

## Efficacy and Mechanism Evaluation Programme

### Proof of concept

All applications to EME must cite some evidence that the intervention could work, i.e. that there is “proof of concept”. How much prior evidence of potential efficacy is needed will vary with the size of the translational step, the scale of the proposed study and the nature of the intervention.

This evidence for proof of concept should come from studies involving patients and may include but is not limited to, epidemiological data, use of interventions in different conditions, and early stage clinical studies.

### Examples of “proof of concept” accepted by the EME Funding Committee

#### 1. Studies backed by epidemiological data or large case series:

A large study where simvastatin was used in patients with acute respiratory failure was justified on the extensive epidemiological data linking prior statin use and better outcomes from pneumonia. This was coupled with data on the acute anti-inflammatory effects of statins in volunteers and patients.

A study looking at the use of blood and clotting factors delivered to accident victims at the scene was based on positive indications from two meta-analyses of observational data, and case series from military medicine.

#### 2. Study based on pilot data:

A study using sildenafil as treatment for intra-uterine growth retardation was underpinned by the current use of the drug in pregnancy for another condition, a 10 patient case series and a small 35 patient pilot study. There was also laboratory work on ex-vivo human samples supporting the postulated mechanism of action.

A 120 patient pilot cross over study of patients with irritable bowel syndrome treated with ondansetron showed a surrogate benefit over a short time period. A larger study was funded to look at the longer-term patient-centred benefits of ondansetron in this condition.

### **3. Study based on data from other large trials:**

Chronic hepatitis C virus infection (genotype 1) is routinely treated with a three drug combination. A factorial design study looked into modulating the treatment duration based on viral load, and also adding a fourth anti-viral agent. There was good evidence from secondary analysis of other large studies that treatment periods in common use might be overly-long.

### **4. Study following on from positive early phase human trial:**

A clinical trial of repeated application of gene therapy in patients with cystic fibrosis was based on data showing the effect of single doses of both the gene and the vector.

A study of activated dendritic cells in hepatocellular carcinoma was based on a case series of 25 patients treated in a phase I study with a greater than expected survival.

### **5. Study based on promising early indications of an effective diagnostic:**

EME funds evaluations of diagnostic tests. A new technique for screening the high number of biopsies of colonic polyps arising from a sigmoidoscopy-based bowel cancer screening programme had been developed. Preliminary studies on both banked embedded specimens and “fresh” specimens suggested it might have adequate sensitivity and specificity. EME funded work to scale-up the process and establish the test performance on a large number of clinical samples.

The details of all EME-funded studies can be found at: <http://www.nihr.ac.uk/eme>

For more detailed information about the different types of information provided by EME funded projects to support “proof of concept” in applications, please see the table below.

Information supplied to demonstrate proof of concept						
Project	Laboratory studies	Experimental medicine studies	Epidemiological or case series data	Pilot data	Small studies from other teams	Supporting large RCTs in similar conditions
<a href="#">Parent-determined oral montelukast therapy for preschool wheeze. (Wheeze And Intermittent Treatment: WAIT)</a> <i>[This study had a component looking at genetic determinants of response to montelukast.]</i>	Leukotriene synthesis varies with polymorphisms of the ALOX-5 promoter gene. ALOX-5 is a rate limiting step in leukotriene synthesis.		Levels of urinary leukotriene metabolites were elevated during acute attacks of preschool wheeze.			Two large studies showed regular montelukast reduced pre-school wheeze attacks by a third.
<a href="#">Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2)</a>	Statins improve epithelial and endothelial function to reduce alveolar capillary permeability and reduce pulmonary oedema in animal and cellular models	Pre-treatment with statins reduces endotoxin-induced pulmonary inflammation in volunteers	Large observational studies have suggested a beneficial effect of prior statin treatment in patients with pneumonia. Results were duplicated in a study of patients in critical care units.	A single centre, randomised, double-blind, placebo-controlled phase II study of simvastatin in 60 patients with acute lung injury conducted by the applicant.	Two studies only published in abstract form. One study in 74 patients with sepsis and pneumonia and one study in 40 patients with sepsis showed some benefit for statins.	

<p><a href="#"><u>The effects of reducing worry in patients with persecutory delusions: an explanatory randomised controlled trial.</u></a></p>	<p>The lead applicant and colleagues developed and published a cognitive model of persecutory delusions.</p> <p>Worry and associated processing were central in the model.</p>		<p>Case series show worry is extremely common in individuals with persecutory delusions, that it is especially associated with more distressing persecutory delusions, and that it is a predictor of symptom persistence or recurrence.</p>	<p>A single centre 24 patient unblinded pilot study was undertaken by the applicant.</p>	<p>Systematic review showed no other published work in this area.</p>	
<p><a href="#"><u>Developing a novel, biopsy-based diagnostic for patient stratification: A Randomised, open labelled study in anti-TNFalpha inadequate responders to investigate the mechanisms for Response, Resistance to Rituximab versus Tocilizumab in Rheumatoid Arthritis patients.</u></a></p>	<p>Histology showing differing B cell-based inflammatory burden in multiple synovial biopsies.</p>	<p>Applicants have developed and validated a novel technique for synovial biopsy. Audit data available on success rates etc.</p>	<p>MRC funded 220 patient cohort with synovial biopsies providing support for likely cause of variable response to rituximab. Post-marketing data on rituximab quantifies variability in response.</p>	<p>Single centre 21 patient pilot undertaken by applicants.</p>		

<a href="#">A randomised, placebo controlled trial to determine the efficacy and mode of action of ondansetron in the treatment of irritable bowel syndrome with diarrhea.</a>	<p>Animal models suggest that 5HT3 receptor antagonists act on enteric neurones inhibiting the gastrointestinal motor and secretory response to feeding.</p>	<p>5HT3 receptor antagonists slow transit in humans, and inhibit the colonic response to feeding.</p>		<p>Large cross over pilot study showed a beneficial change in a surrogate outcome over a short time period.</p>		
<a href="#">STRESS-L: Study into the REversal of Septic Shock with Beta Blockade (Landiolol)</a>	<p>In animal models of Gram-negative sepsis early treatment with propranolol or esmolol reduced mortality.</p>	<p>High circulating catecholamine levels are associated with mortality in patients with septic shock.</p>	<p>The extent and duration of catecholamine therapy are all independently associated with poor outcomes in critically ill patients, after adjustment for disease severity.</p>		<p>Single centre Italian study showed a very large reduction in hospital mortality using unblinded esmolol infusions.</p>	

## **Examples of “proof of concept” not accepted by the EME Funding Committee:**

### **1. Applications declined because there were no data from human studies:**

A surgical implant to improve results from hernia surgery had been developed and undergone laboratory testing. Although the laboratory testing showed promising results, the implant had not been used in human studies and the application proposed a “first in man” study.

A cell therapy for an auto-immune disease had been developed by a study team at one institution which showed promise during in vitro studies. Another institution had already used a similar cell therapy for other conditions, but used different cell lines, culture techniques and processes. As the applicants proposed a study of their own particular cell therapy which, at the point of application had not been given to a patient, it had inadequate proof on concept.

### **2. Applications declined due to paucity of laboratory or clinical data:**

An application was received for a study of a nutritional supplement as a treatment for cognitive decline. The Funding Committee was not convinced that the laboratory data supported a plausible mechanism of action, and two very small RCTs showed minimal benefit.

An application for a study of a novel wound dressing for diabetic foot ulcers was submitted. No early data from studies on patients with these ulcers was available, and there were very limited data on the use of the dressing in other conditions. There was no experimental evidence supporting the use of these dressings.