Diagnostic Evidence Co-operative Oxford

NHS National Institute for Health Research

Evidence to Support the Adoption of New Biomarkers
3 Day Workshop

22 September 22nd – 24th September 2014

Queens College

Oxford

This course is aimed at all professionals working on diagnostic tests including people working in industry, academia, funding and regulation. During these three days, we will provide you with the latest information on what evidence is needed to obtain regulatory approval, how NICE evaluates new diagnostic technology and how to collect evidence to support adoption in routine clinical practice. In addition, we will teach you about different study designs including quality assessment, and how to facilitate uptake in routine clinical practice.

Programme

Monday September 22nd		
09:00-09:40	Registration	
09:40-10:00	Welcome	Dr Ann Van den Bruel
10:00-11:00	Tests as part of a clinical pathway	Prof Carl Heneghan
11:00-11:20	Coffee break	
11:20-12:20	Aligning research and development with clinical needs	Prof Christopher Price
12:20-13:30	Lunch	
13:30-14:30	Different forms of evidence for different types of questions	Dr Ann Van den Bruel
14:30-14:50	Coffee break	
14:50-16:20	Searching for existing evidence to support regulatory approval and other purposes - workshop	Nia Wyn Roberts
Tuesday September 23rd		
9:30-11:00	How to avoid low quality studies - workshop	Dr Ann Van den Bruel & Dr Annette Pluddemann
11:00-11:20	Coffee break	
11:20-12:20	Basic stats in diagnostic studies	Bethany Shinkins
12:20-13:30	Lunch	
13:30-14:10	Evidence for regulatory purposes: CE marking and European IVD Directive	Stephen Lee
14:10-14:50	Evidence requirements to achieve FDA regulatory approval	Sally A Hojvat
14:50-15:10	Coffee break	
15:10-16:40	Evidence for implementation in routine clinical practice – NICE evaluations	Dr Grace Jennings & Sarah Byron
16;40-18:30	Free time	
18:30-19:15	Routinely available data, other resources	Dr Antonis Kousoulis
19:15	Course Dinner	
Wednesday September 24th		
9:00-10:30	Funding for diagnostic test development/opportunities for collaboration with academia	Ravi Chana
10:30-10:50	Coffee break	
10:50-11:50	Economic modelling	Dr Jane Wolstenholme
11:50-12:50	Using evidence to support the business case: the route to adoption	Prof Christopher Price
12:50-14:00	Lunch	
14:00-15:30	Facilitators and barriers for uptake in routine clinical practice – interactive discussion with audience	Dr Caroline Jones
15:30-16:00	Closing remarks	Dr Ann Van den Bruel

Speaker Bios

Ann Van den Bruel is a GP and Academic Clinical Lecturer and researcher focussing on diagnostic tests that help doctors to identify illness and other conditions so that patients may be treated or given a prognosis about the course of illness. It is important to study the added value to tests because a better understanding leads to more efficient healthcare and better outcomes for patients. Over the past years Ann has worked mainly on the diagnosis of serious infections in children, conducting a large scale study in primary care to analyse the value of clinical features for this diagnosis. The study also looked at how laboratory tests can help with diagnosis and hoe parents and doctors view the diagnostic process when a child is admitted to hospital with a serious infection. The results have been used in several guidelines including one on feverish children by the National Institute for Health and Care Excellence (NICE).

Annette Pluddemann, Director Diagnostic Horizon Scan programme joined the Centre for Monitoring and Diagnosis (MaDOx) in January 2009. Annette's research aims to identify innovations in diagnostic technologies likely to have a significant impact in primary care, and disseminating this information to NHS bodies such as the Health Technology assessment Programme and the NICE Diagnostics Assessment Programme.

Antonis Kousoulis is a physician with a background in public health and humanities research. He has completed studies in the University of Athens, Greece, and Imperial College London. He currently serves as the Academic Research Liaison at the Clinical Practice Research Datalink (CPRD) where he also acts as the Business Development Lead for Clinical Trials. He has participated in research protocols in the Clinic of Social Medicine at University of Crete, Greece, the Science and Technology Department at University College London, the Center for Global Tobacco Control at Harvard School of Public Health, and the Faculty of Epidemiology and Population Health at the London School of Hygiene and Tropical Medicine.

Beth Shinkins is a SPCR Research Fellow in Medical statistics with a particular interest in improving clinical utility of diagnostic research. Beth is lead for the methodological workstream of the national institute for Health Research Evidence Cooperative Oxford which aims to improve bed to bedside pathway for new diagnostics in primary care.

Carl Heneghan is a Professor of Evidence-Based Medicine. As a clinical epidemiologist he has extensive experience in systematic reviews, observational and qualitative methodologies. Carl has an active interest in diagnostic reasoning and its impact on decision making.

Caroline Jones is a senior researcher at the Nuffield Department of Primary Care Health Sciences working on a number of studies related to childrens health and diagnostics with the aim of improving early detection of serious illness.

Christopher Price is Visiting Professor in Clinical Biochemistry, in the Nuffield Department of Primary Care Health Sciences at the University of Oxford. He is also a member of the Oxford Diagnostic Evidence Cooperative. He trained as a clinical biochemist and his early career was spent in the National Health Service. He was Professor of Clinical Biochemistry at the St Bartholomews and Royal London School of Medicine and Dentistry from 1988 to 2001, and Director of Laboratory Medicine at the Barts and London NHS Trust from 1993 to 2001. From 2002 and 2005 he was Vice President of Outcomes Research in the Diagnostics Division of Bayer HealthCare. He was Clinical Director of the Cumbria and Lancashire Pathology Commissioning Network between 2009 and 2011.
His interests, today, are mainly in the fields of evidence-based laboratory medicine and outcomes research, in the application of point-of-care testing, disruptive innovation for improve health outcomes, and the requirements for successful adoption of appropriate new technologies.

Grace Jennings joined NICE Scientific Advice as a Technical Adviser in April 2014, after working as a Technical Analyst in NICE Technology Appraisals. Grace graduated in Biomedical Sciences (King's College, London and Berkeley, University of California) before undertaking post-graduate studies at the London School of Hygiene and Tropical Medicine. She obtained an MSc in Control of Infectious Diseases, before completing a PhD entitled 'A policy analysis of biological warfare defence and emerging infectious diseases in an international context'. Her thesis examined the reasons for policy changes towards emerging infectious disease surveillance and response policies and bioterrorism defence programs. It identified some of the implications of the increased emphasis on infectious threats has had globally, economically, politically, and ethically, using quantitative and qualitative methods. She lectures and coordinates outbreak scenario exercises each year as a Visiting Fellow at LSHTM.

Jane Wolstenholme is a senior health economist at HERC, University of Oxford. She has 20 years of experience of conducting economic evaluations for health policy makers. Her main interests include designing and conducting economic evaluations alongside trials and cost-effectiveness models. She is principal investigator and co-applicant on a wide variety of funded research projects. She is a health economics advisor for the RDS South Central (http://www.rds-sc.nihr.ac.uk/) and for the NIHR Diagnostics Evidence Co-Operative, Oxford. She supervises MSc and DPhil students. Jane has published widely and has a book published by OUP, '*Applied Methods of Cost-effectiveness Analysis in Health Care'*.

Nia Wyn Roberts is an outreach librarian and information specialist at Bodleian Health Care Libraries. She contributes to the horizon scanning work stream at the Diagnostic Evidence Co-operative Oxford. In addition, she collaborates with several research units and departments in the University of Oxford, contributing to systematic reviews and teaching literature searching and information management skills.

Ravi Chana is the Business Development Manager at the NIHR Office for Clinical Research Infrastructure (NOCRI) and is part of the Industry team within NOCRI. Within this role his main remit is to facilitate initial engagement between Industry and NIHR Academic Investigators, linking them to form research collaborations and partnerships. The role is very much working with Industry and the NOCRI Infrastructure team to link companies to the most relevant NIHR academics.
After completing a degree in Pharmacology, Ravi gained employment in sales roles in non-health related fields. Prior to joining NOCRI he worked in the Healthcare Industry for over 15 years, undertaking sales, marketing, market access and business development roles, and lastly heading the Health Economics function within a Diagnostics Company. He has also been part of various working groups within the National Institute of Health and Clinical Excellence (NICE) and the British In-Vitro Diagnostics Association (BIVDA).

Sally Hojvat Director of the Division of Microbiology Devices, Office of In-vitro Diagnostic (IVD) Device Evaluation and Safety in the Center for Devices and Radiological Health at FDA. and is responsible for ensuring that all commercial and non-commercial devices developed to detect and diagnose infectious disease agents are safe and effective. Before joining FDA, Dr. Hojvat's spent 18 years in the IVD industry, holding positions in IVD research and development and manufacturing quality control. Her last commercial position was as Director of Clinical Research for the Diagnostic Division of a major U.S. Pharmaceutical Company. Dr. Hojvat received a B.Sc. (Hons.) from the University of Wales, UK, a M.Sc. in microbiology from the University of Alberta, Canada, and a Ph.D. in biochemistry from Loyola University Medical School, Chicago. She completed postdoctoral training fellowships in clinical chemistry (Loyola Medical School) and pharmacology (University of Chicago). Her numerous research publications and presentations are concentrated in the fields of clinical microbiology, pharmacology, neuroendocrinology, human subject protection, clinical research, and the regulation of emerging/neglected infectious diseases and CBRN agents.

Sarah Byron is the Technical Adviser for the Diagnostics Assessment programme at the National Institute for Health and Care Excellence (NICE). She has technical and scientific responsibility for the programme and the development of diagnostics guidance. Since joining NICE, Sarah has been involved in establishing and developing the two new programmes for assessing medical technologies: the Medical Technologies Evaluation programme and the Diagnostics Assessment programme. Sarah is also a member of the Equalities Expert Group and Research Advisory Group at NICE, in additional to participating in work with the European Network for Health Technology Assessment (EUnetHTA). Prior to joining NICE, Sarah completed a PhD in Biochemistry with the University of Manchester and GlaxoSmithKline, and then worked in research and development at AstraZeneca, expanding the gene expression and molecular biology capabilities in neuroscience and cancer research

Stephen Lee heads up a team of scientists investigating problems with a range of medical devices used in healthcare. One of the main areas of work for the team is in diagnostic devices used by healthcare professionals and lay people. In the last year, across all medical devices MHRA processed almost fourteen thousand adverse incident reports, nearly nine hundred Field Safety Notices and seventy seven Medical Device Alerts.
Stephen is chair of the European Commission's IVD working group which provides advice and guidance on the regulation of IVDs and he works closely with the UK team responsible for negotiating the new regulations.
Stephen has worked in the regulation of medical devices since 1996, before that he worked as company microbiologist in pharmaceuticals and as a Biomedical Scientist in the NHS

Abstracts

Professor Carl Heneghan – Tests as Part of a Clinical Pathway

In terms of healthcare, making a correct diagnosis is fundamental to subsequent decisions about treatment. clinicians ability to diagnose accurately is central in assessing prognosis and prescribing effective treatments. However, the strategies clinicians use to arrive at a diagnosis make only a small contribution to current research.Seminal research in the 1970s showed that the commonly taught sequential approach to history taking and examination, resulting in differential diagnosis and ultimately a final diagnosis, is not what practitioners do in reality.

Researchers observed that diagnostic hypotheses are made early in the consultation and guide subsequent history and examination, in a process of hypothetico-deductive reasoning.2 This work sparked debate about understanding the complex strategies used to guide diagnostic tests as part of the clinic pathway.

This session will set out the strategies and methods that are used by clinicians in routine clinical consultations to guide testing and subsequent referral as part of the clinical pathway.

Professor Christopher Price - Aligning research and development with clinical needs

Point of care tests: establishing the determinants of patient benefit

A wide range and growing number of point-of-care (POC, 'near patient') tests which provide rapid 'on site' results are now available. These have the potential to improve outcomes in primary care by optimizing prescribing decisions, reducing referrals, improving efficiency of care, and decreasing costs. A recent survey of general practitioners (family doctors) in five countries indicated that general practitioners would like to use a wider range of POC tests. However whether POC test potential is realized (and whether general practitioners desire for POC tests is a predictor of eventual patient benefit depends on additional factors. Clinicians may express a desire for a POC test, but patients may not like it or it may not be cost-effective. These additional factors include: clinical need, diagnostic accuracy, effectiveness, cost-effectiveness, and clinical need. In this review article we describe these factors together with the types of evidence required to determine whether they have been adequately considered. Failure to consider these factors prevents patient-focused research and development of POC tests that are most likely to benefit patients.

Dr Ann Van den Bruel - Different forms of evidence for different types of questions

In this session, we will explore the different types of questions that could be asked when developing a new diagnostic test. These questions may range from classic accuracy to impact and costs. A variety of study designs may be used to answer these questions, and some designs may provide stronger evidence than others. Using real-life examples, we will discuss the different options and their effects on the confidence we have in the results.

Nia Wyn Roberts – Workshop: Searching for existing evidence to support regulatory approval and other purposes

This session will focus on identifying supplementary evidence to inform the pathway from regulatory approval to the adoption of diagnostic technologies by patients, clinicians and health systems. We will look at refining search methods and selecting appropriate resources for searching for studies on diagnostic accuracy, economic evaluation and process assessment. A point of care testing scenario will be used to illustrate how queries need to be formulated on different search engines to optimise results. Participants will then have an opportunity to develop their own questions and gain practical experience of using the different search engines.

Dr Ann Van den Bruel & Dr Annette Pluddemann - Workshop: How to avoid low quality studies
This workshop consists of an introduction presenting the different forms of bias and variability of diagnostic accuracy studies. We will then put this into practice by reviewing existing studies and identifying possible sources of bias. Strategies to avoid such pitfalls, or how to deal with inevitable sources of bias will be discussed.

Dr Beth Shinkins –Basic Stats in Diagnostic studies
This session will enable you to fully understand and interpret the key results of a diagnostic accuracy study. The calculation of statistics including prevalence, sensitivity, specificity, positive and negative likelihood ratios, and predictive values will be explained, in addition to exploring the relationship between these different measures. The relevance of Bayesian reasoning to diagnostic testing will also be discussed, and how a Fagan's nomogram can help us to visually understand the additional information gained by conducting a particular test.

Dr Grace Jennings and Sarah Byron - Evidence for implementation in routine clinical practice – NICE evaluations
This session will cover the general principles of health technology assessment and the meaning of cost effectiveness, what is meant by value from the perspective of NICE, and how the value proposition links to the need for specific evidence. It will also explain how NICE assesses medical diagnostic technologies, particularly the work of the Diagnostics Assessment Programme which focuses on evaluating the clinical and cost effectiveness of diagnostic technologies to ensure the rapid and consistent adoption of innovative and effective diagnostic technologies in the NHS. This will include covering the types of evidence considered during an evaluation.

Dr Antonis Kousoulis - Routinely available data, other resources
Databases of Electronic Health Records (EHR) are fast becoming an extremely important research tool worldwide. Due to the structure of the NHS, UK records are a valuable resource of information. This session, drawing from the long experience of the Clinical Practice Research Datalink (CPRD), will go in depth describing how to define a diagnosis in EHR, and further exploring ways to validate these diagnoses. We will discuss what evidence are available in routinely collected healthcare records, how these fit with new biomarker adoption, and identify what are the advantages as well as the challenges and limitations of working with EHR data.

Ravi Chana -Funding for diagnostic test development/opportunities for collaborating with Academia.
Who within the NHS can help with diagnostic test research? Who can help gather the clinical utility and cost-effectiveness data required for adoption? When is the best time to engage with the clinical community? Who funds research in diagnostics, should it be industry or NHS? What funding models are available for Industry to access and how can industry access these?
This session will look to answer the above questions and provide some direction to IVD developers on:

- Who can help with delivering clinical research;
- When to engage with clinical research experts;
- How developers can access the right research infrastructure and potential funding mechanisms.

The session will provide an overview of the UK National Institute for Health Research (NIHR), with particular focus on the NIHR Diagnostic Evidence Cooperatives (DECs) and the IVD development pathway.

Dr Jane Wolstenholme - Decision Model-Based Economic Evaluation

Decision analytic modelling is widely used as a means of synthesizing evidence on costs and outcomes to estimate the cost-effectiveness of different interventions and programmes in health care. In particular, these methods are often employed to assess the cost-effectiveness of new diagnostic devices and aid the decision makers of health systems determine whether they should be funded.

This module will provide and introduction to the principles of decision modelling for economic evaluation of diagnostic devices and procedures. By the end of the module you will have some basic understanding of the following:

- Understand the rationale for decision modelling
- Distinguish between trial-based and model-based economic evaluations
- Introduce the different types of modelling used by health economists
- Appreciate the steps involved in the development of a decision tree and Markov model
- Understand the issues with respect to the identification of suitable cost and outcome evidence

Professor Christopher P Price Using Evidence to Support the Business Case: the Route to Adoption

Adoption of new biomarkers, is the translation of invention into practice, based on demonstrating a benefit to patients and other stakeholders. The benefit is defined within a framework of clinical and cost effectiveness. The starting point will be the unmet need which will typically derive from clinical practice and the formal mechanisms of strategic planning and quality improvement. Adoption is viewed from three perspectives, namely outcomes, processes and resources. The business case can be seen as the bridge between the generation of evidence that the unmet need has been satisfied, and the translation of this proof into practice.

The business case begins with the statement of unmet and definition of the current clinical practice and processes, and resource utilization. The core of the case is translation of the critically appraised evidence of effectiveness by identifying how practice, processes and resource utilization will change, as well as building the implementation process.

Dr Caroline Jones - Facilitators and barriers for uptake in routine clinical practice – interactive discussion with audience

Good quality evidence on the effectiveness and cost-effectiveness of new diagnostic tests is vital for uptake in routine clinical practice, but is not enough. In order to promote uptake it is important to identify potential facilitators and barriers to implementation of new tests, so that these can be addressed. This session will consider facilitators and barriers to uptake of tests, including clinician and patient attitudes and concerns, as well as more practical aspects involved in incorporating new tests into clinical settings. It will also consider the ways in which these can be investigated, and what kinds of research evidence are appropriate for answering questions about facilitators and barriers. We will draw upon existing research evidence on barriers and facilitators to adoption of tests, and discuss how these insights can enable more successful uptake.