Project Details	
Project Code	MRCPHS25Ba McGrogan
Title	How safe are antiseizure medications in pregnancy for conditions other than epilepsy?
Research Theme	Population Health Sciences
Summary	Did you know that only 5% of medicines licensed in the UK have sufficient evidence about their safety in pregnancy? Women may be advised not to use medicines in pregnancy due to concerns about harm to their offspring. However, some conditions must be treated throughout pregnancy or a woman's health deteriorates which can also have life changing impacts on her offspring. Evidence is vital to allay fears of harm and inform decision making. This PhD will use Big Data to determine safety of antiseizure medications used for conditions not regularly studied in pregnancy including migraine, neuropathic pain and bipolar. disorder.
Description	Research question: What is the impact of antiseizure medications for non-epilepsy indications in pregnancy? Outline objectives: • To undertake a systematic literature review to determine the current evidence available about antiseizure medications used in pregnancy for non-epilepsy indications. • To form a cohort of women with at least one pregnancy recorded in the Clinical Practice Research Datalink (CPRD) during the study period who receive at least one anti-seizure medication for a non-epilepsy indication during their pregnancy • To determine the prevalence of pregnancy outcomes including loss, or outcomes in the offspring (major congenital malformations, neurodevelopmental disorders) in those prescribed an antiseizure medication compared to those who are not. • Determine whether any exposures or indications lead to an increased risk of these outcomes compared to women who do not have this indication or exposure Why is this topic important: Understanding which medications are safe to use in pregnancy is vital both to ensure that the mother's medical condition is effectively managed during her pregnancy and that her offspring have the best start in life. We have found a high number of women who are prescribed antiseizure medications during pregnancy for non-epilepsy indications including migraine, neuropathic pain and bipolar disorder. Given that current understanding and evidence is mostly in relation to epilepsy indications where doses tend to be higher, understanding the effect of antiseizure medications in non-epilepsy pregnancies is important in helping to untangle medicine, dose and disease effects in order to ensure that women are not denied effective treatments or that more children than necessary are placed at higher risk of developmental impacts. What is already known about this topic? While there is still more to understand about the effects of antiseizure medications in pregnancy in women with epilepsy, studies have demonstrated that a number of anti-seizure mediations, such as valproate, phenobarbital, carbamazepine, increase the risk of adverse

	physical and neurodevelopmental outcomes in the offspring. The major congenital anomaly risk can be as high as 25% at higher doses of valproate with approximately 40% demonstrating neurodevelopmental impacts which are lifelong(1). As a result, much consideration needs to be given regarding initiating or continuing these medications during pregnancy and for valproate and topiramate a pregnancy prevention plan has been put in place, restricting their use in women of childbearing potential. These antiseizure medications and others including gabapentin, pregabalin and lamotrigine can also be prescribed for non-epilepsy indications, including migraine, neuropathic pain and bipolar disorder. There are very few studies and little evidence as to the impact of antiseizure medicines when taken to treat non-epilepsy indications, which are often used at lower doses. Those that have been undertaken have a small sample size indications of interest(2,3), are combined with epilepsy results(3) and only consider birth outcomes(3-4). Regulatory decisions to restrict use is often based upon data from cohorts with epilepsy indications. How does this fit with MRC and the DTP's strategic priorities? This project fits within the DTP's population health priority to evaluate interventions for population health. Within the MRC's cross-cutting themes, data features strongly with an emphasis on gaining insight into health through the use of large data sets and in the training of new researchers to have the skills to use data for research and innovation. Methods There are a number of ways to study medication safety in pregnancy but given that adverse outcomes such as major congenital malformations are rare, large numbers of pregnancies need to be included. The Clinical Practice Research Datalink (CPRD) is a large electronic data source that contains primary care records from 16.5% of general practices in England. We have successfully used the CPRD for pregnancy studies in a number of disease areas (5-7). The PhD researcher will learn to use sequential query language to be able to work with the database and identify the specific cohort of women to be included in this study, collate their information about prescribing, diagnoses, comorbidities and other characteristics and then determine outcomes that occur. The PhD researchers will develop the specific direction of the project according to their interests and background: while some example outcomes of interest are suggested here, it will be up to the researcher in conjunction with their supervisory team to determine which outcomes to focus on. Clinical information, from a specialist clinic for children exposed to medications in utero, will be reviewed to determine the types of symptoms and outcomes seen in childhood. Further, a group with lived experience will be formed to provide additional learning and direction on the outcomes we should be investigating. Similarly in determining the analysis plan, there are a number of options available to be considered both classical epidemiological analyses or machine learning approaches that could garner the power of nonexposed comparator pregnancies in a wider cohort.
Supervisory Team	
Lead Supervisor	

Name	Dr Anita McGrogan
Affiliation	Bath
College/Faculty	Science
Department/School	Life Sciences
Email Address	am399@bath.ac.uk
Co-Supervisor 1	
Name	Dr Helen McDonald
Affiliation	Bath
College/Faculty	Science
Department/School	Life Sciences
Co-Supervisor 2	
Name	Dr Jan Vollert
Affiliation	Exeter
College/Faculty	Faculty of Health and Life Sciences
Department/School	Department of Clinical and Biomedical Sciences
Co-Supervisor 3	
Name	Dr Rebecca Bromley
Affiliation	Manchester
College/Faculty	Division of Neuroscience
Department/School	School of Biological Sciences