Efficacy and Mechanism Evaluation Programme

Mechanistic studies, explanation and examples

EME encourages hypothesis-testing mechanistic studies. These studies can explore the mechanisms of action of the intervention, the causes of differing responses, or promote an understanding of any potential adverse effects and how these could be reduced. They could also contribute to understanding of the disease process.

We will fund hypothesis driven studies that can be tested using sample analysis, images, or other data, usually from the main efficacy study. Commonly these mechanistic studies use the difference between treatment groups in a randomised clinical trial to explore the mechanism of action of the treatment, but we welcome other designs.

It is important that applicants have a clear hypothesis about the mechanisms under study, and can demonstrate how the proposed tests or data analysis will confirm or refute the hypothesis. We will not fund exploratory analyses of samples or data to seek out previously unknown analytes or unexpected associations with outcomes. Examples of exploratory analyses that EME would be unlikely to fund are "biomarker discovery", "proteomics", "peptidomics", "genome-wide association studies", and similar techniques. EME will fund collection and storage of samples for future exploratory analysis where they represent a unique collection that would otherwise not be available, but will not fund the analysis of these samples.

We support mechanistic studies in two ways. The majority of mechanistic studies we fund are integrated within a main efficacy study (see studies EME **08/43/03**, EME **13/50/17** and others as examples). We also support mechanistic studies that use samples or data from on-going or completed clinical studies funded by the NIHR (see study EME **14/205/01** below for an example). Applications for mechanistic studies using samples or data from other NIHR-funded studies are submitted in a single-stage ("straight to full") application process. Please complete the eligibility form available within the Mechanisms of action of health intervention call if you are planning to submit a single stage application.

Examples of EME funded studies with mechanistic components.

Studies where determinants of the treatment response are investigated:

An investigator studied the clinical effectiveness of intermittent parent-determined montelukast as a treatment in pre-school wheezing children. The amount of enzyme that determines the production of the target molecule for montelukast varies with different genotypes of the promoter gene. The investigator

designed a study that investigated the effect of intermittent parent-determined montelukast treatment on pre-school wheeze, whilst simultaneously determining if the treatment effect was modified by the child's genotype. (EME **08/43/03**)

A team of researchers are studying the efficacy of an IL-1 receptor antagonist in pustular psoriasis. It is possible that patients with pustular psoriasis have a deficiency in interleukin-36 receptor antagonist (IL-36RA) leading to unrestrained IL-36 signalling and increased IL-1 production. The investigators will investigate the abnormal IL-1 signalling caused by IL-36 and other gene mutations to determine if they predict response to IL-1 receptor blockade. (EME **13/50/17**)

Studies where the mechanism by which a treatment works is investigated:

A study is using standard clinical pain assessment tools to test whether morphine provides analgesia and increased physiological stability during retinopathy of prematurity screening in neonates. In addition to standard clinical pain assessment the investigators are using recently developed electrophysiological techniques to examine the effects of morphine on the underlying brain and spinal cord activity evoked by the painful procedures, to determine how nociceptive information is transmitted to and processed by the cortex and where morphine interacts with this pathway. (EME **14/187/01**)

In a study of ulipristal acetate against a levonorgestrel-releasing intra-uterine system (Mirena) for the long-term treatment of heavy menstrual bleeding a sub-set of patients will undergo imaging of the uterus using high resolution MRI of the uterine matrix and fibroids and Dynamic Contrast Enhanced MRI to measure uterine perfusion. This will determine if ulipristal influences menstrual bleeding via a reduction in uterine blood flow. (EME **12/206/52**)

Studies using data or samples from other NIHR-funded trials:

Intravenous tranexamic acid may reduce the severity of traumatic brain injury by reducing the severity of intracranial bleeding. It is also possible that tranexamic acid has a direct anti-inflammatory action on the brain which may also be beneficial in patients with a brain injury. An investigator is using brain microdialysis techniques in a sub-set of patients recruited to the HTA-funded CRASH-3 study to determine whether markers of brain inflammation are changed by tranexamic acid and whether this is related to outcome. (EME **14/205/01**)

An EME-funded study aims to understand the mechanisms of change in group-based weight loss and related behaviour change interventions. The investigators are using recordings of group sessions from two randomised controlled trials and a feasibility study, all NIHR funded. Qualitative research methods are being used to extract target features at group level and then determine if they are associated with successful weight loss. (EME **14/202/03**)

Examples of mechanistic components that would be outside EME's remit.

An investigator proposes testing a new intervention to treat exacerbations of refractory asthma with a control group treated according to standard BTS guidelines. She proposes collecting urine specimens at randomisation on all patients. Using physicochemical protein capture and high-performance liquid chromatography with tandem mass spectrometry she proposes to characterise the urinary proteome and then look for as yet unknown differences between "responders" and "non-responders" to the new treatment. Any identified biomarkers might provide the basis for future stratified care.

Comment: there is no proposed mechanism or identified analyte. This is a "biomarker discovery" project. EME would consider funding the sample collection and storage but would not fund the analysis.

A researcher proposes a study of an on-line, self-administered cognitive behavioural therapy (CBT) programme against an attention control for patients with obsessional-compulsive disorder. He requests funding for functional MRI studies in all patients to confirm previous findings that, in patients with obsessional-compulsive disorder, there is an abnormality of fMRI-determined amygdala activation to human face images.

Comment: there is no hypothesis that relates to the intervention under study, the researcher is requesting funding to study the whole cohort to confirm previous studies in this disease.

A very large effectiveness study funded by the NIHR is looking at an agent that may reduce the number of patients who develop metastatic deposits of colonic adenocarcinoma after primary resection. The agent may work via a mechanism involving endothelial cell surface antigens. A researcher proposes an add-on mechanistic study. This involves measuring the expression of these markers in venous biopsies in both groups to see how the treatment changes the surface markers of interest, and parallel work involving in vitro studies on endothelial cell cultures from an immortalised cell line.

Comment: the venous biopsy component would be within EME's remit as it examines one possible mechanism of action of the treatment. Parallel laboratory studies not involving patient material or data are out of remit.

An investigator proposed a study of a structured exercise regimen for rehabilitation of patients with lung cancer treated with pulmonary resection. The control group was "care as usual". She proposed a mechanistic study that included measures of muscle strength, maximal oxygen consumption during exercise (VO_2 max) and ultrasound-determined quadriceps mass.

Comment: the mechanistic component in this study would simply confirm the intervention had the expected effect on measures of physical fitness and does not explore novel mechanisms.