Project Details	
Project Code	MRC22NMHEx Baple
Title	Developing a new blood test to revolutionise diagnosis and management in patients with motor neurone degenerative disorders
Research Theme	Neuroscience & Mental Health
Summary	Motor neurone disease (MND) affects the brain and nerves, causing weakness and paralysis that worsens over time. Currently no test is available to efficiently diagnose or determine risk of developing MND. This PhD studentship combines cutting edge genomic studies with newly developed lipid analytical methods, to develop a revolutionary new cross-cutting blood test for use in the clinical setting to aid diagnosis and therapy development for MND patients
Description	There are many different forms of motor neurone degenerative diseases (MNDs), for which symptoms vary according to how specific motor neurone types are affected. Dependent upon the MND type, a patient may experience progressive difficulties with mobility, strength, speech, swallowing and breathing. Although individually rare, together the many genetic forms of MND represent a significant global heathcare burden. Over recent years the Exeter Rare Disease research group has studied forms of MND present in genetically isolated populations such as the Amish, in which genetic studies are enormously powerful. This approach has enabled the discovery of >15 new MND genes, greatly aiding scientific understanding of these conditions. However due to poor knowledge regarding gene function, there remains a limited scientific understanding of MND pathological processes. Additionally as many MND genes remain yet to be discovered, most MND patients do not have a molecular diagnosis for their condition. As such, no universal test is available to determine an individuals' risk of developing MND, predict disease progression, or monitor treatment response in clinical trials. The overarching objective of this project is to develop a new, cross-cutting test applicable to many types of MND. Such a test would, for the first time, enable doctors to effectively identify people at risk of developing MND and potentially predict the course and severity of the disease. This unique multidisciplinary training programme involves two main aims; 1. Genomic studies to identify new genetic causes of MND. This will utilise our in-house cutting edge genome sequencing facilities and bioinformatics pipelines. Studies will investigate forms of MND present in families from genetically isolated Amish and Palestinian communities, in which known genetic causes of MND have been excluded. In parallel we will investigate large genome datasets (100,000 Genomes and international sequencing programs) to identify UK / global families with genetic forms of MND. This aspect of the study will include confirming a new inherited form of MND recently discovered forming pilot data for this studentship, in which candidate pathogenic mutations have been identified in a phospholipid processing enzyme. CRISPR-Cas9 gene editing, in routine use by the Exeter group, will be used to generate a neuronal knock out cell model of this disease. This will form a crucial resource for comparisons with data from patient cells, outlined in aim 2 below. 2. Revolutionary new clinical-diagnostic test development for MND patients. This aspect stems from recent advances in defining the pathomolecular basis of the condition by the Exeter group, work

	which received extensive news coverage globally (see BBC: https://www.bbc.co.uk/news/health-50821327). As part of this we have developed entirely new methods to analyse cellular lipid (in particular oxysterol-phosphatidylethanolamine) processing pathways, which are central to our hypothesis describing a pathomolecular disease mechanism common to multiple forms of MND (PMID: 31848577). These methods will be applied to investigate samples from neuronal cell models of MND, as well as from MND patients, permitting comparisons to be made across multiple forms of MND. This PhD studentship offers a unique opportunity to undertake cutting-edge research as part of a wider initiative to enhance MND diagnosis and patient care through genomics and clinical biomarker development. It is based within the internationally leading centres the Wellcome-Wofson RILD Institute (Exeter), Neurosciences (Bristol) and Bristol Diagnostic Genetics Laboratory (N. Bristol NHS Trust), in collaboration with a PlexSeq diagnostic (Cleveland, USA) industrial partnership. The successful student will be encouraged to present their research findings at national/international conferences, and publish their data in leading peer-reviewed scientific journals
Supervisory Team	
Lead Supervisor	
Name	Dr Emma Baple
Affiliation	Exeter
College/Faculty	Medicine and Health
Department/School	IBCS, RILD Institute
Email Address	e.baple@exeter.ac.uk
Co-Supervisor 1	
Name	Professor Andrew Crosby
Affiliation	Exeter
College/Faculty	Medicine and Health
Department/School	IBCS, RILD Institute
Co-Supervisor 2	
Name	Professor James Uney
Affiliation	Bristol
College/Faculty	Bristol Medical School
Department/School	Neurosciences
Co-Supervisor 3	
Name	Professor Rachel Butler
Affiliation	Bristol
College/Faculty	Bristol Genomics Laboratory
Department/School	South West Genomic Laboratory Hub
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	