CLINICAL RESEARCH AND DATA MANAGEMENT

Syllabus of the theory papers

CDMT-01 -Preclinical and Clinical Research

Total Hours: 52

Unit – I **10 hours**

Drug Discovery process and Drug designing: Overview of Drug discovery process, Cost of Drug development, Protein Structure Prediction: Comparative and Homology modeling, The Critical Assessment of protein Structure Prediction (CASP), Superposition of proteins using different tools, RMSD, Presentation of protein conformations, Hydrophobicity factor, Shape complementary. Molecular Docking Studies: Structure-based De Novo Ligand design, Drug Discovery – QSAR, Different types of docking approaches (Structure-based, Ligand-based), Mode of interaction studies, Pharmacophore prediction based on the docking analysis.

Unit – II **13 hours**

Preclinical studies: Preclinical drug development, Guidelines for animal studies , Types of Pre-clinical trials, Pharmacokinetics: Overview, Routes of Drug Administration, Absorption (Bioavailability, Active and Passive Diffusion), Distribution (Modes of Distribution), Metabolism (First Pass Effect, Second Pass Effect, Half Life of Drugs, Biotransformation, Importance of CYP families in Metabolism), Excretion (Clearance Rate, Modes of Excretion) and Pharmacodynamics (PD): Receptor Activation, Commonly Targeted Receptors, Signaling Mechanism and Drug Action, Dose Response Curve, Action of Agonist and Antagonist, Efficacy and Toxicity (LD 50, ED 50)

Unit – III **07 hours**

Human Anatomy and Physiology: Introduction to Human anatomy and Physiology and related disorders: Integumentary system, Muscular system, Skeletal system, Circulatory system, Nervous system, Lymphatic system, Respiratory system , Digestive system and Endocrine system.

Unit – IV **09 hours**

Clinical research: Scope of Clinical Research, Good Clinical Practices (GCP), History of clinical research, Nuremberg code, Belmonte report, Thalidomide disaster, Types of clinical trials, clinical trials Phases, Special Clinical Trials, Medical Devices Trials, Un-anticipated risk in clinical research. Investigator Brochure, Informed Consent Form, Sponsor Monitor and Investigator responsibility, SOP in Clinical Trials, Clinical Trial Monitoring, Role of CRA, QA and QC in Clinical Trials, CRF Design.

Unit – V **10 hours**

Study Population and Design: Overview of study design, Issues on generalization. Practical aspects: recruitment (case method example). Selection of the Questions, Types of questions, adverse

effects.Study design:Natural history, frequent errors. Types of studies: Experimental, uncontrolled, RCTs, other designs – equivalence, non-inferiority, observational, retrospective, sample size, bias and confounding. Experimental Design - issues of uncontrolled studies: before and after comparison in a single group, temporal variation of disease, staff, equipment and environment, , learning and psychological effect.. Experimental Design – Randomized Clinical Trials: parallel-group design, stratified parallel group design, parallel group randomized block design, complete cross-over design, simultaneous treatments design, factorial design. Types of randomization: simple , blocked, stratified and Adaptive, Blindness:– unblinded, Single Blind, Double-blind and Triple blind trials, .Dichotomous response variables, Sample size: sample size for repeated measures, equivalency of interventional studies , Estimating sample size parameters, fraud and misconduct.

Unit – VI **05 hours**

Genomics and Personalized Medicine: NGS techniques: Illumina (Solexa) sequencing, Roche 454 sequencing, Ion torrent: Proton / PGM sequencing, SOLiD sequencing, PacBio sequencing and Fourth generation sequencing, Purpose of DNA and RNA sequencing, Cost and speed of each platform; discussions on relative extent of uses, advantages and applications of sequencing in personalized in medicine and Biomarker development.

References

1. A.R.Leach, Molecular Modelling Principles and Application, Longman, 1996.
2. J.M.Haile, Molecular Dynamics Simulation Elementary Methods, John Wiley and Sons,1997.
3. Satya Prakash Gupta, QSAR and Molecular Modeling, Springer - Anamaya Publishers,2008
4. Laurence Brunton, Bruce A Chabner, BjornKnollman (12th Edition): Pharmacological Basis of Therapeutics.
5. Laurence Brunton, Bruce A Chabner, BjornKnollman (2nd Edition): Goodman and Gilman Manual of Pharmacology and Therapeutics
6. Gregory Bock, Dalia Cohen, Jamie Goode, Novartis and J. Craig Venter (2001) From Genome to Therapy: Integrating New Technologies with Drug Development - No. 229.
7. Susanna Wu-Pong, YongyutRojanasakul, and Joseph Robinson (2006): Biopharmaceutical Drug Design and Development.
8. Herbert A Kirst, Wu-KuangYeh, Milton J (2001): Enzyme technologies for pharmaceutical and biotechnological applications.
9. Xinkun Wang, Next-Generation Sequencing Data Analysis

CDMT-02: CLINICAL DATA MANAGEMENT

Total Hours: 52

Unit I **11 hours**

Data Collection and Reporting: Recruitment of Study Participants: strategies and Sources, monitoring, problems, reasons for participation, reducing dropout rates. Participant Adherence: Considerations before participant enrolment, maintaining good participant adherence, adherence monitoring, special populations. Assessing and Reporting Adverse Events: determinants of adverse effects, reporting adverse events. Data collection and quality control: problems in data collection, minimizing poor quality data, training, pre-testing, techniques to reduce variability, data entry, quality monitoring.

Unit II **12 hours**

Clinical Research Site Management: Preparation of protocol, Audits and Inspection of Trial sites, Budgeting of Clinical trials, Multicentric Clinical Trials. Study management: Monitoring process, Coordinating protocol implementation, Internal and external reporting; Performance Measures: timesheet, clinical monitor, Clinical Trial Management. Quality Assurance and Clinical Data Management plan, Data management standardsin clinical research, and Monitoring Database audits, QA group, clinical monitoring . Data privacy, Data Capture: Optical Mark Recognition, electronic data capture, Optical Character Recognition; Data validation, Data presentation, data storage and archival, Handling missing data: imputations and challenges, adjusting for baseline variables. Good Clinical Data Management Practices, Data Management Plan, CRF designing. Serious adverse event data reconciliation,Database closure, Design and analysis of surveys, CDISC standards, Dataset preparation for analysis.

Unit III **07 hours**

Pharmacovigilance: Adverse Event Reporting System And Form, Diagnosis And Managements Of ADRs, Medical Evaluation Of AE Quality System In PV, Expedited Reporting Criteria, PSUR & PBRER, PV Database And Signal Detection,Risk Assessments & Managements.

Unit IV **11 hours**

Guidelines of Medical Coding: Introduction to Physiology and Anatomical Coding, Medical terminology, Professional guidelines for medical coding: ICD -International Classification of diseases, CPT -Current Procedural terminology, Standardization of medical terms, MedRA and other coding dictionaries.

Unit V . **11 hours**

Regulatory Affairs : Historical Perspective, Ethical Issues, ICH-GCP Guidelines I and II, Schedule Y, ICMR guidelines for biomedical research, Regulatory Issues in US, Australia, Japan and Europe (UK), Regulatory Issues in India.

REFERENCE BOOKS

1. A manager's guide to the design and conduct of clinical trials by Phillip I. Good
2. Clinical Trials: Design, Conduct and Analysis by Curtis L. Meinert
3. Clinical Trials: A Practical Guide to Design, Analysis, and Reporting By Duolao Wang, Ameet Bakhai
4. Fundamentals of Clinical Trials By Lawrence M. Friedman, Curt D. Furberg, David DeMets
5. Management of data in clinical trials by Eleanor McFadden
6. Principle and Practice of Clinical Research by John I. Gallin, Frederick P Ognibene
7. Clinical Data Management By Richard K. Rondel, Sheila A. Varley, Colin F. Webb
8. Principles and Practice of Clinical Research By John A Gallin
9. Understanding Oracle Clinical by Safari Books online

CDMT-03: BIOSTATISTICS AND DATA ANALYSIS

Total hours: 52

Unit I **18 hours**

Fundamentals of Biostatistics: Data classification, data distribution, descriptive methods for categorical data, descriptive methods for continuous data. Statistical Tests (note: only basics of statistical tests will be covered), estimation of parameters, comparison of population, proportions, comparison of population means, correlation and regression. Sample Size: dichotomous response variables (two independent samples, paired dichotomous response).Sample size for continuous response variables (two independent samples).Sample size for repeated measures, Sample size for equivalency of interventional studies, Estimating sample size parameters. Survival Analysis: Estimation of the survival curve (Kaplan-Meier estimate).Comparison of two survival curves, covariate adjusted analysis, use of survival analysis in clinical research. Other Issues in Data Analysis Poor quality or missing data, Intention-to-treat analysis, Competing events, Covariate adjustment. Other Issues in Data Analysis 2: subgroup analyses, comparison of multiple variables, use of cut points, meta-analysis of multiple studies. Probability and Normal Distributions, Estimation, Hypothesis Testing, Anova

Unit II **07 hours**

Statistics for clinical trials: Types of data in clinical trials, Computer System Validation: 21 CFR 11, CTM system, Systems Software Validation Issues: auto encoder, User Acceptance Test, SDLC; Oracle Clinical, workflow, Intelligent Character Recognition; Basic Clinical Research tools and Resources for Data Management and Analysis SAS CLINICAL: Introduction to SAS in CDM, components of SAS, Different data types, Base/SAS, SAS/STAT, SAS/GRAPH, SAS/ACCESS, SAS Procedures, SAS Macros, Brief Introduction to SQL, SAS/SQL, SAS Enterprise Guide 4.1

Unit III **13 hours**

Case Study using SAS: TLG (Tables listings and Graphs) of clinical trials in SAS, Tables in clinical trials, Screening failures, Subject disposition, Subject disposition by visits, Premature discontinuation from study medication, Subject disposition by center, Protocol deviation, Demographics and baseline characteristics, Medical and surgical history, Gynecological history, Screening Pap smear, mammography and serum pregnancy test results

Unit IV **14 hours**

NGS data analysis: Downloading the genome sequence, Quality Check & Filtering, Read assembly, Gene prediction, Gene annotation, Advance annotation and analysis, Diseases variant identification, Haplogroup identification, Binding site identification, pathway analysis.

REFERENCE BOOKS

1. Analysis of Clinical Trials Using SAS: A Practical Guide By Alex Dmitrienko, Geert Molenberghs, Christy Chuang-Stein, Walter W. Offen
2. Fundamentals of clinical trials by Lawrence M. Friedman, Curt Furberg, David L. DeMets
3. Medical Statistics: A Textbook for the Health Sciences By Michael J. Campbell, David Machin, Stephen J. Walters
4. Professional SAS Programmer's Pocket Reference by Rick Aster
5. Practical Guide to Clinical Data Management, Second Edition by Susanne Prokscha
6. support.sas.com/documentation/onlinedoc/91pdf
7. Xinkun Wang, Next-Generation Sequencing Data Analysis

CDME: Syllabus of the Elective theory papers

(Choose from any one of the following)

CDME-01- MEDICAL WRITING

Total Hours : 52

Unit I **08 hours**

Introduction & Scope- Origin of technical documentation: ICH guidelines, Basic report writing review Clarity: basic principles of clarity Communication cycle. CTD Triangle: Information on the CTDe of medical writing: The medical literature and Clinical Writing; Scope of clinical writing, Examples of Medical Writing, Required skills, Primary employers; Spectrum of jobs/engagement of clinical writers.

Unit II **10 hours**

Scientific publishing - Scientific Article: Principal parts and content, The medical literature and the scientific publication process, Title, abstract, keywords, introduction, Objectives. Material, methods, results, discussion. Technical Issues in Medical Writing: Tables: Advantages; characteristics of a good table, Figures: Types of Figures, Copyright,Permissions Citations: Referencing; citation-parts; Publication practices and authorship; Scientific Integrity, Misconduct in research; Ethics of authorship, Plagiarism and other forms of misconduct in research, In-text citation styles (APA, MLA), Mendelay and other open access software to formalize citations.

Unit III **12 hours**

Data acquisition, Basic report writing review Clarity: Managing and Sharing Data, Data ownership, Ethical and Data Acquisition Issues. Data Management Concerns, Privacy and Confidentiality. Regulatory writing: Definition of terms: laws, regulation, guidelines, Role of Regulatory Affairs in the Drug Development, The Investigational New Drug (IND) Application as the Platform for Drug Development, Regulatory Environment in India. Regulatory bodies-National and international. Selected regulations and guidance for drug studies (FDA).

Unit IV **10 hours**

Medico-Marketing Writing- Standard Operating Procedures-SOP - Developing Effective Standard Operating Procedures, How to Write Standard Operating Procedures,Writing for Biotech Industry/Pharmaceutical Industry, Pharmaceutical Marketing, Writing An Effective Case Study For A Medical Device, Advertising drugs; Legal considerations. Writing- Vetting of advertisements, Truthful presentation, Essentials for public advertising, Professional advertisement essentials. Minimum requirements.

Unit V **06 hours**

Common technical document (CTD)- India Safety Writing-Safety (MSDS)- industry perspective SAFETY NARRATIVES - Clinical Trials . Other issues: consistency, tracking, delivery Medico-Marketing Writing, Origin of technical documentation, ICH guidelines.

Unit VI **06 hours**

Interpersonal Skills: Understand work output requirements, company rules, guidelines & policies related to the process flow, identifying and reporting issues requiring intervention, delivery of quality work on time & report any anticipated reasons for the delay, importance of team work, resolution of conflicts, multi-tasking, training the team members, knowledge of project management

Reference Books

1. Clinician's Guide to Medical Writing by Robert B Taylor
2. Independent Medical Coding: The Comprehensive Guidebook for Career Success By Donna Avila-Weil, Rhonda Regan
3. The Complete Guide to Medical Writing By Mark C. Stuart
4. Dr. S.S. Khanka, Enterpreneurial development", S.Chand publications

CDME-02: SCIENTIST - CLINICAL RESEARCH & DRUG DEVELOPMENT

Total hours:52

Unit I **10 hours**

Basics of Clinical Pharmacology

Pharmacokinetics and Pharmacodynamics and its clinical applications. Rational Prescribing. Adverse Drug Effects, Toxicology and Drug Interactions.PK-PD study, significance in clinical research.BA-BE study, significance in clinical research. Route of drug administrations, advantage & disadvantages. First Human Dose, Drug Designing and Formulation.

Unit II **10 hours**

Clinical Development

Definitions & Terminologies, History in Clinical Research, Regulations and Ethics in Clinical Research.IND, NDA& ANDA processes, requirements & guidelines. Clinical trial Preparation, Clinical Research Monitoring, Patient recruitment and retention, Adverse Event and Serious Adverse Event Reporting, Agreement and Clinical Trial Budget, Error Fraud and Misconduct QA/QC,Compliance Audit and Inspection, Project and Vendor Management, Finance Management of Clinical Trials.

Unit III **10 hours**

Clinical Evaluation

Scope, Definitions, General principles of clinical evaluation, Source of data/document used in clinical evaluation (stage1), Appraisal of clinical data (Stage2), Analysis of clinical data (stage3).The Clinical Evaluation Report and the role of the notified body in assessment of clinical evaluation data-Examination of design dossier, Evaluation as part of the quality system procedure and Notified body specific procedure and expertise.

Data Science

Study Setup and CRF Designing for a clinical trial, Creating Reports and Transferring data. Clinical data analysis and reporting using software, Understanding and reviewing statistical analysis plan. Creating Analysis Datasets.

Unit IV **10 hours**

Clinical Evaluation /Reporting and documentation

Scope, Definitions, General principles of clinical evaluation, Source of data/document used in clinical evaluation (stage1), Appraisal of clinical data (Stage2), Analysis of clinical data (stage3).The Clinical Evaluation Report and the role of the notified body in assessment of clinical evaluation data-Examination of design dossier, Evaluation as part of the quality system procedure and Notified body specific procedure and expertise. Data Science - Study Setup and CRF Designing for a clinical trial, Creating Reports and Transferring data. Clinical data analysis and reporting using software, Understanding and reviewing statistical analysis plan. Creating Analysis Datasets.

Unit V **06 hours**

Safety and Security at workplace

Different types of occupational health hazards, knowledge of chemical substances, characteristics & safety measures, use of safety gears, masks, gloves & accessories, evacuation procedures for workers & visitors. Health, safety & security issues – types (illness, fire accidents), company policies and procedures, When and how to report, summon medical assistance & emergency services

Unit VI **06 hours**

Interpersonal Skills

Understand work output requirements, company rules, guidelines & policies related to the process flow, identifying and reporting issues requiring intervention, delivery of quality work on time & report any anticipated reasons for the delay, importance of team work, resolution of conflicts, multi-tasking, training the team members, knowledge of project management

References:

1. WHO expert Committee on specification for Pharmaceutical Preparation WHO-GENEVA, 2005 edition.
2. ICMR guidelines-2008, ICMR -New Delhi, 2006 edition.
3. Clinical Research Fundamental and Practice-Vishal Bansal Para Medical Publisher, 2010 edition
4.Pharmacovigilance for Beginners-Dr. S Gunasakaran and R. Salhesh Kumar Tatamani Magalir Co-operative press, 2010 edition.
5. Essentials of clinical Research-Dr. Ravindra B Ghooi amd Sachin C. Itkar Niral Prakashan 2010 edition
6. Basic methods of Medical Research, Aitbs Publishers, India, 2013 edition.
7. Clinical Research quality system manual, Nancy J Stark. 2009

Syllabus of the practical paper

CDMP01: PRECLINICAL STUDIES AND MEDICAL WRITING

1. Sketching of a molecule, preparation of small molecule, Preparation of protein and docking
2. Building a 3D structure of a protein,Pharmacophore mapping
3. Cytotoxic assay
4. Proliferation assay
5. Isolation of genomic DNA from Blood and Agarose gel Electrophoresis.
6. PCR
7. Genome sequencing
8.2D gel electrophoresis
9. Flowcytometry
10. HPLC
11. Animal Handling, Blood with drawal from rat through tail vane puncture, Blood with drawal from rat by retro-orbital puncture
12. Administration of Drugs by oral route, Intravenous injection, Intramuscular injection
13.Abstract writing ,Writing of Introduction in a manuscript ,Writing of Materials and Methods in a manuscript , Writing of Results in a manuscript, Discussion in a manuscript, Writing of conclusion in a manuscript , Referencing(endnote format)
14. Using of Microsoft word , Using of Microsoft excel(incorporating formulae, graphs)
15. SOP writing
16. Protocol writing
17. Management of open clinica
18. eCRF design
19. Randomization, study set up
20. Subject profile preparation

CDMP02: SAS AND DATA ANALYSIS

1. Introduction to SAS
2. Running SAS programs
3. Descriptive information and statistics
4. An overview of statistical tests in SAS
5. Exploring data with graphics
6. using where with SAS procedures
7. Missing values in SAS
8. SAS options
9. Overview of SAS syntax of SAS procedures
10. Common error messages in SAS
11. Inputting raw data into SAS
12. Reading dates into SAS and using date variables
13. Creating and recoding variables
14. Using SAS functions for making/recoding variables
15. Subsetting variables and observations
16. Labeling data, variables and values
17. Using Proc Sort and the BY statement
18. SAS Functions
19. Gene annotation
20. Pathway analysis.