PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Meningococcal B vaccine: incidence of convulsion following vaccination and compliance with timing of vaccine doses in the UK

B. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Meningitis type B is a potentially life-threatening bacterial infection that can poison a person's blood and cause inflammation of the lining around the brain and the spinal cord. A new vaccine against meningitis B was introduced into the UK routine childhood vaccination programme in September 2015. As with many other vaccines, the new meningitis B vaccine may cause high temperatures and fevers in infants in the days following vaccination. There is evidence however that the new vaccine may cause more and higher fevers than the other vaccines. A high fever due to infection or a vaccine carries a risk of a fit/seizure in infants and small children. The purpose of this study is to investigate the possible risk of fits/seizures in infants following vaccination with the meningitis B vaccine by comparing trends of fits/seizures following vaccination both before and after the meningitis b vaccine was added to the routine childhood vaccination programme. Additionally the study will evaluate whether the inclusion of the new vaccine alongside the other well established vaccines is having any impact on infants/parents returning to have their second and third doses of the meningitis vaccine and the other routine vaccines. The results of this study will provide valuable information on the safety of the new meningitis B vaccine.

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Meningococcal B is a bacterium that can cause life-threatening meningitis, a severe acute inflammation of the protective membranes around the brain and spinal cord, and septicaemia. A meningococcal group B vaccine was introduced into the UK routine childhood vaccination programme in September 2015. Based on clinical trial data, this vaccine was shown to be more reactogenic than other vaccines routinely given to infants with high fever rates observed. There is therefore the potential for the meningococcal B vaccine to cause febrile convulsions at a higher rate than other vaccines also. The aim of this study is to investigate this potential risk of febrile convulsions following vaccination with meningococcal B vaccine in an ecological analysis by comparing incidence rates of convulsions following routine vaccination both before and after the introduction of the meningococcal B vaccine into the routine schedule. Additionally compliance with receiving subsequent doses of meningococcal B vaccine and the other routine vaccinations will also be investigated to determine if the introduction of the meningococcal B vaccine is

having an impact on infants/parents returning for subsequent doses on time. The results of this study will provide valuable information on the safety of the meningococcal B vaccine and its impact on the childhood vaccination programme.

D. Objectives, Specific Aims and Rationale

The first objective of this study is to investigate a potential risk of convulsions following vaccination with Meningococcal B vaccine in the UK by comparing the incidence rate with other routine childhood vaccinations.

The second objective is to evaluate potential delays in receiving subsequent doses of Men B vaccine and other childhood vaccinations administered at the same time as Men B vaccine.

Specific aims are to:

- Determine the incidence of convulsions in infants following routine vaccination at 8 weeks, 16 weeks and 12 months of age before and after the introduction of Men B vaccine into the routine schedule.
- Investigate any delays from the routine schedule in receiving further doses of Men B vaccine and other routine vaccinations administered at the same time as Men B vaccine.

The results of this study will provide valuable information regarding a potential risk of febrile convulsions following vaccination with Men B vaccine that will help decide whether a more formal study to investigate this potential risk is warranted.

Additionally the study will provide an indication as to whether the introduction of the Men B vaccine to the routine schedule is affecting patient compliance with either further doses of Men B vaccine or other routine childhood vaccinations. This information is critical to ensure the success of the childhood vaccination programme.

E. Study Background

Meningococcal group B vaccine (Bexsero) was first authorised in the EU in January 2013. The UK introduced Bexsero into the routine childhood immunisation schedule in September 2015 and was the first country to implement a national, routine infant immunisation programme with a Men B vaccine. Bexsero is given as 3 doses recommended at 2 months, 4 months and 12 months of age and is administered concomitantly with other vaccines recommended at those times including: pneumococcal vaccine, DTP/IPV/Hib (5-in-1 vaccine containing diphtheria, tetanus, pertussis, polio and haemophilus influenzae type b), rotavirus, MMR (measles, mumps and rubella) and Hib/Men C (haemophilus influenza type b and meningitis C).

Based on data from clinical trials, Bexsero is known to be more reactogenic than other routinely used vaccines given to infants and particularly when given concomitantly with other vaccines. In the clinical trials the main systemic adverse event was fever, which occurred at very high rates in infants ages 2 and 4 months. As a result, administration of paracetamol is recommended as prophylaxis with the 2 and 4-month vaccinations but not with the 12-month booster dose on the basis that fever rates in this age group were more comparable with other routine vaccinations.

Febrile convulsions occur most commonly in young children aged between 6 months to 3 years (peaking at the age of 1 year) and triggered when there is a sudden rise in body temperature. This rise in body temperature may be the result of a naturally occurring infection but a risk has been seen after vaccination. The risk of a convulsion following MMR is reported to be 1 in 1,150 doses[1] and 1 in 8,500 doses for DTP vaccination after the 3rd dose[2].

Given the increased risk of fever observed with Bexsero during clinical trials it is plausible therefore that there might also be an increased risk of febrile convulsion. This potential exists following all 3 doses of Bexsero. Although febrile convulsions generally occur after 6 months of age, the increased reactogenicity was observed at 2 and 4 months and it is prudent to investigate a risk in these age groups. The 12-month dose coincides with the highest background rate of febrile convulsion so despite the evidence from the clinical trials not suggesting an increased risk with Bexsero in this age group again it is prudent to also investigate this.

The expected increased reactogenicity with Bexsero also has the potential to affect compliance with future doses of Bexsero and other routine vaccines. Published data from Public Health England does not indicate a problem with overall decreased rates of vaccination for subsequent doses of Bexsero[3] or other childhood vaccines[4] . There may still be an impact on the timing of vaccination with parents delaying vaccination for their child however if a child has a reaction to the first dose. The timing of routine vaccination is important to ensure adequate protection against serious childhood diseases but for rotavirus vaccine it is especially important as the risk of intussusception associated with the vaccine is higher for older infants and even a few weeks can make a difference to the magnitude of the risk. It is therefore important to assess whether there is any evidence of delay in receiving subsequent vaccinations.

F. Study Type

This study has two components. The first component is an ecological study to describe the trend in incidence rates of convulsions following vaccination before and after the introduction of Men B vaccine into the routine schedule.

The second component is a descriptive analysis to estimate any delay in the administration of further doses of Men B vaccine and with two other routine childhood vaccinations given at the same time as Men B vaccine (rotavirus vaccine and pneumococcal vaccine).

Both components of this study are considered hypothesis-generating.

G. Study Design

The first part of this study is an ecological analysis to describe trends in incidence of convulsions following routine vaccination before and after the introduction of Men B vaccine into the routine immunisation schedule. The study will determine age-specific incidence rates of convulsion following routine vaccination at 8 weeks, 16 weeks and 12 months of age in the 5 years prior to the introduction of Men B vaccine and during the first 14months of the since its introduction. Additionally the incidence rate of convulsion following the booster vaccinations (MMR vaccine and 4-in-1 vaccine that contains DTP IPV)

at 3 years and 4 months of age during the same period will be determined in order to explore any temporal changes in the rate of recording of convulsions unrelated to the Men B vaccine. The incidence rate within the following time periods post-vaccination will be considered: 0, 1-3, 4-7 days.

An ecological analysis is proposed initially as an exploratory analysis and if a safety signal arises from this analysis then a further protocol will be submitted to ISAC for a formal hypothesis-testing study most likely with a self-controlled case series design.

The second part of this study aims to evaluate any delay in receiving further doses of Men B vaccine and two other childhood vaccines co-administered with Men B vaccine. Timing of vaccination will be investigated for all 3 doses of Men B vaccine at 8, 16 weeks and 12 months, rotavirus vaccine at 8 and 12 weeks and pneumococcal vaccine at 8, 16 weeks and 12 months. Timing of vaccination will be determined from the date of vaccination in relation to date of birth taken as the mid point (15th) of each month as only month of birth is available in the CPRD.

H. Feasibility counts

A preliminary analysis on vaccine uptake in CPRD has found the absolute number of infants receiving their first and second vaccinations with Men B vaccine is approximately 2500 and 2000 per month respectively. Public Health England have recently published a report on vaccine coverage for Men B vaccine that indicates vaccine uptake to be high with around 95% of eligible infants receiving their first vaccine and 90% receiving their second.[3] Vaccine coverage data published by Public Health England also show that coverage rates for the other routine childhood vaccines co-administered with Men B vaccine are over 90%.[4] It is likely therefore that around 2000-2500 infants per month will have a record for these in CPRD as well.

For the ecological study to describe incidence rates of convulsion following routine vaccination at 8 weeks, 16 weeks and 12 months of age on the basis of the estimates above there should be more than adequate patient counts for the 5 years prior to the introduction of Men B vaccine. For the time period after introduction of Men B vaccine, there should be approximately 35,000 infants with data following their first vaccinations at 8 weeks available in CPRD, 24,000 with data following their vaccinations at 16 weeks and around 8,000 with data following the booster vaccinations at 12 months.

For the second part of the study to investigate delays in administration of subsequent doses of Men B vaccine and other routine childhood vaccinations on the basis of the estimates above there should be approximately 24,000 infants with data following vaccinations after the introduction of Men B vaccine at 8, 12 and 16 weeks. A separate analysis will be done to investigate delays at 12 months and as above approximately 8,000 infants should be available for this. For the 2 years prior to the introduction of Men B vaccine there should be vaccination data available for approximately 48,000 infants.

I. Sample size considerations

Table 1 below shows the level of precision that can be expected for incidence rates of febrile convulsion following vaccination at 8 weeks, 16 weeks and 12 months of age assuming the true rate is similar to either MMR vaccine[1] or DTP vaccine[2]. If the true rate is higher than that for MMR vaccine then the estimates will be more precise.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Table 1. Precision of estimates of incidence rates for febrile convulsions following the introduction of Men B vaccine

Incidence rate of febrile convulsion (per 1000 doses)	95% CI Range		
	8 weeks (n=35,000)	16 weeks (n=24,000)	12 months (n=8,000)
0.87 (MMR)[1]	0.60 - 1.30	0.60 - 1.40	0.4 - 1.87
0.12 (DTP)[2]	<0.1 – 0.3	<0.1 – 0.3	<0.1 - 0.71

Incidence rates for febrile convulsion following vaccination at 8 and 16 weeks with Men B vaccine should have reasonable precision assuming the rate is similar to MMR vaccine. The precision is less good following the dose 3 as the sample size is smaller but Men B vaccine is thought to have high reactogenicity so higher incidence rates than MMR are possible. However as this is a hypothesis-generating study even null results are of interest as they generate an upper bound on the true incidence rate (according to the rule of three) and the analysis can be repeated at a later date to improve precision.

J. Data Linkage Required (if applicable):[§]

[§]*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

Not applicable. The need for linked HES data will be considered as part of any future proposal for a more robust hypothesis testing study if required. However, linked data is not yet available following the introduction of the Men B vaccine.

K. Study population

The source population for this study will be acceptable children aged less than 40 months in up to standard (UTS) practices during the period 01/09/2010 – 31/10/2016.

The study population for the ecological study will be infants eligible for routine vaccination at 8 weeks, 16 weeks, 12 months and 3 years 4 months of age and with a vaccination record between 01/09/2010 – 31/10/2016. For the time period prior to the introduction of Men B vaccine this will include babies born prior to 1st July 2015. For the time period after the introduction of Men B vaccine this will include babies born on or after 1st July 2015. Data to be used will be from the patient, practice, clinical, referral, therapy and immunisation tables.

Incidence rates of convulsion within the following time periods post-vaccination will be considered: 0, 1-3, 4-7 days. An incident event will be defined as the first record of a convulsion between days 0 to 7 post-vaccination with no convulsion records in the 2 weeks prior to the event of interest.

The study population for the second-part of the study will be infants eligible for routine vaccination at 8, 12 and 16 weeks and 12 months of age. Additionally infants must be registered with their GP within 1 month of the estimated date of birth (i.e. by the 15th of the following month). For the time period prior to the introduction of Men B vaccine the analysis will include babies born prior to 1st July 2015. For the time period after the introduction of Men B vaccine this will include babies born on or after 1st July 2015. Data to be used will be from the patient, practice, clinical, referral, therapy and immunisation tables.

L. Selection of comparison group(s) or controls

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

For the ecological study the incidence of convulsions following routine vaccination at 8 weeks, 16 weeks and 12 months of age will be described. A comparison of rates before and after the introduction of the Men B vaccine on 01/09/2015 will be performed. Additionally for further comparison the incidence of convulsion will be examined following routine vaccination at 3 years and 4 months where no doses of Men B vaccination are administered. The purpose of this comparator group is to provide information on any seasonal or environmental factors that might affect the before and after comparison of the main analysis and any changes in GP recording practice.

For the second part of the study the time in days from estimated date of birth to vaccination record will be calculated for infants receiving Men B and two other childhood vaccines (rotavirus and pneumococcal vaccine). The distribution of vaccination times will be compared to vaccination timing in the 2 years prior to the introduction of the Men B vaccine. Two years prior to the introduction has been chosen for this analysis rather than the 5 proposed for the ecological analysis as rotavirus vaccine has only been available since July 2013.

M. Exposures, Health Outcomes[§] and Covariates

[§]Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy

The main exposure of interest is vaccination with Men B vaccine (a record for a CPRD product or medical code for Men B vaccine as listed in Annex 1). Other exposures of interest are vaccination with the other routine childhood vaccines co-administered with MenB vaccine - pneumococcal vaccine, DTP/IPV/Hib (5-in-1 vaccine containing diphtheria, tetanus, pertussis, polio and haemophilus influenzae type b), rotavirus and MMR vaccine (measles, mumps and rubella). Code lists for these vaccines are listed in Annex 2.

For the ecological study the outcome of interest is a diagnosis of febrile convulsion (a record for a CPRD medical code as listed in Annex 3). The code list for convulsion has been developed using the CPRD medical browser searching for *convulsi*, *seizure*, *fit* to determine an initial list and then further searches based on similar Read codes e.g. IB6*, F25*. The study will include all convulsions because not all febrile convulsions may be coded as such in CPRD and broader terms may have been used.

All variables required for this study will be sourced directly from CPRD without the need to obtain additional clinical information from the GP.

N. Data/ Statistical Analysis

The ecological study will compare trends of incidence rates of convulsion post vaccination before and after the introduction of MenB vaccine into the routine schedule in September 2015. Quarterly incidence rates of convulsion will be calculated following routine vaccination at 8 weeks, 16 weeks, 12 months and 3 years and 4 months of age (see table below for vaccination schedule) between 01/09/2010 and 31/10/2016.

Table. Routine UK childhood immunisation schedule 2010-2016

	Age of administration				
	8 weeks	12 weeks	16 weeks	12 months	3 yrs 4 months
Men B*	x		x	x	

DTP IPV Hib	x	x	x		
Pneumococcal	x		x	x	
Rotavirus**	x	x			
Hib/Men C				x	
MMR				x	x
DTP IPV					x
Men C†		x	x		

* introduced on 01/09/2015, ** introduced 01/07/2013, † withdrawn 01/06/2013

Infants will be included in the analysis if a vaccination record (for any of the following routine vaccinations: Men B, DTP IPV Hib, pneumococcal, rotavirus, MMR) is found within 1 month of the scheduled age to receive it according to their date/month of birth. Incidence rates of convulsion within the following time periods post-vaccination will be considered: 0, 1-3, 4-7 days. A convulsive event will be considered incident if there is no record of convulsion in the 2 weeks prior to the record. The incidence will be calculated as follows:

Incidence of convulsion = number of infants with a convulsion within 7 days following vaccination in the quarter / total number of infants vaccinated in the quarter.

A binary comparison of the incidence rate prior to the introduction of MenB vaccine and the rate after will be conducted using the Fisher's exact test. Temporal trends before and after the introduction of MenB vaccine will be performed using poisson regression analysis.

The second part of the study will determine the timing of vaccination for each dose of Men B, rotavirus and pneumococcal vaccines in relation to the estimated date of birth (taken as 15th of each month). For the analysis prior to the introduction of Men B vaccine, eligible infants vaccinated between 01/09/2013 – 31/08/2015 will be included. For the analysis after the introduction of Men B vaccine, eligible infants vaccinated between 01/09/2015 – 31/12/2015 will be included.

The results will be presented as Kaplan-Meier curves for infants vaccinated either prior to or after the introduction of Men B vaccine.

All analyses for this study will be performed using Stata version 11.2.

O. Plan for addressing confounding

Both parts of this study are considered to be descriptive and therefore confounding is not specifically addressed.

P. Plans for addressing missing data

Routine childhood immunisations for pre-school children are administered at the GP practice usually by a practice nurse. Details of the vaccinations received should be recorded at the time of administration directly into the patient's medical record. Missing data for vaccinations should therefore be minimal. It is possible, however, that patients may have received other vaccinations privately (including Men B vaccine) that will not be recorded in the CPRD. Men B vaccine was first authorised in the EU in January 2013 and it is therefore possible that in the time period prior to the introduction of Men B vaccine into

the routine childhood schedule that some children may have had it privately. The likelihood however of receiving Men B vaccine privately at the same time as other routine childhood vaccinations seems remote and therefore this is not expected to be an issue.

For the second part of the study investigating delays in vaccination, infants not registered with their GP at (or soon after) birth presents a potential for missing data. For any infants who present late for their first vaccinations and are not registered with their GP previously, it will not be possible to determine whether they have transferred from another practice or whether it is truly their first vaccination. To address this potential source of missing data, this part of the study will only include infants that are registered with the GP within 1 month of their estimated date of birth (i.e. 15th of the following month). This approach will reduce the sample size available but it is likely most infants will be registered with their GP within 1 month of birth and the sample size is large to start with.

There may be missing data on febrile convulsions in the CPRD as some patients may present to hospital rather than their GP. Whilst the information should be sent back to the GP and recorded in the patient medical record, there is the potential that this is not done or that there may be a time delay in the recording of the information. The data in CPRD may therefore be an underestimate of the true number of cases of convulsion. It is not expected that the recording of convulsion in GP systems will have changed over the study period however and this underestimate will not affect the comparison between time periods prior to and after launch of Men B vaccine. If required, any further hypothesis testing study can include linked HES data to hopefully reduce the likelihood to missing convulsions.

Q. Patient or user group involvement (if applicable)

There is no patient or user group involvement in this study.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results from this study will be communicated internally within the MHRA upon completion of the study and reported to the Department of Health Joint Committee on Vaccination and Immunisation. Any final reports will be submitted for publication in a peer-reviewed journal following review by the MHRA.

S. Limitations of the study design, data sources, and analytic methods

The main limitation of an ecological study is the causality inference. There may be other factors such as an increased in circulating viruses that could explain why incidence rates for convulsion may have changed if there were any changes. The rationale behind including an analysis for infants aged 3 years and 4 months who are not scheduled to receive Men B vaccine at that time is to provide information on any other factors that could affect convulsion rates over time.

For both parts of the study, there could be misclassification of the ages of infants. In CPRD, the month and year is recorded in the patient records, however the day of birth is missing due to patient anonymisation. Infants could potentially be one month younger or older than calculated based on the assumption all infants were born on the 1st day of the month of birth. It is therefore proposed to calculate date of birth from the mid point (15th) of the month so that the maximum error is 2 weeks.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
As mentioned above, there could be missing cases of convulsions in CPRD, where patients present to hospital and the event was not reported to their GP or captured in the records. Therefore the true incidence rate of convulsion could be underestimated but this potential for missing data is unlikely to have changed over the study period and therefore should not affect the comparison before and after the introduction of Men B vaccine.

T. References

1. Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of Convulsion and Aspectic Meningits following Measles-Mumps-Rubella Vaccination in the United Kingdom Am J Epidemiol 2007; 165:704-709

2. Farrington P, Pugh S, Colville, A, Flower A, Nash J, Morgan-Capner P, Rush M, Miller E. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps rubella vaccine. Lancet 1995; 345:567-69.

3. Preliminary vaccine coverage estimates for the meningococcal B (MenB) immunisation programme for England, update to the end of August 2016**.** https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/555057/hpr3216_menB.pdf

4. Quarterly vaccination coverage statistics for children aged up to five years in the UK (COVER programme): January to March 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/531021/hpr2016_COVER.pdf

List of Appendices *(Submit all appendices as separate documents to this application)*

Annex 1 – List of Read and product codes for Men B vaccine
Annex 2 – List of Read and product codes for rotavirus, pneumococcal, DTP IPV Hib, MMR and Hib/Men C vaccines
Annex 3 – List of Read codes for convulsion