



Pan African Thoracic Society and American Thoracic Society

MECOR

**Methods in Epidemiologic, Clinical & Operations Research
(MECOR)**

Level 2 Course Syllabus

Monday, October 10 – Friday, October 14, 2011

ACKNOWLEDGMENTS

**The Nuffield Foundation is the primary sponsor of the
2011 MECOR Course in Kenya**

Additional support has come from:

**Kenya Medical Research Institute
(In partnership with the University of Nairobi and the Division of
Tuberculosis and Lung Disease)**

American Thoracic Society

Liverpool School of Tropical Medicine

Société de Pneumologie de Langue Française

Our sincere thanks to all who have seen the vision and support this program

**Ruth N. Mkoji - KEMRI
Elizabeth Kendi – KEMRI**

**Jane Ardrey - PATS Administrator—Liverpool School of Tropical Medicine
Helen Barry—Liverpool School of Tropical Medicine**

**2011 ATS MECOR Course Staff
Fran Du Melle - Senior Director**

**International Programs and Activities, American Thoracic Society
American Thoracic Society, 61 Broadway, New York, NY 10006-2747 USA**

E-mail: fdumelle@thoracic.org

Level 2: Advanced Clinical Research Methods

Instructors

Shannon Carson, Director
James Kiari
Lawrence Mufami
Brian Faragher
Phil Hopewell
Maxwell Akanbi (TA)

Welcome to MECOR Level 2! This course is an extension of what you learned in Level 1, but it will introduce you to many new topics. The Aim of the course is to help you design and begin to operationalize clinical and epidemiologic research studies. Formal Goals and Objectives are the following:

Goals

1. Adapt knowledge of “traditional” epidemiology into an understanding of clinical epidemiology
2. Learn practical elements of study design beginning with establishing a research question and proceeding to systematic review of the literature, defining and measuring outcomes, and basic principles of data analysis and sample size estimates.
3. Learn practical approaches to operationalizing a study including writing and presenting a study outline, working with collaborators, organizing personnel, and data collection and data management.
4. Learn how to assess research questions for feasibility and begin to explore funding options.

Objectives

1. Participate actively in topical lectures
2. Participate actively in small group study design sessions
3. Learn how to perform Pulmonary Function Tests at research standards
4. Write a 2-page outline describing the design of a new study
5. Create a 10 minute formal presentation of a new research proposal

The course is taught in a very interactive fashion – students are expected to participate actively in lectures by asking and answering questions during all of the sessions. Many of the lectures will not include formal slide presentations but instead will be group discussions of relevant topics. Most of the materials that will be covered in topical lectures are covered in the textbook Designing Clinical Research by Stephen B. Hulley. Students are advised to obtain this textbook prior to the course and to read as much of the textbook as possible ahead of time. If it is not possible to obtain a textbook, a limited number of textbooks will be provided for use during the course. Any edition of the textbook will be sufficient.

In addition to the large group sessions and lectures, a significant amount of time will be spent in small groups, each of which will consist of 4 students and an instructor. The purpose of these Design Groups is to work on your personal research proposals. Ideas will be presented by each design group, and comments and feedback will be provided by colleagues to help refine the study proposal. Each student is expected to develop their own research proposal and be able to present to the class by the end of the week. Formal collaborations among students in the course is welcome and encouraged, however if 2 students are collaborating, 2 proposals should be developed by the pair. In order to make the most use of the time and resources available for the course, students are encouraged to have at least 2 potential study ideas in mind

when they arrive. Completed studies are not appropriate. Ongoing studies are appropriate only if they are very early in the design stage and amenable to changes in methods and analysis strategies.

This year's course will also include formal training in performance of Pulmonary Function Testing. Even those who are already trained in this procedure will benefit from review, as the training will be according to international research standards. Students' current understanding of procedures can be compared and updated if necessary.

| Level 2 Competencies | |
|------------------------------------|--|
| Research Design | <i>Understand the basis of clinical epidemiology as an approach to diagnosis, prognosis, and treatment of disease</i> |
| | <i>Understand the application of study design to clinical studies</i> |
| Research Question | <i>Apply and adapt epidemiologic questions to clinical and health services problems</i> |
| Systematic Review | <i>Understand roles and methods of systematic review, meta-analysis</i> |
| Population Selection | <i>Develop feasible & valid approaches to sampling</i> |
| Measurement Procedures | <i>Balance precision & accuracy in measurements; Be able to design & pre-test a study questionnaire.</i> |
| Quality Control | <i>Know effective approaches to monitoring quality of data gathering and data entry</i> |
| Descriptive Statistics | <i>Review statistical methods in level 1; understand bivariate and multivariable techniques used commonly in clinical studies</i> |
| Measurements of Association | <i>Review measures of association from Level 1 and understand how prevalence affects the relationship between risk, odds, and hazard ratio</i> |
| Sample Size and Power | <i>Know basic methods to determine sufficient sample size for planned study</i> |
| Sources of Error | <i>Bias, confounding chance; type I and II errors. Reliability, validity, accuracy & precision</i> |
| Multivariate Analysis | <i>Understand role of multivariable modeling including logistic regression and survival analysis</i> |
| Ethics and Informed Consent | <i>Know & follow current standards of ethical treatment of human subjects; understand role of IRB.</i> |
| Study Outline | <i>Be able to present research protocol developed in course</i> |

Outline of Course

1) From 'Traditional' Epidemiology to 'Clinical' Epidemiology.

This module will form a bridge from the material on traditional epidemiology and review basic concepts that will be used throughout the clinical epidemiology section.

- *Differences between traditional and clinical epidemiology.*
 - Emphasis of traditional epidemiology on description of disease incidence and causal relations.
 - Emphasis of clinical epidemiology on using evidence to inform decisions in individual patient care.
 - Does this patient have a disease? Evaluation of diagnostic tests.
 - What happens to patients with this disease? Prognosis and natural history.
 - What effect will this treatment have on this patient? Evaluation of therapies.
 - Should this treatment or diagnostic test be used? Decision and cost-effectiveness analysis.
- *Distinctions between traditional epidemiology and clinical epidemiology can get very fuzzy particularly in areas like pharmacy-epidemiology. Similarly, there is significant overlap in methods and research questions between clinical epidemiology and health services research or outcomes research.*
- *Common study designs.*
 - Use of cross-sectional, cohort, and case-control designs with prospective and retrospective data gathering in clinical epidemiology just as they are used in traditional epidemiology. Meta-analysis is used in both traditional and clinical epidemiology. Qualitative methods will also be introduced as a method to inform and understand quantitative methods and set of methods that can be well-suited to low budget research.
 - The experiment (typically, the randomized controlled trial) is not used in traditional epidemiology but is an important tool for inferring causality in clinical epidemiology.
 - 2 additional methods of data synthesis are used in clinical epidemiology: cost-effectiveness analysis and decision analysis.
- *Common methodologic concepts.*
 - Bias - A study's results deviate from the truth because the sampled population, data, or analysis deviates from the intended question.
 - Confounding - Shared variables impose an apparent association.
 - Effect-modification – Association only present in one stratum.
 - Chance - Random variability yields false results.

2) Elements of a research proposal

This module will orient you to the basic elements of well written research proposal

- | | |
|-------------------------------------|---------------------------|
| - <i>Research question</i> | - <i>Hypotheses</i> |
| - <i>Study design</i> | - <i>Study population</i> |
| - <i>Variables and measurements</i> | - <i>Sample size</i> |
| - <i>Data analysis</i> | - <i>Limitations</i> |
| - <i>Implications</i> | |

3) Feasible study designs for limited funds

Good research is not necessarily expensive – in this module you will learn how to get the most out of the least expensive study designs and methods.

- *Surveys*
- *Chart review*
- *Secondary data analyses of existing databases*

Common Clinical Research Categories

1) Diagnosis

Diagnostic tests are essential to clinical practice. Assessment of the usefulness of diagnostic tests must answer the following questions:

- *How accurate is this test? All around the 2x2 table: sensitivity, specificity, accuracy, predictive values. ROC and its area as single overall measure of test discrimination.*
- *If doctors think in terms of predictive values, why are tests reported as sensitivity and specificity?*
- *From information to decisions: how accurate a test needs to be depends on the decision.*
- *Evaluating studies of diagnostic tests*
- *Generalizability*
 - expertise and experience of test setting
 - spectrum bias
- *Chance with particular reference to the confidence interval around zero and 100%*
- *How to evaluate tests when there is no criterion standard or when continuous results are provided.*
 - Categorical results: kappa and measures of inter-observer variability.
 - Continuous results: Bland-Altman plots.

2) Prognosis

Making prognoses is an important and difficult clinical task. Investigators should understand concepts behind prognostication, how to use prognostic data, and the pitfalls of prognostic studies.

- *Many different types of prognostic information available to clinicians:*
 - Disease staging (cancer)
 - Risk models (APACHE)
 - Clinical prediction rules
- *Differences between clinical prognosis and risk adjustment.*
- *What is the role of confounding and causal inference in studies of prognosis?*
 - Differences between multivariate modeling when the goal is generate an unbiased estimate of one of the coefficients (that is, when the goal is determine the unconfounded “effect” of the exposure) versus multivariate modeling for prediction when the goal is a model that is accurate (calibration and/or discrimination) and generalizable.
- *Identifying relevant prognostic variables.*
- *Generalizability - a key factor in assessing the use of prognostic data.*
- *Expressing prognosis*
 - Rates, relative rates, hazards and hazard ratios.
 - Median survival
 - Probability of event

3) **Assessing attitudes and perceptions**

Understanding patients and clinicians knowledge, attitudes, and perceptions is an important area of research.

- *Survey design and validation*
- *Existing instruments versus developing your own*
- *Available population versus target population*
- *Response rates and bias*
- *Limitations of cross-sectional data and associations*

4) **Therapy**

Ultimately, questions about therapy are questions about causation. Does the treatment cause the improved outcome? Causality is hard to prove and requires an experimental study design.

- *Inference from randomized experiment*
 - What is the purpose of randomization?
 - Reducing confounding to chance.
 - The purpose of Table 1. Do the P values in Table 1 mean anything?
 - What is the purpose of blinding? *To reduce bias.*
 - Do randomization and blinding serve any role in enhancing generalizability?
 - What are the limitations of experiments? *Efficacy and Effectiveness*
- *Inference from observational studies*
 - What are the advantages of observational studies in evaluating medical treatments?
 - Potential for confounding - particularly confounding by indication.
 - Advanced techniques for addressing confounding in observational studies of medical treatments.
 - Confounder scores
 - Propensity scores
 - Instrumental variables
- *Expressing the effect of a therapy*
 - Relative risk
 - Risk reduction
 - Attributable risk, Number Needed to Treat

Level 2 Course Faculty

Shannon S. Carson, Course Director
Associate Professor of Medicine
University of North Carolina School of Medicine
Chapel Hill, North Carolina, USA
scarson@med.unc.edu

Dr. Carson conducts clinical research and health services research in pulmonary and critical care medicine. His primary interests are in acute lung injury, outcomes of prolonged mechanical ventilation, and comparative effectiveness research in COPD. He is chief of the Division of Pulmonary and Critical Care Medicine at the University of North Carolina and has served as the program director of the fellowship training program. He is active in the critical care assembly and the behavioral sciences assembly of the ATS. He has been teaching MECOR courses since 2003 including courses in Africa, South America, and Turkey.

James Njogu Kiarie
Consultant Obstetrician Gynaecologist Kenyatta National Hospital
Senior Lecturer University of Nairobi Department of obstetrics and Gynaecology
jkarie@swiftkenya.com

Dr. Kiarie coordinates HIV/AIDS activities in Kenyatta National Hospital under four thematic areas: adult care and treatment, paediatric care and treatment, prevention and psychosocial support, and research and training. As an Honorary Lecturer in the Department of Obstetrics and gynaecology he has been lecturing and tutoring undergraduate and postgraduate students and supervises thesis development. He supervises programs to prevent mother-to-child HIV transmission and to promote HIV counseling and testing. He also conducts clinical trials and translational studies in HIV treatment and transmission.

Lawrence Ndungu Muthami
Principal Research Officer
Kenya Medical Research Institute
muthamilawrence@yahoo.com

Dr. Muthami is a medical statistician and practicing research scientist at the Kenya Medical Research Institute. He has served as the trial statistician for multiple randomized controlled trials of treatments for infectious diseases conducted in Kenya, Uganda, Sudan, and Ethiopia. He has also conducted meta-analyses and participated in operations research sponsored by international agencies. He is a senior Lecturer at the University of Nairobi and directs a Medical Statistics Course.

Brian Faragher
Senior Lecturer in Medical Statistics
School of Tropical Medicine, Liverpool, UK
faragher@liverpool.ac.uk

Dr Faragher is a Senior Lecturer in medical statistics at the Liverpool School of Tropical Medicine.. In addition to providing statistical support and advice to clinical, epidemiological and laboratory based researchers within LSTM and abroad, and contributing extensively the LSTM postgraduate teaching programme, he pursues his personal research interests including the development of statistical methods for analyzing clinical trials / observational studies with discrete outcome measures and the application of

structural equation models to clinical research databases; these statistical interests are currently being applied primarily to studies in the fields of malaria, TB and HIV.

Philip Hopewell

University of California San Francisco
San Francisco General Hospital
San Francisco, CA 94110
email: phopewell@medsfgh.ucsf.edu

Dr. Hopewell is Professor of Medicine at the University of California, San Francisco, based at San Francisco General, where he served as chief of the Division of Pulmonary and Critical Care Medicine from 1989-98 and Associate Dean 1998-2004. Dr Hopewell continues to practice clinical pulmonary and critical care medicine at San Francisco General Hospital. In addition, he directs the Frances J. Curry International Tuberculosis Center, a center for training, research and consultation in tuberculosis. Dr. Hopewell's research interests have centered on clinical and epidemiological aspects of tuberculosis and on tuberculosis control interventions.

PATS-MECOR Level 2 Course Schedule

| | Oct 10 | Oct 11 | Oct 12 | Oct 13 | Oct 14 |
|------------------------|--|---|--|---|-----------------------------------|
| Module 1 | Introductions and Goals From Traditional Epidemiology to Clinical Epidemiology (All) | Basic Statistics: Bivariate statistics (LM) | Approaches to confounding: matching, stratification, randomization, and models (BF) | Research organization: Data Management and Data Analysis (LM) | Designing Clinical Trials (SC) |
| | Elements of a research proposal (SC) | | | Operations Research (JK) | Review (All) |
| Morning Break | | | | | |
| Module 2 | Systematic Reviews (SC, LM) | Design groups meet | Design groups meet. Revisit Confounding in context of proposed studies | Design groups meet | Design groups meet |
| Lunch | | | | | |
| Module 3 | Building your research proposal: feasible research questions and study designs with limited funds (JK,PH) | Building your research proposal: Sample Size and Power (BF) | Survey Research: Sampling and Instrument Development (JK) | Survival analysis (BF) | Present Proposals |
| | Building your research proposal: measuring variables (Outcome, Exposure, Confounder, Covariates) (SC) | Designing studies of occupational lung disease (BN) | | Prognosis (SC) | |
| Afternoon Break | | | | | |
| Module 4 | Design Groups Meet | Design Groups Meet | Design Groups Meet | Design Groups Meet | Present Proposals |

Design groups: 3 groups meet with faculty to discuss their research proposal (all faculty present). SC = Shannon Carson, BF = Brian Faragher, JK = James Kiare, LM = Lawrence Muthami, PH = Phil Hopewell, BN = Ben Nemery