Project Details	
Project Code	MRC21PHEx Henley
Title	Joint modelling of adverse events and drug response in electronic health record databases
Research Theme	Population Health
Summary	Clinical decisions about drug therapy require an understanding of whether treatments are safe and effective. For some medications patients who respond well may also be at increased risk of side-effects. The student will develop statistical methods to explore the links between the benefits and harms of treatments using electronic health record data. This approach will be applied to help identify personalised treatment strategies for patients with Type 2 Diabetes.
Description	Clinical decisions about choice of drug therapy should be based on an understanding of both efficacy and safety. Randomised trials provide the gold standard of evidence for making such decisions but have important limitations, particularly when considering risk of adverse events. These include insufficient sample sizes to detect rare but serious drug reactions, a relatively short duration of follow-up and exclusion of participants at greatest risk of adverse events based on criteria such as co-morbidities or age. Post-marketing surveillance of new drugs, therefore, plays a vital role in ensuring that patients receive safe treatments but brings up new challenges. An increasingly important approach is to study adverse events using longitudinal data from electronic health records (EHR). An issue with using these data, however, is the problem of confounding by indication whereby selection for treatment is based on factors, such as disease severity, that are related to prognosis. In many cases the sources of confounding are unmeasured, preventing adoption of standard adjustment methods to remove bias. Recent advances in quasi-experimental methods make it possible, under relevant assumptions, to address directly the bias that arises when relevant confounders are omitted. One promising strategy is prior event rate ratio (PERR) adjustment. The Exeter team have developed a statistical framework for PERR adjustment and successfully applied this to EHR data on side-effects to second-line therapies for type 2 diabetes, validating the results against outcomes of randomised trials. This project will extend the work on drug side-effects in EHRs to incorporate treatment response, by using joint models for longitudinal and time-to-event data. It is hypothesised that there may be an interdependency between longitudinal blood glucose (HbA1c) response and risk of certain side effects but this is difficult to test reliably using standard methods. The student will develop cutting edge methods for longitudinal modelling and causal inference, using them to explore how risk of adverse events relates to drug response for commonly prescribed diabetes medications. This offers a potential framework for optimising treatment decisions for patients based on a combination of outcome and adverse event profiles. Methods that allow for combinations of repeated biomarkers (eg HbA1c), terminal events (eg death) and recurrent events (eg hypoglycaemia) will be evaluated. The project is a collaboration between the Universities of Exeter and Bristol drawing on their combined strengths in statistical methodology development and observational data modelling. Tiilling and Hughes will provide expertise

	on joint modelling of longitudinal and time-to-event data. Henley and Rodgers (Exeter) will provide expertise on methods for addressing unmeasured confounding in EHR data, with further clinical support provided by the University of Exeter's world leading diabetes research team.
Supervisory Team	
Lead Supervisor	
Name	Professor William Henley
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Institute of Health Research
Email Address	w.e.henley@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Lauren Rodgers
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Institute of Health Research
Co-Supervisor 2	
Name	Professor Kate Tilling
Affiliation	Bristol
College/Faculty	
Department/School	School of Social and Community Medicine
Co-Supervisor 3	
Name	Dr Rachael Hughes
Affiliation	Bristol
College/Faculty	
Department/School	School of Social and Community Medicine
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	