

## **Title: Clinical Research, Data Management and Biostatistics using SAS**

### **Draft proposal for addition of new courses to the existing Clinical Research and Clinical Data Management (CRCDM) Courses**

#### **INTRODUCTION**

1. There is huge potential for indigenous and outsourced clinical research in India as per Ernst & Young report put up as discussion paper at a recent conference organized by FICCI in Delhi in Oct 2006. The following lines are quoted from the same paper: I quote: “Clinical Research requires specific cognitive and communication skills to handle complex issues. Such knowledge resides with specialists, such as clinical research associate, clinical team leader, project manager, clinical supply manager, quality assurance manager, medical and regulatory affairs manager, data manager and head of clinical operations. Training of these professionals in GCP standards would go a long way to strengthen the CR industry. Specialized training requirements may include, training on clinical trial process, development of standard operating procedures and GCP and applicable regulatory guidelines. Only 10% of the present requirement of the 10,000 trained persons presently required in the healthcare industry are trained and certified annually. The requirement may grow as high as 50,000 trained people over the next five years. Such a large

number of trained people cannot be attained in India without the concerted efforts of both the public and private sector.” Unquote

2. Department of Bioinformatics, Pune University, in collaboration with Bioinnovat Research Services Pvt. Ltd. conducts a certificate course in Clinical Research and Clinical Data Management (CRCDM) since Nov. 2005. The Syllabus has been approved by the academic bodies of UOP and has also been appreciated by experts from ICMR and DST. This is the basic course giving an overall understanding of the clinical trial processes. After this course the participant is able to support the process as clinical research associate. The employment scene of past student from this course is encouraging.
  
3. To fulfill the expected growth in manpower requirement and the future needs of the pharmaceutical industry more courses are needed at different levels. Private institutions do conduct some courses for training such manpower. However, these are more like coaching classes. True growth of knowledge in this field can come through education programmes conducted by Universities. At present no university in India has started courses in this field. It is hence considered necessary to add new course in clinical research to impart wider skills needed in this area. With the globalization of the pharma industry it has become imperative to update and upgrade these courses so that Indian pharmaceutical industry can face the global challenges and maintains its growth in this vital segment.

4. Each of the new courses will be between 15-25 credits, which include both direct teaching, assignments and project. Students who have completed the certificate programme of University of Pune after completion of one of the new courses will be eligible for the award of a diploma from the UOP. Fresh students who will complete one of these courses will be eligible for a certificate. These courses to begin with will be started in two centres of Pune and extended at other centres in the country.
5. The fees for each new course will be Rs. 60,000.
6. It is proposed that each new course will be for a period of 3-4 weeks (Monday- Saturday) with around 8 hrs teaching for day.

## **CRM 301**

### **Medical writing and scientific publications:**

(375 hrs: 75 hrs teaching + 100 hrs assignments +200 hrs project)

### **OBJECTIVE**

Course on medical writing and scientific publications is designed for investigators and manager involved in preparation of various documents used in clinical trials such as protocols, new drug application, study reports, SOPs, papers for publication and submission to the regulatory authorities etc. Medical professionals need training in writing skills, as this is not covered in medical curriculum.

### **Prerequisite:**

Course is designed for graduates in medical, dental, nursing, veterinary sciences, pharmaceutical sciences and postgraduates in biology, biotechnology, bioinformatics, IT, or management. Certificate course in clinical research and data management of Pune University (or and equivalent course) is prerequisite for fresh candidates, but can be waived for those who have at least two years work experience in clinical research.

### **Course structure:**

**(75 hrs)**

- Basic introduction to medical writing terminology
- Overview of drug development, regulation and sequence, clinical background and drug discovery

- Pharmacological testing and pre-clinical research
- Filing of INDA, clinical trials protocols, phases of clinical research, filing of NDA
- Documents of drug submission and for medical community
- Writing of research reports, clinical trial reports
- Supportive documents for investigational brochure for clinical research, publication for medical community, authorship and ethical issues
- Manuscript preparation, material for professional meetings, poster and slide presentation in seminars and conferences.
- Promotion material for marketing keeping in view the legal and ethical issues.
- Literature search, discuss appropriate view of theory and conceptual frame work in research
- Selection of methods used in design, sample size, and data collection procedures that are appropriate, specific research questions.
- Purpose of literature reviews, reviews familiarities with library services and on-line databases.

**Assignments some examples: \***

**(100 hrs)**

- Critical evaluation of a published research article
- Conduct a literature review and summaries the findings.
- Preparation of a research proposal.
- Critical evaluation of research reports
- Conduct literature research on an assigned topic.

- Preparation of promotional material for marketing keeping in view the legal and ethical issues.

**Project:** (200 hrs)

\*All given assignments will be related to the areas of clinical research and trials.

## **CRM 302**

**A. Safety Pharmacology studies for Human Pharmaceuticals including Regulatory Toxicology**

**B. Regulatory affairs including audits**

(375 hrs: 100 hrs teaching + 100 hrs assignments +175 hrs project)

### **OBJECTIVE**

- A. The objective of the course is to train students to identify undesirable Pharmacodynamics properties of a substance that may have relevance to human safety.
- B. To evaluate adverse pharmacodynamics and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies.
- C. To investigate the mechanism of adverse pharmacodynamics effects observed/ or suspected.

The course also includes a number of regulatory guidelines which need to be followed during manufacture of pharmaceuticals like GMP, SOP, schedule M, ICH harmonization process, inspection of the regulatory agencies, preparation for audits etc. validation procedures, guidelines for controlling impurities and assessment of herbal medicines.

### **Prerequisite:**

Course is designed for graduates in medical, dental, nursing, veterinary sciences, pharmaceutical sciences and postgraduates in biology, biotechnology, bioinformatics, IT, or management. Certificate course in

clinical research and data management of Pune University (or and equivalent course) is prerequisite for fresh candidates, but can be waived for those who have at least two years work experience in clinical research.

**Course Structure:**

**(100 hrs)**

Safety Pharmacology studies -

- Definition of toxicology, descriptive mechanistic, regulatory, forensic and clinical toxicology. Human health risk assessment, hazard identification, predication and management.
- Toxicology tests in animals, acute sub-acute and chronic.
- Duration and dose ranging studies
- Dose selection, Pharmacokinetic and Pharmacodynamics end points
- Dose response relationship, acute verses chronic exposure, idiosyncratic reactions, interaction between chemicals
- Preparation of protocols
- Mutagenic studies in vitro and in vivo ,an overview
- An overview of carcinogenic studies its process and procedure transgenic mouse models
- Carcinogenic and ultimate risk to humans
- Factors to be considered for conducting carcinogenic testing
- Reproductive toxicology (An overview)
- Molecular and Biochemical bases of toxicity
- Species and strains selection of animals
- National and International guidelines for testing drugs and pharmaceuticals (ICH process and guidelines).



- Quality control and safety measures (GLP), responsibility of study directors, reporting of study results, storage and retention of records and materials, GLP audits.
- Alternative methods of assessing toxicity, in vitro models, cell lines, their use and limitations.
- Regulatory aspects of Bioavailability and Bioequivalence studies
- Animal pharmacokinetics and toxicokinetics

**Regulatory affairs including audit –**

- Revised schedule M,
- Standard operating procedures (SOPs)
- Good manufacturing practices guide for Active pharmaceutical ingredients
- Pre-appraisal inspections, WHO guidelines
- FDA inspections
- Pharmaceutical equipment validation, a vital component of QA during manufacturing
- Concept of Total Quality Management
- Documentation in pharmaceutical industry
- Table of contents of typical dossier
- GMP guidelines on the validation of manufacturing process
- Methods to develop and maintaining strict compliance
- Schedule Y requirements and guidelines on clinical trial for import and manufacture new drug
- Regulations and requirements for controlling impurities
- Guidelines for the assessment of herbal medicines

- Finger printing of medicinal plants with markers/ biomarkers.
- Preparation of DMF, NDA and ANDA
- ICH harmonization process

**Assignments some examples:**

**(100 hrs)**

- Preparation of protocols for toxicity studies, acute, sub-acute and chronic.
- Drug interaction and idiosyncratic reactions.
- Preparation of SOPs.
- Sample preparations of DMF, NDA and ANDA for different drugs.
- Regulatory requirement of controlling impurities and what is the present status.
- Preparation of dossier.
- International Regulatory Authorities (USA, UK and Europe)
- Schedule Y
- Importance of protocol

**Project:**

**(175 hrs)**

## **CRM 303**

### **Curriculum for site management and clinical monitoring program**

**(375 hrs. 100 hrs teaching + 100 hrs assignments+ 175 hrs Project)**

#### **Objective:**

The basic objective of this course is to provide information regarding coordinating and managing day-to-day activities of a clinical research study, operational, inter-personal and data management of the process. Staff requirements and construct time lines to target the appropriate study population and to store, shift and dispense a study drug or device as well as how to review some documents, case report forms protocols and study budget. Basis of data management and regulatory compliance at the study site. Reporting and managing serious adverse events on site, development of recruitment strategies and clinical study budget.

#### **Prerequisite:**

Course is designed for graduates in medical, dental, nursing, veterinary sciences, pharmaceutical sciences and postgraduates in biology, biotechnology, bioinformatics, IT, or management. Certificate course in clinical research and data management of Pune University (or and equivalent course) is prerequisite for fresh candidates, but can be waived for those who have at least two years work experience in clinical research.

**1. Drug Development Process**

Review FDA approved process for development and approval of a drug, role of key player in drug development.

**2. Informed consent process and human subject protection**

Key events in history that have impacted human subject rights, review informed consent process and describe regulatory requirements.

**3. GCP Regulation and Guidelines**

Key concept in regulatory application such as GCP, regulation guidance and ICH guide lines. Review mandatory regulations of FDA that apply to sponsor investigator and IRB.

**4. Collection of Regulatory Documents, Review and Submission**

Review the regulatory documents which must be collected and maintained, discuss the role of these regulatory documents, identify strategies to ensure their accurate completion, review management of study files.

**5. Adverse events (AE) and Serious adverse events (SAE)**

Introduction of AE and SAE to the management that occur during the conduct of a clinical study, outline regulatory expectations for the identification, documentation and reporting of these events to the sponsor and FDA. , review process and the system involved in safety management and pharmacovigilance in both domestic and global trials.

## **6. The Protocol and Data Management**

Review the purpose of the protocol and key factors both from CRA and site prospective, and their role in handling protocol departures, types of data collection and regulatory requirement and industry standards for collecting retrieving and analyzing subject data.

## **7. Site interactions**

Review communication skills and concepts for interacting with site personnel; indicate key principles for establishing productive work relationship and strategies for handling site problems.

## **8. Managing clinical supply/ laboratories**

Review CRAs role and regulatory responsibilities for managing clinical supply laboratories and test articles accountability during the conduct of a trial. Address issues of test, noncompliance and the policy to prevent or address noncompliance.

## **9. FDA inspections**

Review the purpose of FDA inspections, preparation for an FDA inspection, activity during an inspection, and outcome of an inspection activity following FDA inspections

## **10. Source Document Verification**

A brief review of basic data management concepts, discuss actual process of source documentation verification, addressing CRAs responsibilities, strategies and helpful hints for attacking data and problem resolution.

## **11. Training Orientation**

Review role of monitor trainee including site objectives, pre-approval requirements for site visits, site visit planning, site visit expenses and expense forms, site visits SOPs and documentation and sign of for training to perform independent site visits.

## **12. Interim visits**

Review the activities that take place during interim site visits and discuss the methodology for solving the most common problem that occur at investigative sites.

## **13. Site close out audit and inspections**

Familiarize new CRAs with activities that occur at the end of a trial and their responsibilities for completion of these activities.

### **Assignments :** **(100 hrs)**

- Discuss legal and ethical issues to be considered in subject selections.
- Issue of women and minority group in clinical research
- What factors will you keep in mind in selecting the site?

### **Project:** **(175 hrs)**

## **CDM 301: Bio-statistics using SAS techniques**

**(375 hrs. 75 hrs teaching + 100 hrs assignments+ 200 hrs Project)**

This program has been designed to provide advance Bio-statistics training and its application with SAS for a diverse range of students. It is primarily aimed at those wishing to become trained professionals and wanting an in-depth theoretical and practical statistical knowledge. From this course candidates will

- Be able to demonstrate a broad understanding of the value and basic principles of Bio-statistics methods in health and medical/clinical research.
- Develop the practical and technical skills with SAS software for better interpretation of the data from clinical studies.

### **Aim:**

To enable students to use correctly Statistical methods of particular relevance to evidence based health care and to advise on application of these methods using SAS for interpretation of the results.

### **Eligibility/ requirements:**

All students must have computer knowledge. All students admitted to this course are expected to have passed CRCDM course or have passed graduation with Mathematics or Statistics as one of the subject.

### **Content:**

**(75hrs)**

#### **A.**

- Introduction and revision of conventional methods for contingency tables, Chi-square tests.

- Measures of frequency and associations, odds ratio, relative risk.
- Distribution theory.
- Categorical data and GLMs.
- Key concepts of estimation and construction of Normal theory.
- Hypothesis testing, correlation.
- Role of ANOVA, regressions and confidence interval.
- Methods of inference based on likelihood theory.
- Main types of study designs.
- Sources of error- Chance, bias, confounding, association of causality.
- Evaluation of published papers.

## **B. Introduction and use of SAS**

- Environment of SAS.
- Library structure in SAS.
- Data steps and Proc step.
- Manipulating the data- Converting the numeric data to character and visa versa.
- Using logical operators and where conditions.
- Merging of the datasets.
- Writing the data into multiple datasets.
- Debugging errors in the program.
- Writing the procedure- Tabulate, Univariate, Means, Median, Mode, Report, Sort, Mixed, Transpose etc
- Creating the html reports.
- Importing the data to SAS and exporting the data from SAS.
- Overview of SAS macros.



## **C. Introduction to Databases System**

1. Basic Concepts of Database
2. Database System in Organization
  - A. Data Sharing and Database: Types of Sharing.
  - B. Strategic Database Planning.
  - C. Database and Management Control
  - D. Risks and Cost of Databases
  - E. Separating Logical and Physical Data Representation
  - F. Database Development (Database Development Life Cycle)
3. Data Modeling Using the Entity-Relationship Model (ER-Model)
4. Relational Data Model
  - A. Relational Model Concepts
  - B. Relational Model Constraints
  - C. Update Operations on Relations
  - D. Defining Relations
  - E. The Relational Algebra
  - F. Additional Relation Operation
  - G. Examples of Queries in the Relational Algebra
  - H. Relational Database Design Using ER-to-Relational Mapping
  - I. Introduction to Relational Calculus
5. An Introduction to SQL
  - A. Data definition in SQL
  - B. Queries in SQL
  - C. VIEWS in SQL
6. Record Storage and Primary File Organization
  - A. An Introduction

- B. Secondary Storage Devices
- C. Buffering of Blocks
- D. Placing File Records on Disk
- E. Operation on Files
- F. Files of Unordered Records (Heap Files)
- G. Files of Ordered Records (Sorted Files)

**Assessments:** **(100 hrs)**

Describe distribution theory.

Write a note on types of study designs.

Practical for data management.

Some examples for practical using SAS.

**Project:** **(175 hrs)**

## Reference books and suggested reading:

1. Asher R. How to present your article. *BMJ*, 2: 502, 1958.
2. Stephen Lock Thornes's better medical writing, Pitmen Medical, 2nd Ed. 6. 1977.
3. Fraser HS. Writing a scientific paper. *West Indian Med J*; 44 (4): 114-24, 1995.
4. Bradford Hill A. Logical order for a scientific paper. *BMJ*; 2: 870, 1965.
5. Gustavii B. How to write and illustrate a scientific paper. Cambridge Univ P. BMA 2003.
6. Hall GM. How to write a paper. *BMJ Books*. BMA 2003.
7. Montgomery S.L. Chicago guide to communicating science. Univ of Chicago P, BMA location: T 11.4. 2003
8. Peat J. Scientific writing: easy when you know how. *BMJ Books*, BMA location: T 11.4 .2002.
9. Mattsson, J. L., P. J. Spencer, and R. R. Albee, "A Performance Standard for Clinical and Functional Observational Battery Examinations of Rats," *Journal of the American College of Toxicology*, 15: 239 .1996.
10. Irwin, S., "Comprehensive Observational Assessment: 1a. A Systematic, Quantitative Procedure for Assessing the Behavioural and Physiologic State of the Mouse," *Psychopharmacologia* (Berlin), 13:222-257. 1968.

11. Haggerty, G. C., "Strategies for and Experience with Neurotoxicity Testing of New Pharmaceuticals," *Journal of the American College of Toxicology*, 10:677-687. 1991.
12. Murphy, D. J., "Safety Pharmacology of the Respiratory System: Techniques and Study Design," *Drug Development Research*, 32: 237-246. 1994.
13. Analysis of clinical trials using SAS: Practical guide.
14. Statistical methods for clinical trials (Biostatistics) by Mark X, Norleans (Hardcover, Jan 15, 2001).
15. ICH (ICH Harmonized Tripartite Guideline for GCP E6 (R1) 10<sup>th</sup> June 1996.
16. Good Clinical Practice: consolidated guidelines UOP. Jan 2007.
17. Operational guidelines for ethics committees that reviews Biomedical Research, WHO Geneva 2000.
18. Drugs and Cosmetics (2<sup>nd</sup> Amendments) Rules MOHFW Notification 20th Jan 2005.
19. Guidelines for Industry.  
Bioavailability and Bioequivalence.  
Studies for orally administered drug products-General consideration. U.S. Department of Health and human services. Food and Drug administration.  
Centre for Drug and evaluation and Research (CDER) March 2003.
20. Guidelines for Bioavailability and Bioequivalence studies

CDSCO, DGHS, MOHFW, GOVT.OF INDIA.March2005.

21. Saranjit Sing. Drug stability testing and shelf life determinations according to international guidelines. Pharmaceutical Technology. June 1999.
- 22.Judy, P. Boehlert. Impurities- Where are we now? Pharmaceutical Technology. June 1997.
- 23.Pharmacological Basis of Therapeutics. Goodman and Gillman. 8<sup>th</sup> Edition, 2006.
- 24.Essentials of Medical Pharmacology. Tripathi. 5<sup>th</sup> edition, 2003.
- 25.Lawrence, D.R., Bennett, P.N. Evaluation of drugs in man, therapeutic trials, Clinical Pharmacology, Churchill Livingstone, 8<sup>th</sup> Edition, 1979.
- 26.Database Management and Design.  
By Gary W. Hansen, James V. Hansen, Prentice Hall, 2nd edition, 2002.
- 27.Fundamentals of Database Systems.  
By Ramez Elmasri, Shamkant B. Navathe, T. Benjamin. 2nd edition, 2002.
- 28.Database System Concepts  
By Henry F. Korth, Abrabam Silberchatz, Mc Graw Hill. 4<sup>th</sup> edition, 2002.
- 29.An Introduction to Database Systems.  
By C.J. Date, Addison Wesley. 7<sup>th</sup> edition, 2003.
- 30.United States Food and Drug Administration.  
(<http://www.fda.gov/>).

31. FDA Center for Devices and Radiological Health  
(<http://www.fda.gov/cdrh>).
32. MeddiQuest Consultants Information Site  
(<http://www.meddiquest.eu>).
33. Medicines and Healthcare Products Regulatory Agency (UK)  
(<http://www.mhra.gov.uk/>).
34. Europa Medical Devices  
([http://ec.europa.eu/enterprise/medical\\_devices/index\\_en.htm](http://ec.europa.eu/enterprise/medical_devices/index_en.htm)
35. New Approach Organization (<http://www.newapproach.org/>).
36. Global Harmonization Task Force (<http://www.ghtf.org/>).
37. MeddiQuest: Internation Regulation Consultants Information Pages ([http://www.meddiquest.com /](http://www.meddiquest.com/)).
38. Regulatory Affairs Professionals Society  
(<http://www.raps.org/>).
39. The Organisation for Professionals in Regulatory Affairs  
(<http://www.topra.org/>).
40. ICH M3 Timing of Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (FDA, 1997).
41. ICH S6 Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (FDA, 1997).
42. Fundamentals of clinical research. [www.cra-training.com/testimonials.org](http://www.cra-training.com/testimonials.org).
43. <http://books.google.com/books/sas?hl=en&q=clinical+trials>
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