

EME PROGRAMME

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FOREWORD



Professor Sir Alex Markham

Chairman of the (OSCHR) Translational Medicine Board
[May 2007 to December 2009]

Professor of Medicine, University of Leeds

The Translational Medicine Board was set up by the Office for Strategic Coordination of Health Research (OSCHR) in 2007. The Board was established to work with the OSCHR partners to develop a coordinated, coherent, fully aligned research strategy in translational research.

As Chair of the Translational Medicine Board I was delighted to work with the Medical Research Council (MRC) and the National Institute for Health Research (NIHR) as the recommendations from Sir David Cooksey's report, *A review of UK health research funding*, were implemented.

The Efficacy and Mechanism Evaluation programme has been an important outcome of that partnership. Funded by the MRC and managed by the NIHR as the lead organisation for clinical trials and evaluation, it sits between the MRC Developmental Clinical Studies scheme and the Health Technology Assessment programme as part of a managed translational pathway. This report demonstrates just how closely all of these programmes are working together to ensure that proposals to evaluate promising new interventions are pulled through to the most appropriate funder. Close coordination between these programmes must bring benefits to the research community. Equally importantly, I have no doubt it will lead to significant benefits for patients over the coming years.

I was delighted to speak to the EME Board at a seminar during its meeting in June 2009. It was fascinating and informative to discuss different perspectives on the progress that has been made in advancing translational medicine and also to reflect on what still needs to be achieved, with some of the UKs leading researchers in this area. The commitment from this group to ensuring that advances in basic science are translated into better health through high quality research was extremely impressive.

This report provides an overview of some of the highlights of the programme's activity during the last year. I am particularly pleased to see the quality and breadth of research that has already been funded and note that the projects build on excellent preclinical and early clinical study results. I would like to take this opportunity to wish the EME programme and its Chairman continued success in the coming years. It has made an excellent start.

EXECUTIVE

Insight into the EME Board



Professor Rajesh Thakker
Chairman of the EME Board

Since its first meeting in 2008 the Board has considered an incredible breadth of proposals, covering a wide range of disease areas and potential interventions. The quality of the proposals submitted this year has resulted in the programme committing its full allocated budget of £13m. The EME portfolio now includes 19 projects with 11 of these already contracted and the first patients have been recruited. You can find details of some of these projects in this report.

In this year alone the Board has considered over 75 preliminary applications and 22 full proposals. We have funded 12 proposals subject to the applicants providing satisfactory responses to specific points of feedback. All of these proposals were thought to be competitive at an international level. I have been impressed with the studies that have been submitted and how well they fulfil the EME remit of science driven studies in clinical medicine. It has also been encouraging to see how many applicants have used this programme to include mechanistic evaluation within the main efficacy study.

Although the Board needs to be convinced about the research question itself, Members have also been very interested in how investigators are intending to answer it. Applications linked to a recognised clinical trials unit that clearly outline who the methodological collaborators and the trial statistician are seemed to have a competitive edge. The inclusion of well worked up sample size calculations has also been a factor in the successful progress of new applications.

I am particularly pleased to note that the Board has funded several projects which build on early clinical studies funded by the MRC. We will continue to work with them and other research funders in the coming year to make the most of opportunities to "pull through" promising interventions from early clinical studies into the EME programme.

Occasionally applications submitted to the EME programme have not fallen within its remit, and were better aligned to the remit of another part of the post-Cooksey managed translational pathway. Those deemed too early in development for the EME programme, we have discussed with colleagues at the MRC to determine the more appropriate route for submission. If within the remit of another MRC programme we have provided the principal applicant with a point of contact.

Where submitted proposals are for interventions for which efficacy has already been established, the EME programme has worked closely with the Health Technology Assessment (HTA) or other NIHR programmes to transfer them accordingly. The advantages of being based within the NIHR Evaluation, Trials and Studies Coordinating Centre have been realised in this process as although applicants have the opportunity to reframe and resubmit their proposal, most of these applications have been considered on the original application form. We know that the success rate for applications that have transferred to EME is very similar to those that applied to EME directly, indicating that the process is working well.

I am very much looking forward to the coming year – particularly to seeing these new EME projects reach early milestones in their protocols and the breadth of the existing portfolio increase.

Rajesh Thakker was appointed Chair of the EME Board in early 2008. He is the May Professor of Medicine at the University of Oxford, and a Fellow of Somerville College. His main research interests include the molecular basis of disorders of calcium homeostasis. He has been the recipient of many prizes which include Young Investigator Award from the American Society for Bone and Mineral Research (ASBMR) (USA), the Raymond-Horton Smith Prize (Cambridge University), the Society for Endocrinology (UK) medal, the European Journal of Endocrinology Prizes (EFES), the Graham Bull Prize from the Royal College of Physicians (UK) and most recently the prestigious ASBMR Founder's Award (Louis V Avioli).

Positioning EME



Professor Ian Cree
Director of NETSCC – EME

This year has seen the EME programme start to move into steady state. We have worked to build on and improve our application process, and we are now able to provide a funding decision in around 8 months from the submission of a preliminary application. To achieve this we have received invaluable support from researchers, service users and methodologists in reviewing applications promptly.

Post-award we are working closely with the first EME funded researchers to actively support them in starting up their studies. We set milestones for reporting which allow us to monitor progress against key objectives within the study, and ensure that our management post-award is appropriate for each individual study.

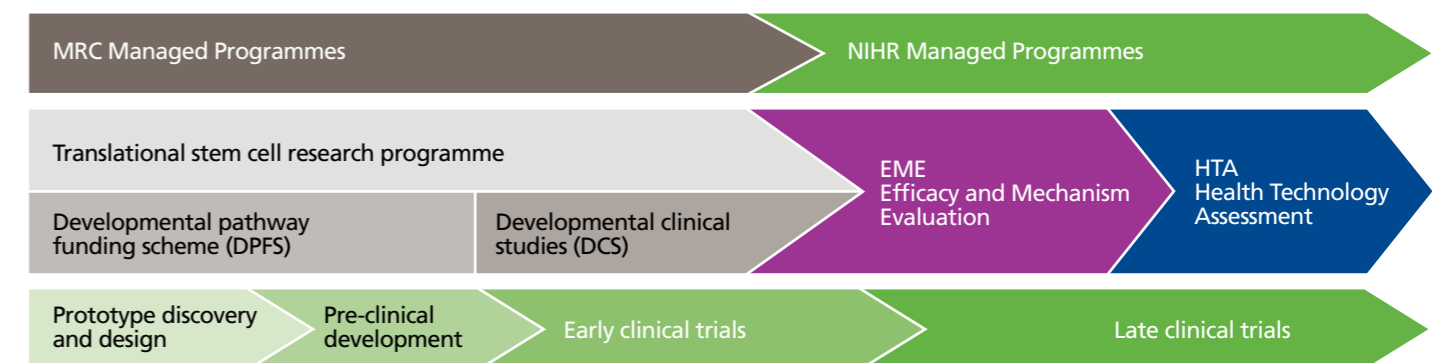
We have put a significant focus on communications activity this year. Of course this involves many of our stakeholders, including Board Members, peer reviewers and applicants who are all vital in communicating about the EME programme to their colleagues and collaborators. As part of this work I wrote to the Deans of Medical Schools at the start of the year and have since presented at numerous meetings at universities across the UK from Belfast to Dundee, Exeter, and Swansea.

The formats of these meetings were all very different and some included a session on EME within the broader context of a translational research meeting. It was wonderful to meet so many people who are interested in translational research. Some researchers were primarily involved in early clinical trials, others in late phase trials and on occasion I felt that these two groups coming together could generate some really interesting studies for EME. There was significant discussion about the range of new opportunities for funding presented by the MRC and NIHR across the translational pathway. Many people commented that previously they have had research ideas but they had not known where to go. Things have changed!

Communications with applicants are key to our work. The EME programme iterates with applicants at a number of stages during the application process. We initially provide feedback on applications which are determined to be out of remit or not competitive for funding during the first checks that are undertaken on new applications. Applications which proceed to the EME Board receive feedback, whether they are successful or not, and further feedback is provided on all full proposals considered. Proposals are often funded subject to specific points of feedback being addressed and individual Board Members get involved in helping applicants to respond to feedback after their proposal has been funded. Following contracting, my team works closely with the chief investigator to provide support through the start up process.

Looking to next year, we will be developing more structured methods of working with both the MRC and other research funders who fund early clinical studies to secure the progression (known as pull-through) of promising interventions along the translational pathway. Equally we are aware that this is a two way process and that some clinical ideas generate scientific research, a process known as reverse translation. In addition we will be looking at how we can respond more proactively to priority research areas to promote active translation of research into practice.

Professor Ian Cree took up his post as Director of NETSCC – EME in late 2008. Ian is Professor of Histopathology and Director of the Translational Oncology Research Centre in Portsmouth. Trained as a general pathologist with a PhD in immunology, Ian's research career has been based on investigating disease mechanisms and then acting on the information obtained to improve diagnosis or treatment. Ian's current research interests are mostly cancer-related, but the previous studies have included infectious disease, asthma, and ophthalmology.



The Managed Translational Pathway

FUNDED PROJECTS

Studying the efficacy of mesalazine treatment for patients with IBS



Professor Robin Spiller,
Professor of Gastroenterology,
Nottingham Digestive Diseases Centre,
University of Nottingham,
£744,964 estimated research cost

Irritable Bowel Syndrome (IBS) affects around 10% of the population who at some time suffer from abdominal pain or discomfort, bloating and irregular bowel habit. IBS patients' bowel habit varies with approximately one third having mainly diarrhoea (IBS-D), one third mainly constipation and one third a mixed bowel habit. Many patients show hypersensitivity of the gut to distension. Recent evidence suggests this may be due to low grade inflammation in the gut which may also cause diarrhoea.

Current surveys show that most patients are dissatisfied with available treatment. Recently, there have been several small studies suggesting a benefit of mesalazine in IBS. Mesalazine is an inexpensive safe drug which is widely used to treat bowel inflammation in ulcerative colitis. Mast cells release substances which have been shown to excite nerves responsible for intestinal pain and their number correlate with the pain severity experienced in IBS. One of these small studies involved 20 patients and showed that mesalazine reduced the number of mast cells in the large bowel. This was a small study and further research is required to confirm these results. The present study will focus on the IBS-D subgroup; patients who suffer from increased bowel frequency with urgency, which is among the most disabling of IBS symptoms.

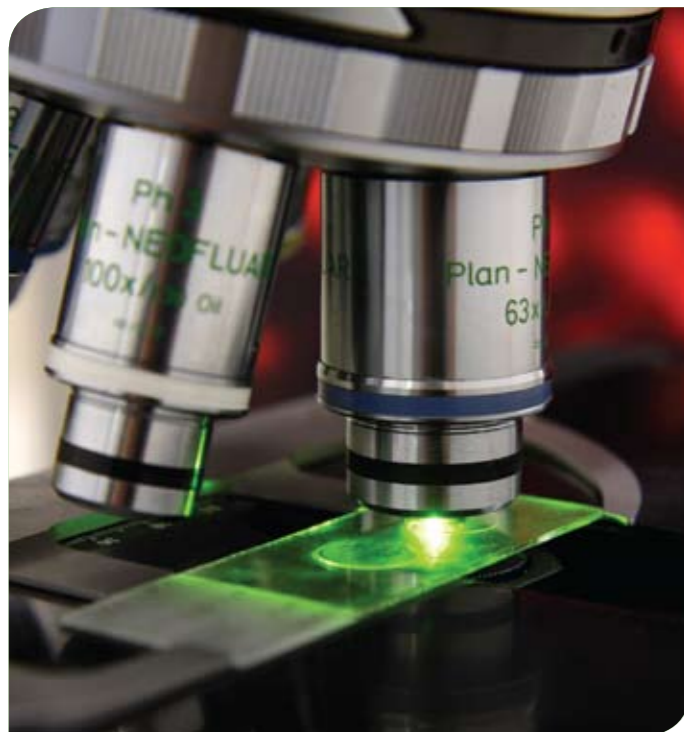
The current study will provide each patient with 12 weeks' treatment of identical-looking pills containing either mesalazine or placebo. Before and after taking the treatment, patients will have a flexible endoscope passed into the lower bowel and a biopsy taken to determine the number of inflammatory and mast cells present.

A number of outcomes will be recorded to determine the efficacy of mesalazine compared with placebo. One measure will be whether mesalazine reduces the stool frequency and improves the patients' overall IBS symptoms. Another measure will be whether mesalazine reduces the number of mast cells or reduces the secretion of mast cell products from the biopsies. These products increase the tone of the small bowel causing the bowel to narrow and therefore increase the rate of passage through it. A magnetic resonance imaging (MRI) scan of the abdomen, which is a simple, non-invasive test, which is acceptable to patients, will examine the size of the small bowel to help predict who may benefit from mesalazine treatment.

If at the end of the trial the patients feel they have benefited from treatment they will be prescribed mesalazine on an ongoing basis. This study could explain why mesalazine works in certain patients which should enable better targeting of this inexpensive safe treatment to a large group of patients who currently have no satisfactory treatment.

"This project addresses a real clinical need, reducing the abdominal pain associated with IBS, using a drug that is cheap and generally safe. Importantly, the study also aims to use current understanding of disease pathogenesis to determine whether mast cell numbers in the bowel mucosa and mast cell products in faeces are useful biomarkers of likely treatment response."

Professor Moira Whyte,
Deputy Chair, EME Board (University of Sheffield)



Immunotherapy for children with peanut allergy



**Dr Pamela Ewan and
Dr Andrew Clark,**
University of Cambridge,
£671,247 estimated research cost

Peanut allergy is the most common cause of fatal food-allergic reactions. Population studies have shown that peanut allergy affects 2% of children, with tens of thousands of children in the UK at risk of allergic reactions. Spontaneous resolution is rare and patients are not only at risk of anaphylaxis but live with fear and the inconvenience of restricted food choices and the need to carry emergency adrenaline injections at all times. There is no treatment for this condition except to advise patients to avoid peanuts; up to 55% of children have accidental reactions every year, a significant number of these are severe. A novel disease-modifying treatment to improve patient care is therefore needed.

The present study will investigate the efficacy of a new treatment which has been successfully tested in a pilot study. The pilot study demonstrated success in all 18 participants; no severe reactions occurred. The families involved reported that the therapy has transformed their lives, as reflected by increased quality of life scores.

In this larger study the research group intend to recruit 104 peanut allergic patients and randomise them to treatment and control groups. The control group will be advised to avoid peanuts during a five-month waiting period (i.e. the current standard practice).

The treatment group will receive increasing amounts of peanut flour by mouth over five months. Doses of peanut flour will be increased every two weeks in hospital and the same doses then taken daily at home between hospital visits. Patients will take the highest dose (approximately five peanuts) for six weeks. After the main study, those patients with persistent allergy who had been randomised to the control group will also be offered the treatment.

The success of the study will be measured by the number of patients in each group who do not have an allergic reaction to a peanut challenge test. Blood laboratory tests will also be analysed throughout the study to determine whether the treatment alters the allergic response, to identify biological markers to help predict which patients are likely to have most success with this treatment. Changes in patients' quality of life scores before and after the intervention will also be recorded. If successful, this treatment could be made widely available across the NHS with considerable benefit for patients.



"The importance of enabling sufferers to lead a normal life without the fear of severe allergic reaction cannot be overestimated."

John Collard,
Clinical Director of Allergy UK

FUNDED PROJECTS

Improving the efficacy of treatments for depression



Professor Ian Nicol Ferrier,
Institute of Neuroscience,
Newcastle University
£999,002 estimated research cost

Depression is one of the most common mental health problems, with at least one in six adults suffering from the condition at some time in their life. The need for improved treatment has been recognised by the Department of Health and others with a recent plan to provide more psychological therapy.

An incomplete response to antidepressants is frequently reported and one of the causes of this has recently been attributed to the stress hormone, cortisol, which is often elevated or poorly controlled in depression. Laboratory and clinical research evidence suggests that this hormonal variation reduces the benefits of antidepressants, resulting in a poor outcome and memory problems. Recent small studies have demonstrated that giving treatments to reduce cortisol or block its harmful effects for periods of one to three weeks overcome these negative consequences.

The EME programme has funded the Antiglucocorticoid augmentation of antiDepressants in Depression (ADD) study to investigate metyrapone, a drug that decreases cortisol levels, in people who have not recovered from depression using standard antidepressants. The study will involve a team of researchers from three centres in the UK who are experienced in dealing with patients with difficult to treat depression.

Patients recruited to the ADD study will be assessed to determine the effectiveness of metyrapone compared with placebo for improvements to their day-to-day life. The patients will be closely monitored for side effects, although initial studies investigating metyrapone have reported few adverse effects. The study will also record a range of clinical and psychological outcomes including cortisol levels, brain wave patterns and results from memory and decision-making tests. These outcomes have previously been validated by an MRC-funded trial investigating cognitive impairment in bipolar disorder.

The study will also provide evidence for whether metyrapone could be used more widely by patients not responding to standard treatments for depression. It may also lead to the development of new anticortisol treatments to help tackle the major problem of poor outcome from depression.

“The EME team were very helpful throughout the process in terms of giving us the opportunity to respond to critiques of the study.”

Exploration of the role of genes in targeting therapy for pre-school wheeze



Professor Jonathan Grigg,
Centre for Paediatrics,
Barts & the London School of
Medicine & Dentistry,
£1,794,050 estimated research cost

A quarter of all UK children will have at least one attack of wheeze during the preschool period. Severe attacks of wheeze in young children are usually triggered by viral-colds. The majority will only wheeze with colds but attacks may be severe,

repeated and requiring medical attention. This pattern is termed “episodic” preschool wheeze. A minority of children wheeze both with and between colds – a pattern called “multi-trigger” preschool wheeze. This distinction is generally blurred, with preschool children changing their pattern of wheeze over time. Asthma therapies that are effective in older children with classical “allergic” asthma may not necessarily be effective in preschool wheeze.

Recently, montelukast, an oral medicine that blocks leukotriene, which narrows the breathing tubes, has shown benefit in preschool wheeze. However, only modest benefits have been reported in studies involving large numbers of children. This may be because a large proportion of preschool children do not respond to montelukast but a subgroup responds well as a result of variations in their leukotriene-producing genes. Therefore, an understanding of the role of leukotriene genes and leukotriene production in preschool wheeze may better target montelukast treatment in this age group and inform the development of new therapies.

The present trial will build upon the current scientific evidence. It will assess whether intermittent montelukast therapy is an effective

Predicting patient responsiveness to stroke treatment using new imaging techniques



Professor Joanna Wardlaw,
Clinical Neurosciences,
University of Edinburgh,
£263,974 estimated research cost

Stroke is a devastating disease with few effective treatments. Stroke is usually caused by a blockage to a blood vessel in the brain. One of the main treatments is thrombolytic, or “clot busting”, drugs. Although one of these drugs, alteplase, has been licensed for use within three hours after stroke for over ten years, it is not widely used because of fears about its safety, doubts about the benefits and concerns about which patients most gain from treatment.

The Third International Stroke Trial (IST-3) (for which Professor Wardlaw is the Imaging Lead Investigator), aims to provide convincing evidence for the benefits and safety of alteplase if given intravenously up to six hours after stroke in patients who have had a computed tomography (CT) scan to exclude bleeding as the cause of stroke. Funded by the MRC, IST-3 has recruited 2130 patients, with a target total of more than 3100 by mid 2011. It is already the largest randomised trial of a thrombolytic drug, which is a reflection of the expertise amongst the trial organisers and participating centres.

CT scanning is currently the most widely available brain scanning method. However, newer imaging techniques, such as CT perfusion or magnetic resonance (MR) diffusion and perfusion imaging, may reveal where the blood flow to the brain has been reduced by a blockage. These scans should indicate whether or not the reduced blood flow has caused brain death in those areas and therefore better predict whether alteplase therapy may be beneficial.

treatment strategy in preschool wheeze. The trial aims to determine whether there is a genetically highly-responsive subgroup of children. The trial will incorporate several novel aspects. Parents will be able to adjust the use of oral montelukast to their child's symptoms, enabling children with “episodic” and “multi trigger” patterns of preschool wheeze to be recruited. Children's leukotriene genes will also be assessed, primarily the ALOX5 gene, to ensure an equal number of potentially “treatment-responsive” children receive the active drug (montelukast) and the placebo.

The trial will recruit 1300 children with a history of preschool wheeze and allocate them to groups with “responsive” and “less responsive” leukotriene genes, focusing on the ALOX5 gene. Parents will be issued with the trial medication; 50% will be given montelukast and 50% will be given placebo. Parents will give the trial medication whenever their child develops a cold and stop the medication when wheeze resolves. Parents will also be able to give the trial medication for wheeze between colds. Children receiving placebo medication will continue to receive normal inhaled therapy.

A number of IST-3 and other centres are interested in using these newer imaging techniques to help improve patient selection. The EME programme has funded a sub-study embedded in the main IST-3 trial to analyse data from the IST-3 trial centres around the world where these newer imaging methods are already in use.

A group of clinicians and expert image analysts will evaluate a range of different analysis approaches that are currently available. Data from approximately 300 patients involved in IST-3 trials are expected to be available for analysis, which would effectively double the information that is currently available in this area. This trial should also provide more definite evidence for the efficacy of newer, less available and more expensive scanning techniques in patients being considered for thrombolytic treatment.

“The additional funding awarded by the EME programme is extremely timely because it will allow us to collect and analyse in depth the blood flow imaging that is already acquired in patients randomised in IST-3.”

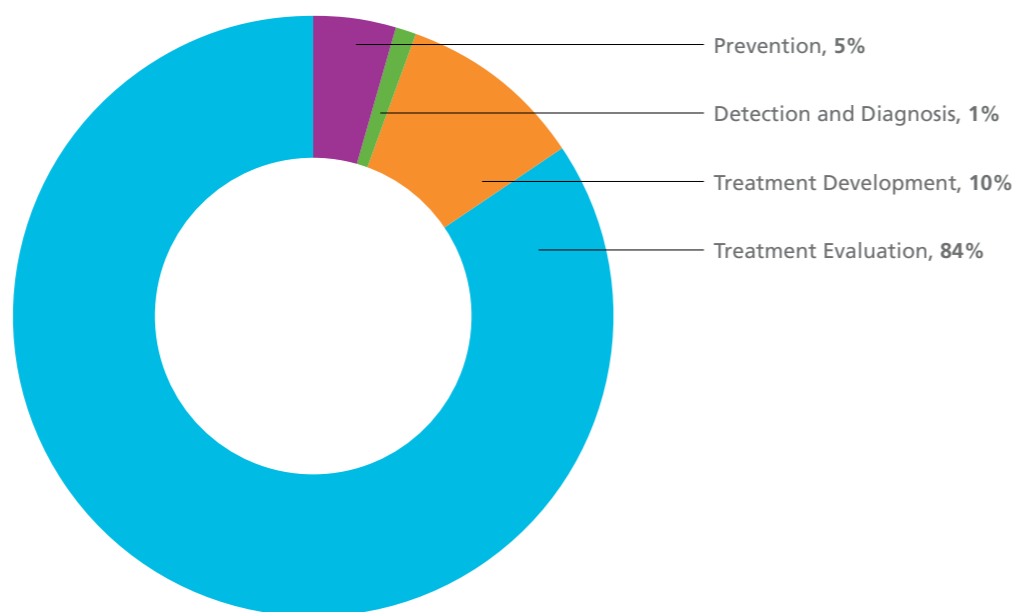
Each child will be studied for 12 months and during this period the trial will assess the number of unscheduled attendances to a medical practitioner for wheeze. At the end of the trial, the efficacy of montelukast will be measured by the difference in response to montelukast between the two ALOX5 gene groups. The trial will also measure many other genes that may influence response to montelukast, as well as the amount of leukotrienes that are excreted in the urine before and during attacks.

“In the past, clinical trials and mechanistic studies have tended to be funded separately. By combining the two, my EME-funded study will have an immediate benefit to children as well as signposting new therapeutic approaches.”

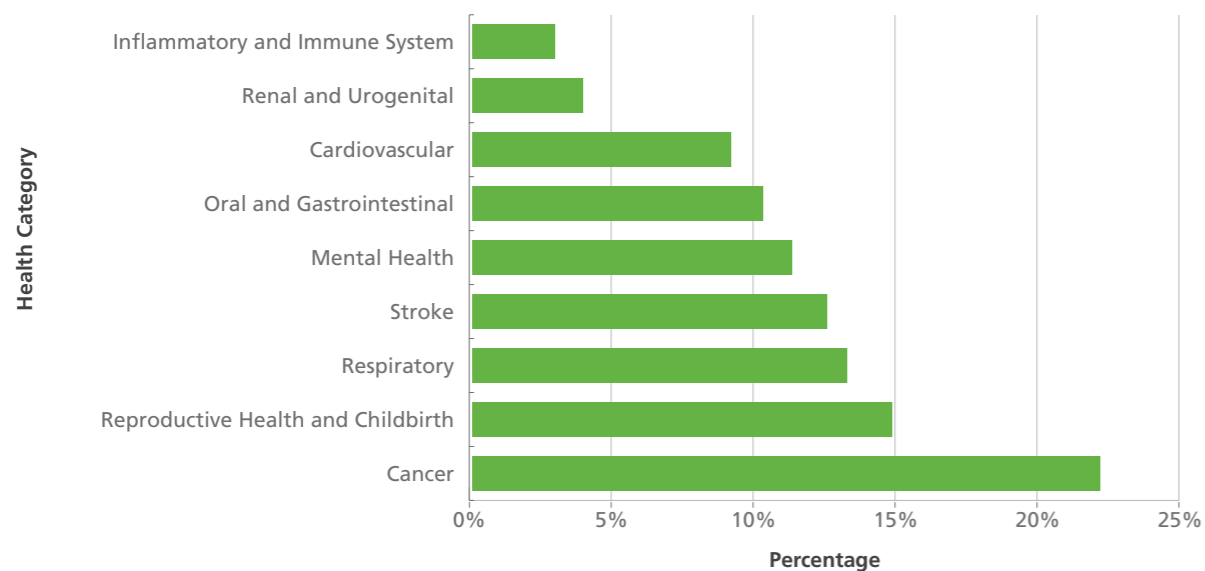
EME PORTFOLIO

As our portfolio grows we look forward to funding applications across the full breadth of health categories

Proportion of funds allocated* by research activity



Proportion of funds allocated* by health category



*subject to contract

EME BOARD

April 2009 – March 2010

Dr Cindy Billingham

Head of Biostatistics and Assistant Director for Research Methodology, Cancer Research UK, Clinical Trials Unit, University of Birmingham

Professor Andrew Bradley

Department of Surgery, Addenbrooke's Hospital, University of Cambridge

Professor Martin Brown

Professor of Stroke Medicine, Department of Brain Repair and Rehabilitation, University College London

Professor David Cameron

Director, National Cancer Research Network, NCRN Coordinating Centre, University of Leeds

Professor Rona Campbell

Professor in Health Services Research, University of Bristol

Professor Andrew J Carr

Nuffield Professor of Orthopaedic Surgery, Nuffield Department of Orthopaedic Surgery, University of Oxford

Professor Graham Dunn

Professor of Biomedical Statistics, University of Manchester

Professor Richard Eastell

Professor of Bone Metabolism, Northern General Hospital, Sheffield

Professor Diana Elbourne

Professor of Health Care Evaluation, London School of Hygiene and Tropical Medicine

Professor Kim Fox

Professor of Clinical Cardiology, Royal Brompton Hospital

Professor Jayne Franklyn

Head, School of Clinical and Experimental Medicine, University of Birmingham

Dr Simon Gates

Health Sciences Research Institute, Warwick Medical School Clinical Trials Unit, University of Warwick

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Professor of Child and Adolescent Psychiatry, University of Cambridge

Professor Pierre Guillou

Professor of Surgery, University of Leeds

Professor Ian Harvey

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Professor David R Jones

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Professor of Clinical Pharmacology, University of Liverpool

Professor Judith Stephenson

Chair of Sexual and Reproductive Health, Royal Free and University College Medical School

Professor Jonathan Weber

Director of Research, Imperial College London

Professor Moira Whyte

(DEPUTY CHAIR)
Professor of Respiratory Medicine, University of Sheffield

Professor Bryan Williams

Professor of Medicine, University of Leicester

Professor John G Williams

Professor of Health Services Research and Consultant, University of Wales Swansea

“On behalf of the Board, I would like to thank colleagues who have assisted the EME programme this year by offering their services as referees. It is the help of more than 200 volunteers that ensures we can maintain the standards of rigor in processes and feedback that our funders and applicants value.”

Professor Rajesh Thakker
Chairman of the EME Board

For the latest information on our work, details of application deadlines and support when making an application please go to

www.eme.ac.uk

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