, has documented the performance characteristics, and has proven that they have the facilities to support the continuing provision of those reagents. They have also shown that the assay will provide clinically useful data in at least one situation. That clinical setting is often one of diagnosis, not therapy, and is virtually never analogous to the needs of clinical research. And the FDA is not in the (primary) business of seeing to the standardization of results across methods. Using the PTH example again, it becomes very important to use the proper method for the clinical setting, because the *contribution* of the PTH fragments to the measurement varies from kit to kit, and the *concentration* of the PTH fragments is a function both of the underlying disease and of the patient's renal function. Another illustrative example: gastrin exists in three different active amino acid fragments (Big, little, and mini-gastrin, just for the record), each of which can also exist in both sulfated and non-sulfated forms. The common assays on the market usually measure only one of these six forms, and are "validated" only for diagnosis of a gastrinoma. The role of gastrin in appetite control and meal processing cannot be completely determined with the current assays. And results vary three-fold across methods.

Data combinability across methods

The demands of the ISS are particularly stressful because one is likely to encounter every one of those 29 different ways to measure AST and the 11 ways to measure PTH when looking across studies and across time. Comparison of reference ranges and units of measure are inadequate for combining, and even misleading in many cases, since labs often accept a manufacturer's range without regard to how that range was determined and without concern whether that range is appropriate for the clinical populations the lab is serving. Even the one word statement of the method – immunoassay, or enzymatic, for example – are grossly inadequate.

The rigorous way to evaluate data combinability is one used by the better labs. Labs with facilities in multiple locations face a similar dilemma when they make claims that their results are combinable across all sites involved in a trial. The minimum data needed to evaluate combinability include: 1) instrument used; 2) underlying chemical basis for the method and the source of reagents (manufacturer); 3) reporting format, including upper and lower limits of reporting (the clinical reporting range, or CRR); 4) analytical specificity in terms of the calibrator used and its traceability to a reference standard; 5) antibody cross-reactivity with all important isoforms of the analyte; 6) units of the assay; and 7) imprecision at at least two levels of the calibration curve. A method comparison study using authentic human samples – not spiked samples or samples using artificial matrices – drawn from both normals and from persons with disease and comprising at least 40 samples, then provides objective data to detect and document the relationship between the assays in terms of correlation and proportional or constant bias.

Prospectively, that approach optimizes the likelihood of achieving a data set which is acceptable for common statistical analysis, regardless of the lab producing the results. Parenthetically, it makes the laboratorian's job a lot easier also, since he/she can interpret the results regardless of origin.

Sponsor's Obligations, and the Laboratory's Obligations

In order to reduce future dilemmas and the consequence of lost time and possibly lost data or loss in statistical power, both the sponsor and the laboratorian have certain responsibilities.

The analytical methodology absolutely must be matched with the needs of the protocol, or the data is useless, and I doubt any sponsor wishes to throw away the money or waste the time. The sponsor therefore has the obligation to recognize that there are various ways to measure most analytes and that not all of them will be correct for their studies and the laboratorian has the obligation to be able to work with the sponsor to select the proper methodology for the key analytes in their study. That requires three actions:

1) The sponsor must share sufficient information with the laboratory scientist to allow them to understand the full context of the measurements, both in terms of the specific trial and in terms of the drug's target. The protocol and the Investigator's Brochure are usually sufficient, but one without the other is not.
2) The laboratorian must have sufficient understanding of the biochemistry of drug activity and efficacy surrogates (as distinguished from diagnostic surrogates that most lab assays are used for) to properly determine the particular form of the analyte that is required for this trial and to determine if their assay will measure that form with both the specificity and sensitivity required.
3) The laboratorian must recognize the particular, and peculiar, needs of clinical research when assays are validated. The clinical validation ranges and decision points are often different in research than in a diagnostic setting. Many of the assays we use in drug development as potential surrogate markers do not have utility in diagnosing or treatment, so the clinical validation becomes a challenge of working with a cohort of patients to document the power of the assay to predict clinical outcomes. That requires close teamwork between the lab and the clinician and the researcher.

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Getting Started with Electronic Lab Transfers

By Patti Compton (Pfizer) and Jim Streeter (Pfizer)

Intro

For most clinical trials it is laboratory data that comprises the majority of data collection points, and, for the most part, this data is transferred electronically. Thus the manager's role has expanded to include the oversight of lab transmissions. This component of data capture generally encompasses the rules and the methods by which vendors generate, populate, and transmit production data transfers. This article outlines several factors critical to the successful transfer of lab data.

Establishing a Relationship

When working with a new vendor a qualification process specific to data transmissions is actually helpful to the establishment of the vendor relationship. This process commences either concurrently or after activities such as accreditation or system compliance have been verified. The qualification process consists of assessing capabilities with respect to: file formats, file transfer frequency, file transfer method, transfer type and hard copy requirements.

File Format: Defining the file format includes delineating both the syntax as well as the content. This, of course, depends largely on system and standards requirements of your data repository. Syntax can include such items as delimiters, column attributes (i.e. length, alphanumeric), or mark-up labels. Data content for this process includes contents of the file (e.g., data in the columns, meta-data), name of file, as well as conventions on file contents (e.g. "missing" lab tests). If systems are not initially compatible it may be necessary to consider preprocessing either by the vendor or the pharmaceutical company or both. Preprocessing in this instance refers to modification of the file's format and not the content (e.g. changing a file from fixed column position to comma delimited). In addition, developing a decision tree based on key fields that your repository requires (i.e. patient number, accession number, etc.) is likely to facilitate both decisions as well as requirements for preprocessors.

File Transfer Frequency: Transfer frequencies may vary between studies as well as within a given study. It is important to understand vendor capacity to provide multiple files and to set expected turnaround times for study initiation, conduct, and closeout. The schedule may also be influenced by projected data cleaning activities.

File Transfer Method: Most companies have established secure and compliant methods by which to receive files. While these are generally host-to-host, facilitating automated version control and preprocessing of file transfers, it may be necessary however for a vendor to support other methods where data may be handled by other organizations (such as a CRO).

Transfer Type: While transactional (or incremental) files allow for a faster availability of data, facilitating tracking and enrollment as well as other milestones, cumulative files may still be preferable for shorter studies. In addition, it may be necessary to confirm vendor capabilities if your particular study requires either a subset of patient data to be sent or special blinding needs.

Hard Copy: A lab should be able to generate a hard copy of the data sent. During the qualification process at least 50 actual samples should be compared against the hard copy.

Sample Survey to establish vendor capabilities

File Format Schemas	SAS, ASCII, XML, Other
File Format Specifications	CDISC, Oracle Clinical-BDL, LOINC, Other
File Transfer Frequency	Daily, Weekly, Monthly, Ad Hoc
File Transfer Method	Internet, Modem, CD, Diskettes, Other
Transfer Type	Incremental, Cumulative, Subsets, Blinded data

A completed qualification process would minimally include two successful test transfers: one to verify capability to send data and ensure content; one to verify change management. While the first file provides the validation of requirements and specifications, a second file is necessary to validate change management. Change management refers to modifications to data by the vendor after a transmission has previously been submitted. The need to modify data points arises under many different circumstances: wrong patient number, retest, visit date change, etc. Depending on the systems used, this can be tricky. It is important to test changes to key as well as non-key fields.

Lastly, a communication plan needs to be established. The process of file notification (if not automated) needs to be determined. An issue management plan needs to be agreed upon with both process and contact names. In the case of standing vendor relationships it is helpful to have periodic (i.e. quarterly) performance review meetings—for feedback, to discuss metrics and ongoing issues as well as to announce any anticipated changes.

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Lab Assays: All Methods are NOT Created Equal

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Method innovation is a cornerstone of laboratory progress. We can now measure almost anything at any concentration, but we still must be able to interpret the results. Increased utilization of the laboratory to identify, validate, perform, and interpret surrogate markers of clinical activity and efficacy is a significant key to accelerating drug development. Tighter linkage between the analytical method and the protocol needs will not reduce the number of methods available, but will reduce the confusion resulting from the multiplicity. ■

Getting Started with Electronic Lab Transfers

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The qualification process is dependent both on technical compatibility *as well as* capability. Thus in addition to being time consuming this process can be highly variable, lasting anywhere from 2 weeks to1 year! It is critical to lay out ahead of time a schedule for requirements to be established and delivered. And within a context of very short time lines a contingency plan would also be in order.

Production Data

Once a vendor relationship has been established, work can proceed at the study level. With each new protocol, schedule and content requirements need to be given to the vendor. File transfer frequency needs to be established for each protocol as well as any special transfer needs. Expected lab parameters with naming conventions, treatment codes, and units also need to be provided. Additionally, patient numbers and investigator site information must be provided to the vendor. Other expectations such as alert flag ranges should be established at this time.

Prior to the first production transfer for each protocol, a test file containing at least 10 patient's data should be sent and compared against hard copy. This will serve to verify requirements were met. As part of ongoing quality assurance, a quarterly review of 3 samples against hard copy should be compared for each protocol.

Re-qualification

The qualification process should be redone or reconfirmed if any of the major components described of the lab data transfer process are changed by either the pharmaceutical company or the vendor. Examples of this would include additional requirements of the data transmission syntax (i.e. a new data type), or modifications to any of the programming used to generate or manage the data.

Final Notes

Over the past two years, there have been extensive improvements within the industry to help standardize transmission of lab data. Standard nomenclature will assist with enhancements to related technologies such as lab viewing systems and lab reporting. As pharmaceutical organizations implement recognized standards such as CDISC, LOINC and XML, oversight of data transmissions promises to allow for quicker establishment of vendor relations, automated quality control, and expanded expertise with enhanced familiarity of terms and codes. ■

Central Laboratories: The Big Picture

Considerations in Auditing Clinical Laboratories

By Dorcie McKniff Jasperse, Ph.D. (McKniff & Associates, Ltd.)

For many clinical trials, Central Laboratories function far more like a Sponsor and/or Contract Research Organization (CRO) than simply a facility that analyzes biological specimens received during clinical trials. Today's Central Labs are highly automated, have tremendous throughput, and reach far deeper into clinical trials than local laboratories ever dreamed of in the past. And with this automation, has come a far greater blurring of authority, responsibility, and control of the laboratory data than ever before. For this reason, the role of the Central Lab must be fully appreciated by Sponsors in general and Data Managers in particular so it may be tightly managed. Such management is critical given that, for many clinical trials, laboratory data are not only primary safety data upon which medical and regulatory patient safety are judged, laboratory data are also often primary efficacy data. Without proper management, oversight and controls in place, the integrity of the entire clinical trial can come into question.

What is of particular importance is that much of laboratory data generated by Central Laboratories are in and of themselves source data and knowing how they come to be generated and managed by the laboratory is critical to being able to have full confidence in their integrity. So what should we look for when it comes to collecting, managing and producing high quality laboratory data in our clinical trials? First, let's look at the major steps involved in the collection, capture and management of laboratory data produced by today's Central Laboratory. After the generation of the protocol by the Sponsor, the Central Laboratory can be involved in some or all of the following process steps:

- Specimen Collection
  - Kit assembly/manufacturing at the laboratory
  - Kit distribution to the site
  - Kit receipt from the site
    - Subject identity verification
    - Subject demographic verification
    - Sample collection verification
- Specimen Analysis
  - Test ordering
  - Specimen routing
  - Specimen traceability through holds, cues, storage, aliquoting, and testing
- Data Capture
  - Test equipment result generation
  - Equipment/software interface
  - Database creation
  - Test result database population
  - Query generation and resolution
  - Direct site contact and interaction
  - Alert flag settings
  - Panic flag settings
  - Chain of custody reporting
  - Blind maintenance and blind breaking
- Patient Safety Reporting and Report Management
  - Report Design and control
  - Distribution to Sponsor, Investigator and Medical Monitor
    - Telephone
    - Fax
- Electronic Data Transmission to the Sponsor or CRO
  - Format definition
  - Media type
  - Transmission Frequency
  - Authorized personnel to request data transmission
  - Authorized personnel to request data revisions
  - QC procedures
- Other miscellaneous tasks
  - Kit inventory and expiratory management at the sites
  - Intercountry procedural standardization
  - Language requirement management

As one can see from this extensive laundry list of activities, all of which have quality gates associated with them, it is clear that control is paramount to producing high quality laboratory data in which Investigators, Sponsors and Regulatory bodies can have full confidence. Think about it, all of these activities take place without a single Case Report Form and almost every step is automated, the original Electronic Data Capture model. Play a short game of "What if?" with any one of the activities and it is easy to see that problems with any step in the process or lack of follow through are of major concern. Documentation of all processes and agreements should therefore be complete, current and stellar.

What used to be simply a highly technical process of specimen analysis has evolved into a gigantic exercise in process design and production controls over top of a vast array of increasingly complex technical procedures. Since most of these processes are controlled through automation, it is crucial that processes and data integrity are controlled through sound software development practices that are appropriately and sufficiently challenged.

The Summer 2003 issue of Data Basics discussed one Central Laboratory's approach to complying with 21 CRF Part 11. Since today's Central Laboratories operate much more as a CRO these days and must be managed as such by the Sponsor. Therefore, the Minimum Standards and Best Practices of the Good Clinical Data Management Practices should be observed with regards to external laboratory data and vendor management.

Other considerations in evaluating the capabilities of a Central Laboratory include:

- For international trials, if multiple Central Laboratory locations will be employed, do they have standardized policies, procedures and work instructions?
- Are there any operational differences among these laboratories?

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Central Laboratories: The Big Picture

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- Is communication and coordination among the laboratories well documented and controlled?

Of primary interest to the FDA are the agreements between the Sponsor and the Central Laboratory and any other CRO if involved. Such agreements should clearly delineate all roles and regulatory responsibilities and therefore should only be in writing, and handled as controlled documents with the appropriate corporate authorities and technical personnel having review and approval rights. In the event of an FDA inspection of the Sponsor, these documents will typically be requested and reviewed by the FDA Investigator. Although FDA does not generally perform Central Laboratory site inspections, the FDA Investigator will want to know the full extent of the Central Laboratory's involvement in the clinical trial and that the assigned roles and responsibilities between the two parties were documented in writing and followed in practice.

Because of the fully integrated nature of Central Laboratory operation, many Auditors approach the audit of a Central Laboratory as a combination of a Quality System audit, Good Clinical Practice audit and CRO audit with a healthy dose of an evaluation based on the Guidance for Industry, Computerized Systems Used in Clinical Trials thrown in for good measure. Although, this sounds a bit overwhelming, it really boils down to auditing basics, does the Central Laboratory:

- Say what they do?
- Do what they say?
- And document it?

This, of course, is half the battle for any Auditor. The other half is, if the Central Laboratory does all of these things, is what they are doing acceptable to the Sponsor and can the resulting data meet the regulatory standards required by the FDA? For even though the Central Laboratory is perhaps performing all of the previously delineated functions it will always remain the responsibility of the Sponsor to ensure data integrity and patient safety. Always.

After discussing all of these laboratory activities we haven't even yet touched on the reliability and accuracy of the actual laboratory test results themselves. Here, the FDA does not have direct jurisdiction (other than approving some diagnostic tests used by the laboratory), rather, certifying bodies are responsible for inspecting and accrediting and/or certifying laboratories. By using a certified and/or accredited laboratory, a Sponsor can hope to be assured that there has been technical evaluation of test accuracy and precision through outside and independent proficiency testing (PT). Basically, PT involves a laboratory receiving samples from the testing body, producing results and comparing those results to the known standard of the sample. Imagine if laboratory tests were inaccurate, not only would data integrity be at risk, think of patient safety. The consequences are almost unimaginable.

In the United States, the two most common certifications expected by Sponsors and reviewed by Auditors are the ones issued by The College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA). Other certifications are typically held by Central Laboratories in other countries and should be confirmed when performing international monitoring visits, Clinical Investigator GCP audits and/or Central Laboratory evaluations or audits.

CLIA certification is required by the Secretary of Health and Human Services for any laboratory that examines "materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of human beings." The program is administered by the Centers for Medicare and Medicaid Services (CMS) in conjunction with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). The requirements for these certifications and/or accreditations are easily located on the web. Typically, foreign countries have their own certifying or accrediting bodies that either have their own standards or may invoke particular ISO standards as their basis for certification.

Laboratory certification and/or accreditation typically means that when a laboratory receives a specimen they have demonstrated that they can accurately perform a set of specific laboratory tests and procedures and may have some elements of a Quality System in place. However, these certifications and/or accreditations should in no way infer that the laboratory is sufficiently able to perform the complex EDC operations and Data Management functions expected of a CRO, that is the responsibility of the Sponsor.

In the end, for laboratory data as well as all other clinical data, it all comes down to good clinical practice, does the "standard for the design, conduct, performance, monitoring auditing, recording, analyses, and reporting of clinical trials…provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected." ■

Please Note:

SCDM does not sell its membership list and does not condone the use of the on-line membership database for electronic broadcast marketing activities.

A "Prescription" for Success when Working with a Central Lab

By Sandra Dunlavy and Paddy Hanlon (MDS Pharma Services Central Lab)

The following article takes an amusing approach in describing the means of establishing and maintaining a strong relationship between a Central Lab and a Sponsor. It contains the prescription package insert for the data and project teams of both companies to follow while working together.

Having been prescribed the appropriate Central Lab for your study, it is important that you understand the impact it may have on your health and how to achieve the maximum benefits. The following health reminder will provide you with important information on the proper use, precautions and possible side effects of this important therapeutic agent.

Before Using this Medicine:

To ensure good health, prior to commencing your study, clearly define and align expectations with signed agreement on:

1. Timelines: defining milestones (i.e. event) and the associated deadlines (i.e. timing);
2. Data specifications: file structures, input from sponsor (specific coding, specific datasets). Standards across protocols translates into efficiency and cost benefits;
3. Delivery of data: identify recipients, frequency, encryption, mode of delivery (lab reports, electronic data transfers, ECG traces, etc);
4. Timely feedback: Was the data received? Are there any queries relative to the clinical data, in order to clean data in real time, to reduce time from last patient visit to database lock?;
5. Special data requirements: blinding criteria, special flagging, interim analyses, DSMB requirements;
6. Quality control: defining data checks and Q.C. of data;
7. Regulatory compliance: audits (internal, external friendly audits), 21 CRF Part 11, GCP;
8. Global reach and limitations: knowing and acknowledging strengths and weakness;
9. Metrics: turn around time, timeliness to study start, response rate, query resolution turn around time, timeline between last patient's last visit to database lock.

How to Use this Medicine:

To ensure expectations and deliverables will be met without adverse events:

1. Define and document roles and responsibilities: including contact information (email, telephone, fax, hours, preferred means of communication);
2. Define communication pathways: global data teams, regional data teams, cross functional teams (who to communicate with);
3. Document escalation procedures: who to contact when early signals arise of any potential divergence from the plan (if raised early, preemptive measures can be taken to prevent minor issues becoming major); written template to record issues, resolution actions, timelines serve as tools for communication among teams;
4. Conduct regular meetings: written agendas, minutes, documented action and follow-up items;
5. Determine accountability on both sides: this ties back to clearly defined roles, responsibilities and expectations;
6. Solicit alternate forms of feedback: surveys (vendor and/or sponsor), business development.

Cautions while Taking this Medicine:

"What we anticipate seldom occurs, what we least expect generally happens"
Benjamin Disraeli

Should any divergence from the plan occur:

1. Share information as it becomes available;
2. Notify teams immediately of any potential divergence from the plan;
3. Follow the established communication pathways;
4. Follow the escalation procedures;
5. Be proactive, communicate upfront;
6. Allow each party enough time to complete their commitments;
7. Strive for mutual agreement, being considerate and reasonable.

Possible Side Effects:

Providing your Central Lab with data specifications after the study has started or just prior to interim analysis can be linked to poorly defined expectations leading to such symptoms as difficulty sleeping, mood changes, nervousness, increased appetite, or indigestion.

Altering data specifications can lead to added risk of anxiety by both parties.

Consult your central lab data manager as soon as possible if you experience any of the above symptoms.

Additional Information:

Please keep your data specifications on hand at all times during the course of the study. Do not be afraid to share your Central Lab experiences with others .Regular communication of problem and success stories can help revise the package insert as appropriate, to ensure good health. ■

Global Challenges for European Laboratory Data Managers

By Sam Singh (Pivotal Laboratries)

As chairperson of The Association for Clinical Data Management (ACDM) Laboratory Data Special Interest Group (SIG), I am responsible for arranging meetings where speakers are invited to raise awareness and stimulate debate on all topics related to laboratory data. The ACDM Lab SIG was formed in early 2001 and is open to anyone who works or has experience with clinical laboratory data. The main aim of the SIG is to bring everyone together to discuss all aspects of lab data, increase awareness of all developments within our industry and share best practices.

Currently we have representatives from Pharma, CROs, EDC companies and Central Labs who work with various types of lab data - Haematology, Biochemistry, Bacteriology, X- ray, ECG etc. The SIG has an active interest in other organisations associated with lab data and a representative from CDISC regularly attends our meetings to give an update on the CDISC lab model. The SIG is now in its fourth year, we currently have a membership of over 100, and we are hoping to increase this number by offering a more varied look at clinical laboratory data.

We have had many highly successful and well attending meetings over the years. We have had meetings at GSK, Roche, Pfizer, P&G, Leo and AstraZeneca. Some of the topics we have covered include:

- Introduction to CDISC - CDISC - lab module update
- Handling laboratory data - Difficulties with Format Specifications - Lab Data Loading procedures
- ECG Data Management - Clinical Imaging data collection - Bacteriology data
- Local v Central Labs
- QA requirements for a central lab
- Request Form Design
- Lab Questionnaire Analysis
- Introduction EDM Forum - “eLIM” - EDC - Central lab integration
- Problems with reference ranges - Alternatives to reference ranges - Lab Data interpretation
- CDISC Lab format – a Pharma/Lab companies perspective

Members are encouraged to participate and contribute in any way they can – the majority spend most of the time cursing labs for not providing clean, structured and meaningful data! Surprisingly, most of the issues raised by the members are the same points Data Managers were making 10 years ago. However some members have raised issues that cause them problems when handling laboratory data generated from global projects. Some of these challenges facing Laboratory Data Managers are:

- Reference Ranges
  - Some countries make use of difference reference ranges than others
  - Some reference ranges may be different due to patients ethnic background
- Units
  - Conventional vs. SI (Standard International) units
- Test names
  - BUN vs. Urea
  - No Standardisations used
- Time differences
  - Urgent communications can be a problem as time zones vary
- Language
  - Some documents cannot be translated 100%
- Global databases
  - Are not always populated with the latest laboratory data

Global studies are here to stay and handling data from several sources and continents forms a large part of a Clinical Data Manager’s role – be it loading lab data / CRF data or resolving data queries. Standardisation IS the way forward! Many of the members agree that a lot of the work being carried out by CDISC for standardisation should help in data transfer and agreed standards (for example Logical Observation Identifiers Names and Codes - LOINC®) being used universally. Other issues can be down to terminology problems and understanding local customs.

Members concluded that it is vital for Pharmaceutical companies to have all parties concerned agreeing to data formats specifications, communication channels, frequency of data transfers, timelines, data cleaning responsibilities and contact details – ALL documented BEFORE the project starts. If these agreements exist and are followed then the majority of the issues Data Managers face would be greatly reduced.

To express an interest or to find out more information about this SIG, please contact Sam Singh, head of Information Services, Pivotal Laboratories (s.singh@pivotal-labs.com). ■

Good Clinical Data Management Practices (GCDMP) is available to download from the SCDM website, www.scdm.org. To date, over 800 people have downloaded GCDMP from all over the world.

Journal of Clinical Data Management Feasibility Survey Results Analysis

By Kit Howard (Kestrel Consultants) in collaboration with Lynda Hunter (PRA International) and Alec Vardy (CV Therapeutics)

Introduction

The SCDM Board of Trustees (BoT) is considering launching a Journal of Clinical Data Management, and has sponsored a survey of the SCDM membership to determine the interest in such a publication. The survey was intended to assess the overall support there might be for a journal devoted to CDM, as well as to gain insight into the major factors that could determine the scientific and financial success of such a journal. The survey was kept relatively short to increase participation, with the expectation that subsequent surveys may be administered to delve more deeply into specific items. Following is a description of the survey methodology, content, and conclusions. While it is recognized that conducting a survey electronically by definition limits the potential audience, and tends to bias the results towards those who are comfortable with electronic media, it was felt that the results were still useful.

Methods

The survey was designed by the SCDM Publications Committee, approved by the BoT, and administered through Zoomerang, an online survey service. It consisted of 18 multiple choice questions and one free text question. Most of the multiple choice questions provided an 'other, specify' text box. No question was mandatory. Questions were worded such that they could apply to non-SCDM members as well as members. The questions covered reading habits, potential journal content, subscription and media preferences, and demographics. The survey was activated on 5 December 2003 and was closed on 29 December 2003. Invitations to participate were sent via e-mail to the full SCDM mailing list, which numbered 2239. Results were analyzed using the bar and cross-tabulations charts provided by default by Zoomerang.

Results

Obviously this was neither a scientific nor a validated survey. The respondents were self-selected among those who do not take much of December off. They were likely to be those who felt most strongly about the issue, and those who had the fewest end-of-year deadlines. All that said; there were still some interesting observations that could be drawn from the responses.

From the 2239 invitations sent, 398 individuals responded, or 17%. This is a reasonable response rate for a non-incentivized survey, particularly when conducted close to the holidays. Blank records were excluded from the analyses. Individual question response rates were very high, with over 96% responding to every 'check only one answer' question. Two-thirds of the respondents were female, and one-third was male. Eighty percent had worked in CDM for at least three years, and 78% currently work in CDM. Fifty-three percent were in management, the balance in non-management roles, with about 80% in pharma or CROs. SCDM currently does not have the data to determine how these percentages compare to the demographics of the membership, so it is not known if these responses are representative of the membership.

From the results, it was clear that there is considerable support in SCDM for a journal, particularly among those for whom data management is a current professional focus. The bulk of the respondents wished to receive the journal as part of their membership, were willing to pay for it, and vastly preferred to have access to a paper copy (although many also desired electronic access). There was very little difference between professional levels in terms of how valuable respondents perceived a journal subscription to be. By contrast, while the majority of respondents felt that the journal would be a major benefit of membership, those who had been in the field of CDM for longer tended to be less certain as to its value. This may be a reflection of the dichotomy between management and non-management interests, and suggests a careful balancing of content in each issue between strategic and operational items.

Although the concept of what constitutes a scientific journal seemed to be a bit unclear to a number of the respondents (listing among others the Wall Street Journal), it appeared from the pattern of interest in the proposed topics that they were interested in original research as well as a much broader range of material. A *very* rough categorization and summarization of the topics that were rated to be of most interest to respondents, using very imprecise and admittedly overlapping categories, suggested that the strongest areas of interest were regulatory issues, the future of CDM/CDM changing roles, career development, training/certification/tutorial/tips topics, management issues, business issues, international topics, EDC and technology, and original research. The original list topics and responses are summarized in Table 1.

From a logistical perspective, some additional useful observations were possible. The vast majority of the respondents indicated that they read advertisements for jobs, products and services in the journals they currently read, and a significant proportion of those had taken some type of action in response to the ads. This will obviously be relevant information for the companies who would consider advertising in the journal. About 80% of respondents indicated that they would in some way retain the journal, either themselves, in the library or circulating it to others. This may be one of the driving factors behind the desire to keep paper, although others are certainly possible.

Conclusions

The overall conclusion appears to be that it is worthwhile for the SCDM to continue to explore the establishment of a Journal of Clinical Data Management. There is support among the membership, and a willingness to absorb the costs of such a journal. It must be noted that this survey largely reflects the opinions of SCDM

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Journal of Clinical Data Management Feasibility Survey Results Analysis

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members only. The international data management community is being invited to complete the survey via the International Network of Clinical Data Management Associations, and their ideas and opinions will be incorporated as appropriate into the design as the journal progresses. Additional next steps include a refinement of the potential content, identification of editorial staff, and further financial analyses. If all remains positive, journal launch will occur in 2005. ■

Table 1. Topics of Interest to Survey Respondents

Topics receiving at least 10 responses	Number of responses
Regulatory	120
Career Devel/jobs	114
Best practices/tips/tricks	94
EDC/technol/database topics	75
Management/ staffing	70
Future of CDM/CDM Roles	66
Business, metrics	57
International	54
Basics Tutorials/Training	53
Original research	45
Standards	24
Data Quality	18
Recognition of CDM Importance	12
Crossfunctional interfaces	11
Process definitions	10
Miscellaneous others	65
Total responses	888

SOCIETY FOR CLINICAL DATA MANAGEMENT

2004 FALL CONFERENCE

2004 Fall Conference Clinical Data Management in a Global Environment

October 3-6, 2004 • Fairmont Royal York Hotel • Toronto, Canada

Watch for Preliminary Program to be mailed in June
For more information, please visit www.scdm.org/events/

People News Column

News from AMSTAT

Paula K. Norwood

ASA Fellow Paula King Norwood has received the 2004 Biostatistics and Data Management Career Achievement Award from the Pharmaceutical Research and Manufacturers of America (PhRMA) for her significant contributions to biopharmaceutical statistics and leadership for industry statisticians and data managers over the past three decades. The award was presented to Dr. Norwood on March 9, 2004 at the Annual PhRMA Biostatistics and Data Management Leaders meeting.

Paula had an illustrious career in statistics following the attainment of her Ph.D. in Statistics from Virginia Tech. Paula established the Biostatistics Department within Ortho Pharmaceutical Corporation (now Johnson & Johnson PRD) and all of the supporting functions including Scientific Programming, Clinical Data Coordination, and Data Entry. In 1990 Paula was promoted to Vice President in J&J and in 1994 was named Fellow of the American Statistical Association. Paula retired from J&J in 2002.

Solution to Last Month's CDM Puzzle

This Career Achievement Award recognizes individuals with outstanding and sustained contributions to PhRMA and to the statistics and data management professions. Specific criteria are:

- Demonstrated leadership and promotion of statistical and data management concepts in applied settings
- Service to the statistical or data management professions through active participation in professional societies or trade organizations
- Development and deployment of methodological advances

Previous recipients are Noel Mohberg, Bruce Rodda, Carl Metzler, Irene Chow, Lyman Ott, John Schultz, Stan Schor, Charlie Sampson, David Salsburg, Mike Free, Bob Assenzo, Joe Ciminera, and Joe Dressner.

Please contact info@scdm.org if you have questions about registration for upcoming meetings, advertising, renewal of membership, or if you need to provide updated mailing/contact information.

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