2013

The Clinical Research and Data Management Course Proceedings

KING KHALID UNIVERSITY HOSPITAL MEDICINE AUDITORIUM

APRIL 29, 30, 2013 9 CME CREDITS

BIOMARKERS RESEARCH PROGRAM | King Saud University

Message from the Chairman

Assalamualaykum!

We all know that good clinical data fuels good clinical research, and good clinical research improves not only human lives but the world as a whole. To be part of this noble and ever evolving world of scientific research process requires discipline, focus and of course, enthusiasm. As a clinical scientist myself, I know that the profession I have entered is not, and never will be for the faint-hearted. As a matter of fact, it is a lifetime journey of successes and failures, of satisfaction and frustration. But above all, it is a journey of dedicated hard work leading to discoveries and milestones that have the potential to change and advance human health.

As the deputy director of the Biomarkers Research Program and over-all Chairman of the Data Management Course, I am extremely pleased and so proud of you all, our dear participants. You are what this course is about, and the knowledge that you will learn at the end of this short course will undoubtedly provide you a strong foundation, as you begin your sterling career in scientific and clinical research. The opportunity to learn is given to you, and your presence confirms that you are ready to seize this opportunity, and make the most out of it.

To our select and distinguished speakers, I am grateful for providing your valuable time, and in sharing your knowledge and real-world experiences in data management and clinical research. Your expertise serves as an inspiration to us all. More importantly, your generosity motivates the young and promising generation of researchers to harness their skills. Your contribution to this course undoubtedly assures continuity of what we all strive for: good clinical research.

Lastly, I am thankful to our ever supportive Rector, his excellence, Professor Badran Al-Omar, the staff and members of the Biomarkers Research Program, as well as our beloved sponsors. They strongly believed in our cause, and their generous support has definitely been a major driving force in realizing this short course that we all should take advantage of.

Sincerely,

Professor Nasser M. Al-Daghri
Deputy Director
Biomarkers Research Program
Director
Prince Mutaib Chair for Biomarkers of Osteoporosis Research

PROGRAM SCHEDULE

Monday April 29, 2013

Time	Title	Speaker
08:00- 09:00	Registration/Breakfast	
09:00-09:30	Opening Ceremony	
09:30-10:15	Introduction to Clinical Research	Dr. Mohamad Al-Tannir
10:15-10:45	Coffee Break	
10:45-11:45	History of Clinical Research: A Merging of Diverse Cultures	Prof. George Chrousos
11:45- 01:15	Lunch break & Prayer	
01:15-02:15	Introduction of ICH-GCP	Dr. Mohamad Al-Tannir
02:15-03:15	Roles and Responsibilities of Study Team	Dr. Shaun Sabico
0315-03:45	Coffee Break &Prayer	
03:45- 04:30	Research Ethics Committees/ Institutional Review Board: Procedures and Problems	Prof. Omar Kasule

Tuesday April 30, 2013

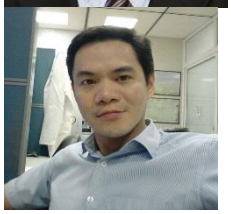
Time	Title	Speaker
08:00- 09:00	Breakfast	
09:00-10:00	Essential documentation in Clinical Research	Dr. Mohamad Al-Tannir
10:00-10:30	Coffee Break	
10:30-11:15	Pre-Analytic Phase: An Important Component of Clinical Research	Dr. Gyanendra Tripathi
11:15-12:00	Data Management: Ethico-Legal Considerations	Prof. Omar Kasule
12:00- 1:15	Lunch Break & Prayer	
01:15-02:15	Clinical Trials: Making Sure Everyone is on the Same Page	Dr. Philip McTernan
02:15-03:15	Clinical Data Validation	Prof. Nasser Al-Daghri

RESOURCE SPEAKERS

Prof. Nasser Al-Daghri, PhD (BRP-KSU, KSA)
Clinical Data Validation

Dr. Mohamadd Al Tannir (KFMC, KSA)
Introduction to Clinical Research
Introduction of ICH-GHP
Essential Documentation of Clinical Research

Prof. George Chrousos (Athens University, Greece)
History of Clinical Research: Merging of Diverse Cultures



Dr. Shaun Sabico, MD (BRP-KSU, KSA)
Roles and Responsibilities of the Study Team

Prof. Omar Kasule Sr. MB ChB (MUK), MPH (Harvard), PhD (KFMC, KSA)
Research Ethics Committes / Institutional Review Board: Procedures and Problems
Data Management: Ethico-Legal Considerations

Dr. Gyanendra Tripathi, PhD (Warwick University, UK)
Sample Preparation, Storage and Use

Dr. Philip McTernan, PhD (Warwick University, UK)
Clinical Trial Process

Introduction to Clinical Research

Dr. Mohamad Al Tannir, DMD, MPH

Clinical research is different than clinical practice. In clinical practice, one used established treatments while in clinical research evidence is collected to establish a treatment.

The clinical research consists of three main stages:

1. Identification of the research idea ---› formulating the research question ---› literature search ---› Refined research question. This stage aims to clarify what is intended to do and what are the expected outcomes.
2. The second stage initiates with the conversion of the refined research question to a specific hypothesis, selection of the appropriate study design, calculating the sample size, writing the protocol that should be submitted for IRB approval prior to any data collection.
3. Analyzing data, interpreting the results and writing the final report are the main tasks of the third stage of a clinical research.

History of Clinical Research: A Merging of Diverse Cultures

Prof. George P Chrousos, MD

Clinical Research encompasses A. "Patient-Oriented Research", i.e., Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects and includes (1) Development of new technologies, (2) Mechanisms of human disease, (3) Therapeutic interventions, and (4) Clinical Trials. B. Epidemiologic and Behavioral Studies and C. Outcomes Research and Health Services Research. We have the first evidence of Clinical Research in writings by Imhotep in Ancient Egypt circa 2850 BCE. Also, we have plenty of evidence on Chinese and Greek Medicine starting around 500 BCE. Hippocrates, a Greek physician, was born about 460 BCE and died about 370 BCE. He described the Hippocratic method according to which observation was paramount. He suggested that "A great part of the art is to be able to observe." He dissociated medicine from theology and philosophy, established the science of medicine and provided physicians with the highest moral inspiration and code. Galen, another Greek physician, who lived six centuries after Hippocrates (129- 216 CE), crystallized all the best work of the Greek medical schools and remained an unchallenged authority for >1,000 years. About the same time, Soranos of Efesos wrote the first treatise in Obstetrics, Gynecology and Pediatrics. At the end of the first millennium, Iranian and Arabic Medicine advanced greatly. Al Rhazi (865-925) discovered the use of alcohol as antiseptic, made contributions to medicine, alchemy, and philosophy and wrote the second treatise on pediatrics. He described a meningitis 'study' dividing intervention group (bloodletting) versus control to determine efficacy of bloodletting. A little later, Ibn Sina - Avicenna (973-1037) was a leader in pharmacy, philosophy, medicine and pharmacology. He wrote the *Canon of Medicine*, the main European medical textbook of 14^{th} –16^{th} c. Its text contains 1^{st} known treatise on clinical trials and provided the foundation for a systematic approach to drug testing. In his Treatise on Drug Testing, in the chapter titled *"The recognition of the strengths of the characteristics of medicines through experimentation" he suggested that* 7 conditions for experimentation are required: 1. Drug must be pure… 2. Drug must be tested for only 1 condition… 3. Drugs must be tested in contradictory disease states… 4. Strength of drug must be proportionate to severity of diseases… 5. Time at which medicine's therapeutic effect becomes apparent must be considered… 6. Drug must be observed for continued action… 7. In order to understand strength and effect, drug must be tested in humans before judgment… Scurvy was a major health problem for the British Navy in the 1700's. James Lind, a naval surgeon, conducted a clinical trial in 1747 to assess the utility of three therapies for scurvy. In the 1800's, Ignatz Semmelweis studied puerperal sepsis in Vienna over the protestations of his chief; he noted that the sepsis rate was three times higher in Division 1 than in Division 2. Divisions were identical except medical students performing autopsies worked in Division 1, midwives in Division 2. In 1784, King Louis XVI of France

appointed Benjamin Franklin to a Royal Commission to judge legitimacy of animal magnetism as a medical cure. He performed a single-blind, placebo-controlled trial and noted a clear placebo effect. In What Makes Clinical Research Ethical? (Ezekiel J. Emanuel, MD, PhD; David Wendler, PhD; Christine Grady, PhD *JAMA* 2000;283: 2701-2711) suggested 7 universal requirements : (1) Value —enhancements of health or knowledge must be derived; (2) Scientific validity — research must be methodologically rigorous; (3) Fair subject selection —scientific objectives…and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for subjects; (4) Favorable risk-benefit ratio —within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) Independent review —unaffiliated individuals must review the research and approve, amend, or terminate it; (6) Informed consent —individuals should be informed about the research and provide their voluntary consent; (7) Respect for enrolled subjects —subjects should have privacy protected, the opportunity to withdraw, and well-being monitored.

Introduction of ICH-GCP

Dr. Mohamad Al-Tannir, DMD, MPH

Good Clinical Practice (GCP) is the international ethical and scientific standard expected in all stages of design, conduct, and reporting of clinical trials. This lecture is intended to raise the clinicians' awareness of GCP before embarking on any clinical research. It will explain the importance of GCP, and defines the investigator responsibilities in clinical trials as well as the submission guidelines to the Institutional Review Board taking into account mutual responsibilities to ensure patient safety. It will highlight the procedures of monitoring visits; the role of the monitors and what is expected from them. Special focus will be on Serious Adverse Events (SAE) responsibilities and reporting, in addition to essential documentation and need for appropriate archiving.

Compliance with GCP will provide assurance that data are reported, results are credible and accurate, and that the rights, safety, confidentiality, and well-being of trial subjects are protected.

Roles and Responsibilities of the Study Team

Dr. Shaun Sabico, MD

Study teams are formed when researchers with a common objective work together for a specific goal or research project. These researchers can come from various fields, or experts in the same field. With an efficient study team, tasks are accomplished at a faster pace and with a reduced workload as well as reduced work pressure than when it is done by an individual. Furthermore, members of the study team can learn from one another, with an assurance of support and back up in times of crisis. Each study team member takes pride in his/her own contribution to the team, and each accomplishment takes a step further in the ultimate accomplishment of the study project. The roles and responsibilities of the study team are fixed, but can be tailored according to each members' expertise as well their willingness to get involved. In this presentation the individual team members with their designated tasks are highlighted and their roles emphasized.

RESEARCH ETHICS COMMITTES / INSTITUTIONAL REVIEW BOARD: Procedures and Problems

Professor Omar Hasan Kasule Sr., MB ChB (MUK), MPH (Harvard), PhD

The functions of IRB are to (a) initial evaluation and approval of research proposals to make sure they fulfill the requirements of the Saudi regulations on human research and the international consensus Good Clinical Practice Guidelines (b) follow up and approval of matters arising in the course of the research: protocol amendments, protocol deviations, adverse events, and ethical violations (c) monitoring of study execution by checking on vital issues such as proper consenting procedures, confidentiality of the data, and complete and up to date documentation.

Membership of the REC must have a diversity of medical professional competencies to make sure that for every project reviewed there is a member from the relevant discipline and not necessarily the sub-discipline. Membership must also include both clinical and basic science competencies. At least one of the members must be a normal community representative with no affiliation to the institution.

All research however simple it may be must be submitted to the REC Chairman. The Chairman will determine which proposals are exempt because they have no patient safety or ethical implications and go ahead to approve them immediately. The chairman can also approve expedited proposals (minimal patient risk) and if need be can consult one or more members of the committee. Protocols, investigator brochures, and consent documents of proposals with potentially significant patient risk are sent to all REC members for review with those from the relevant disciplines being asked to make a more detailed analysis and make a presentation to the REC. Outside experts may be consulted. If the issues are complicated the investigator may be invited to the meeting to explain.

The two main considerations in REC decisions are: (a) informed and voluntary consent following full disclosure of risks and benefits of the research (b) patient safety based on careful weighing of benefits and risks. Other considerations are: (a) confidentiality, (c) qualification of the researchers, (c) research facilities (d) conflicts of interest. REC decisions are best taken by consensus but if this is not possible the decision will be based on a simple majority of the members attending if the quorum is assured. The decision can be full approval, conditional approval, or rejection. If the investigator fulfills the missing information the chairman may approve a conditional approval without returning to the full committee.

RECs encounter several problems in their work. They usually have no enough resources (financial, secretarial, office space) for their work. The Chairman spends most time in administrative issues and making and communicating most of the decisions that are subsequently endorsed by the committee. Delegation of decision

making to the chairman expedites REC work and reduces researcher frustration. Members busy in their clinical work may not have enough time to study the proposals in detail. Many research proposals are not well written and if strict criteria were followed they should be rejected without consideration but this will discourage research; REC normally gives researchers advice on improving their proposals. International sponsors of research from the Pharma industry have increased the administrative workload of RECs by requiring so many documents and certification to conform to research regulations in their respective countries. Sponsored research is over-documented and the sponsor expect REC to review and approve many documents that have no direct relation to research ethics. Because of lack of clear regulations, RECs face problems in making decisions on research that involves storing tissue and genetic material as well as sending it for research in collaborating laboratories overseas.

Essential Documentation in Clinical Research

Dr. Mohamad Al Tannir, DMD, MPH

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. Any or all of the documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority.

Pre-Analytic Phase: An Important Component of Clinical Research

Dr. Gyanendra Tripathi, PhD

Advances in instrument technology and automation have simplified tasks in laboratory diagnostics reducing errors during analysis thereby improving the quality of test results. However studies show that most laboratory errors occur in the pre-analytical phase. The quality of data produced from clinical research is dependent on sample collection methodology, including processing, storage and to some extent on transportation. A wide range of variables may affect the results for a patient from whom a specimen of blood, body fluid or tissue biopsy has been collected, including the procedure for collection, handling and processing before analysis, which constitutes the pre-analytic phase. Physiologic variables such as lifestyle, age, gender and conditions such as pregnancy, are some of the pre-analytic phase factors that affect laboratory results. Endogenous variables such as drugs or circulating antibodies might interact with a specific method to yield spurious analytic results. As new markers are being proposed on a regular basis, pre-analytic problems associated with their measurements also require careful scrutiny and considerations. Therefore, this presentation will highlight the factors which need to be considered while collecting clinical samples for research.

DATA MANAGEMENT: ETHICO-LEGAL CONSIDERATIONS

Professor Omar Hasan Kasule Sr., MB ChB (MUK), MPH (Harvard), PhD

Abstract

Data includes words, numbers, images, and voice most often in an electronic form. Modern information technology handling large and multiple datasets has spawned new ethical issues that researchers dealing with a single research data base in one institution did not face. These issues are: data costs, data ownership, data confidentiality, and patient safety based on data validity. These ethical issues arise at the stages of data sourcing / collection, data editing, and data storage and retrieval. They also arise in the processes of data sharing and data integration. Data editing and validation can lead to biases that will eventually impact on patient safety through wrong research data and conclusions.

Operational data generated by hospitals, health insurance companies, and administrative units is not collected with due care to ensure research-quality accuracy (accuracy, coverage) and lies unused in data banks while researchers apply for and get grants to collect new data for their research purposes. The defects of these data bases can be overcome by instituting quality control programs and using multiple sources for cross validation. The data can be used for research by permission of the legal owner; laws and regulations are not yet clear on this issue because potential owners include the patients, the physicians, and the institutions. The issue of ownership leads to another question whether routinely collected data can be sold to researchers. A corollary to this is whether researchers can engage in selling or buying data with other researchers or commercial marketing and advertising agencies.

Data integration and **data sharing,** facilitated by modern information technology, enable access to more data in other institutions for analysis and standard setting. Information technology provides the algorithms for fast integration. **Data sharing** involves allowing other researchers to access data. Both integration and sharing are an ethical imperative to advance knowledge that benefits patients. Integration and sharing have been used mostly in genomic sequencing, nuclear mapping, imaging, clinical trials, and organ transplantation research. Integration and sharing enable researchers, present and future, to draw upon a larger data base but are associated with ethical issues of intellectual property, informed consent, privacy, and confidentiality are followed. Codes, standards, policies and mapping at local and international levels are being developed to address these issues. Owners of data collected at great expense are reluctant to share or integrate it with others without proper acknowledgement of intellectual property. Informed consent from patients is needed for data sharing unless fully anonymised. Data privacy and confidentiality are assured by use of secure data portals and cryptography.

Data processing within one research project has its own ethical issues. The data manager could introduce biases, random or non-random, in the processes of

adjusting for missing data, data transformation, and creation of derived variables. Data processing mistakes underlie several types of bias: misclassification, selection bias, and sampling bias. Any mistakes introduced at this stage will impact the final research results and eventually affect patient safety due to clinical interventions based on false research. The usual procedures for data privacy and data confidentiality must be respected. As far as possible personal identifiers should not be accessible except to a few selected members of the research team. The data should be kept locked up or in password protected computers. If the computers are connected online the institution should have policies and software to assure data security.

Clinical Trials: Making Sure Everyone is on the Same Page

Dr. Philip McTernan

Understanding the requirements of clinical trials begins with a clear knowledge of not only the type of clinical trials the researchers desires to undertake but also how this relates to the different type of clinical trials they reside within, whether this is pre-clinical or Phase I-IV. From this basis this session will explore two specific clinical trials (1) those involving medical intervention during surgery with the collection of tissue samples for analysis in the secondary care situation; (2) and those that occur in the primary care clinic which may involve dietary/medical supplement intervention. From these examples the session will highlight the importance of communication between staff, ensuring clear workflow plans and an understanding of responsibility for specific components of the trial. This session will also highlight how subtle errors can have a dramatic impact on the trial detailing the importance of clarity of communication, sample coding and personnel responsibilities within the trial. The session will draw upon prior experience of involvement in such trials and the highs and lows of this patient based data management research. This will lead into the second session on how to handle the samples and insight of further complications that can arise.

Clinical Data Validation

Prof. Nasser M. Al-Daghri, PhD
King Saud University

Human errors while inevitable can be minimized with the right attitude and the proper training. Reporting scientific information that is accurate and reproducible is the hallmark of good science. This is where data validation steps in. Data validation is an integral step in clinical research. It involves 2 processes: data validation/editing which reviews data for completeness, accuracy and logic, and discrepancy resolution, which verifies or corrects incomplete and/or inaccurate data. Continuous review of data is necessary to ensure obvious data errors, inconsistencies, data that is not meaningful, omitted data or additional hand written data. The entire step of clinical data validation while painstaking, is mandatory for good clinical research. It minimizes faulty information and gives credibility to the research team in their standing as reputable scientists. In this presentation, the basics of clinical data validation is given, different factors and activities that lead to error, data cleaning and first hand experiences in ensuring accuracy of data within the research team.