| Version | Last edited | Initials | Comment |
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| 0.1 | 2021-04-06 | RL, AA, SB, PC, SC, GD, LG, JL, RO, MP, RR, FT, RL | Initial draft – Wales specific analyses based on previous Scottish EAVE SAP. |
| 0.2 | 2021-04-20 | TS | Shared with DaCVaP group for comment and input |
| 1.0 | 2021-04-28 | AA, FT, SB, RO | Release version |
| 2.0 | 2021-09-08 | AA, FT, SB, EL, RO, RF, JH, GD, JL, RL | Developed in light of suggestions and update in manuscript review |
| 2.1 | 2021-11-23 | FT, SB, RO, CR, AZ, RL | SCCS is the primary method for analysis and implementation of censoring at outcome event and sensitivity for death [1,2] |
| 2.2 | 2021-12-02 | AZ | Add positive and negative controls : hip fracture, anaphylaxis, coeliac disease |
| 2.3 | 2022-01-17 | RL | 29+ days period is considered as baseline: main analysis 0-28 days broken down into weekly intervals |
| 2.4 | 2022-01-25 | AZ, RL | Full year data for 2021 and addition of Booster and third dose analysis |

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| **SAIL project number:** | WMC_ |
| **SAIL project title:** | *Working title:*<br>Risks of adverse clotting and bleeding events following COVID-19 vaccination in the population of Wales |
| **Lead authors:** | Fatemeh Torabi, Stuart Bedston, Rhiannon Owen |
| **Co Author(s):** | *All people who want to opt in, please add your name here. Alphabetical order please:*<br><br>Ashley Akbari, Peter Collins, Simon Cottrell, Gareth Davies, Lucy Griffiths, Emily Lowthian, Jane Lyons, Ronan A Lyons, Malorie Perry, Richard Roberts, Utkarsh Agrawal, Amaya Azcoaga-Lorenzo, Jillian Beggs, Declan T Bradley, Gareth Davies, Richard Roberts, Ting Shi, Collin Simpson |
| **Proposed dates:** | The initial piece of work that we agree on should aim to fit within the following timelines *(with preliminary work already started in support of generating this workplan and prior work):*<br>Updated<br>Start date: 8th of September 2021<br>Analysis completion 20th of September 2021<br>updated draft 23th of September 2021 |

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| | First draft of outcomes and start of internal revision process Early Oct 2021 |
| **Aims:** | For this run we will update coverage: up to 2021-12-31 (C19-cohort20 (Lyons et al, 2020) & vaccine – WLGP and PEDW are all available on or over this date)<br><br>Overall aim is to assess the safety of Pfizer BioNTech and Oxford AstraZeneca COVID-19 vaccine and the mRNA based booster dose. We will achieve this by:<br>(a) Studying the incidence and relative risk of mild-to-moderate and severe adverse haematological and vascular events as well as Ischemic stroke and Myocardial Infarction (MI) of interest identified through primary care data, hospitalisation through secondary care data and death from mortality data following vaccination **first, second, third and booster dose** (to be included in the manuscript) doses in the Welsh population.<br>(b) Describe the study population who experienced outcome event by subgroups including age groups (16-29,30-39,40-49,50-59,60-69,70-79,80-89,90+) clinically vulnerable, ethnicity (White, Indian, Pakistani, Bangladeshi, Other Asian, Black Caribbean, Black African, Chinese, Other Ethnic group, Unknown).<br>(c) To compare post-vaccination risk of adverse events to the post-infection risk following a record of PCR confirmed positive COVID-19. |
| **Study design:** | Our primary analysis will be a self-controlled case series analysis (Farringdon et al. study for adverse events and self-controlled case series (SCCS) study for mild-to-moderate adverse events. We will also explore other methods relevant to the data and outcomes of interest. See Links section for SCCS overview. Data from multiple sources will be linked using unique patient identifier: Anonymized Linkage Field (ALF).<br><br>The population under study will be all individuals found in the C19_COHORT20 alive and living in Wales during study period:<br>• Eligible to receive a vaccination;<br>• Aged 16 or older<br>• Sex is known;<br>• Registered with a GP practice (and have minimum of 180 days period of registration prior for data availability);<br>• No previous adverse event of interest from (in one year clearance window before vaccination from 2019-12-07). |

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| **Data sources:** | • **ADDD:** Office for National Statistics (ONS) register of all deaths relating to Welsh residents, including those that died outside of Wales. D if for refreshed *Daily*.<br>• **ADDE:** Office for National Statistics (ONS) register of all deaths relating to Welsh residents, including those that died outside of Wales. Historic dataset. E is for *Extract*.<br>• **CDDS:** COVID-19 Consolidated Deaths dataset.<br>• **CVVD (WIS):** Vaccination records from the Welsh Immunisation System (WIS). Covers date of vaccination and type also has flags for adverse events immediately following vaccination (to be used by caution).<br>• **PATD:** Active COVID-19 PCR testing and results.<br>• **PEDW:** Patient Episode Dataset for Wales.<br>• **WDDS:** Welsh Dispensing Dataset.<br>• **WDSD:** Welsh Demographic Service Dataset.<br>• **WLGP:** Welsh Primary Care – GP dataset.<br>• **WRRS:** Wales Results Reporting Service – Pathology data for all tests and results across Wales.<br><br>In practice, we will be using the following derived data sets:<br>• **C19_COHORT20**: All individuals alive and living in Wales from the 1st January 2020 with follow-up to 31st of December 2021 which utilises ADDE, PEDW, WDSD and WLGP.<br>• **C19_COHORT20_MORTALITY:** A cleaned and organised table of mortality records, refreshed daily which utilises ADDD, ADDE, CDDS and WDSD.<br>• **C19_DERIVED_VACCINATION:** A cleaned and organised table of vaccination records, refreshed daily. |
| **Exposures of interest** | First, second, third and booster doses of Pfizer-BioNTech and Oxford-Astra-Zeneca vaccines.<br>*Note Moderna has only been included in booster analysis* |
| **Outcome of interest** | Mild-to-moderate and severe adverse events following immunisation (AEFI), derived from the safety results of the pre-licensure vaccine clinical trials, common side-effects related to influenza vaccines and an unpublished study protocol of an ongoing observational study.<br><br>A primary outcome (to produce timely results) will focus on primary care, hospitalisation for bleeding and clotting events, following COVID-19 vaccination and infection separately. (see appendix I for clinical code list). We will also include any immediate recording of side-effects (anaphylaxis) to in primary care and vaccination records of cases this will be used as a positive control as it is expected to be |

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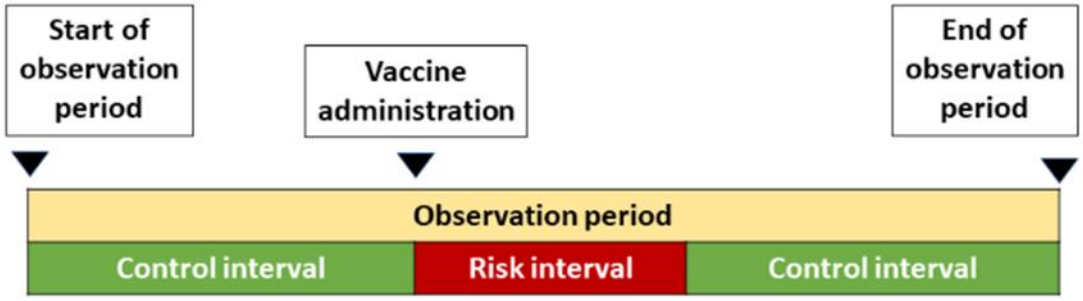
| | directly correlated with vaccination, we will also use hip fracture as a negative control as its occurrence are most likely independent of vaccination.<br><br>We will include first event in the study period and exclude anyone who had an event from 7th December 2019 to 7th December 2020.<br><br>We will assess feasibility of establishing a path to identify Vaccine Induces Thrombocytopenia and Thromboembolic event (VITT) by using the WRRS data source will be used to capture thrombosis related tests such as:<br>• Platelets < 150<br>• Fibrinogen < 2g/L<br>• D-dimer > 2,000ug/L<br>• Positive HIT assays |
| **Controls and confounders** | Note the SCCS study design addresses time-invariant confounders. |
| **Statistical analysis:** | We will provide descriptive statistics of all outcome events for population sub-groups broken down by vaccination status. These includes:<br><br>• Stats for the proportion of the population who received at least 1 vaccine by age group (Due to vaccine rollout, a larger proportion of 60-79 would have been vaccinated). This will inform out additional subgroup analysis looking at age-related relative risk<br><br>• Stats for the proportion of the population who received at least 1 vaccine by deprivation quintile. This will inform our additional subgroup analysis for "lifestyle" type diseases that are often associated with more deprived populations. However our analysis have shown that the vaccine negative side effects seem to be random (this is probably an important finding given the impact of COVID on deprived communities).<br>• Summary table of the number of events and characteristics of those with and without the events in each of the pre-vac, vac, post-vac intervals. This will inform our main analysis by both first and second dose.<br><br>**Missing data**<br>Due to available GP data in SAIL only covering 80% of the population, we will be immediately excluding the other 20%.<br><br>**Pseudo-index date for unvaccinated individuals**<br>For some of the adverse events there is the possibility of a temporal change in the risk over the observation period. To take this into account, we will capture all the events during observation window of 7th of December 2020 (start of vaccination program in Wales) |

onward to also include data from unvaccinated individuals who experienced the adverse event. These individuals will be assigned a pseudo-exposure date based upon the median date of vaccination for the age and season. We will then use interaction tests to compare the rates of adverse events in a) the risk period compared to the pre-risk period and b) the risk period compared to the post-risk period among vaccinated and unvaccinated individuals. If there is evidence of a significant interaction with a higher risk ratio among the vaccinated individuals, then this suggests that there is a potential adverse event associated with vaccination.

**SCCS approach**

For mild-to-moderate adverse events, the self-controlled case series (SCCS) study design[3] [4] will be used to determine the relative incidence of adverse events for exposed time periods (periods following vaccine administration) compared to unexposed time periods (pre- and post- vaccination periods unrelated to vaccination) in individuals who present with the outcome of interest (mild-to-moderate adverse events). For more severe and event dependent safety outcomes, the nested case control study will be conducted.

SCCS study design tests whether the risk of an adverse event is higher at post-vaccination period compared to other periods that are temporally unrelated to vaccine administration. The main advantage of this case series method over other methods of analysis is that it only includes individuals who have been vaccinated *and* those with adverse events. As a result, adequate statistical power can be obtained with relatively small sample sizes. In addition, all confounders that do not vary with time over the observation period are implicitly controlled for. The number of adverse events in the pre-defined risk intervals will be compared to pre-defined control intervals. Risk intervals refer to post-vaccine administration periods (from day 0 of first dose vaccination) to the pre-specified time at risk and control intervals refer to pre- and post- at risk periods over the observation period of the study. Risk and control intervals will also be determined in relation to vaccine dose administration (e.g. between first and second doses of the vaccines).



The exact duration (in days) of the risk and control intervals will be determined for each AEFI outcome based on severity level (mild-to-moderate, severe and typical onset) and vaccine type separately. We will use the Benjamini-Hochberg procedure to control the False Discovery rate of testing a large number of hypotheses related to each pre-specified adverse events of interest. The analysis of the SCCS will be undertaken using a stratified analysis where the comparisons of the different risk periods are made within individuals. The safety of the vaccines will be assessed using matched logistic regression models with an offset for the length of the risk period. To avoid biases the risk periods are not censored at death or leaving a practice. Odds ratios (OR) will be used to compare the risk of events in the exposure period post vaccination in comparison to the risks in the pre-vaccination period. Unadjusted and adjusted ORs will be provided including their 95% Confidence Intervals (CIs).

**Analysis of thromboembolic, haemorrhagic and idiopathic thrombocytopenic purpura (ITP) events**

An incident-matched nested case-control study (NCCS) will be conducted to determine the likelihood of those presenting with thromboembolic, haemorrhagic and ITP events having been vaccinated up to 28 days previously, compared with those without these recorded events. People who presented with thromboembolic, haemorrhagic and ITP events over a 12-week period (7 December 2020 to 28 February 2021) will be identified using appropriate Read and ICD-10 Codes. Historic records of cases will be checked for as long as records exist. Individuals with a previous ITP event will be excluded from the study.

Those without a previous record will be deemed to have experienced an incident (first-ever) diagnosis of a thromboembolic, haemorrhagic and ITP event on that date. Current understanding is that age is the most significant risk factor. Each incident case will therefore be matched by age and sex with five controls, patients with no past diagnosis of thromboembolic, haemorrhagic and ITP disease on the same date, selected randomly from the primary care practice population from the age-sex matched population. Diagnosis dates of the cases will be considered the index dates for the controls.

Records of both cases and controls will then be checked for the 28 days previous to the index date for a previous ChAdOx1 and BNT162b2 vaccination (and Moderna).

**Addressing potential sample selection bias**

It is possible that sample selection bias could be induced in the SCCS study design if inclusion in the study is related nontrivially to the adverse outcome of interest. This may be particularly true for severe adverse events. For example, if an individual has a cardiac arrest

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| | or death then they are less likely to be vaccinated and thus less likely to be included in the study. We will therefore carry out a nested case control study for severe and event dependent adverse events, e.g. thromboembolic, haemorrhagic and ITP adverse events. Cases will be those with a severe adverse event seeking primary or secondary health care. Controls will be those without a severe adverse event. The cases will be matched to controls in age, sex, Health Board, socio-economic status / SMID and comorbidities. A 1:5 case-control match will be considered based on the volume of available data. The safety of the vaccines will be assessed using matched logistic regression models. Odds ratios (OR) will be used to estimate the odds of being vaccinated amongst cases compared to controls. ORs will be calculated by the regression coefficients of the model. Unadjusted and adjusted ORs will be provided including their 95% Confidence Intervals (CIs).<br><br>Acknowledge the potential ascertainment bias within the AZ vaccinated group from increased self-identification of signs/symptoms of thrombosis.<br><br>**Sensitivity analysis**<br>We will consider exploring different time intervals following administration of the vaccine to define suitable risk intervals. For SCCS study design, at-risk post vaccination period (28 days) will be compared with 90 days pre- and post- control periods temporarily unrelated to adverse outcome of interest.<br>1- Excluding the unvaccinated individuals<br>2- Excluding and only including those with a death record<br>3- Separating out the post vaccination control window and observing the effect |
| **Output plan:** | This work will form one academic output submitted to peer review journals, with uploading of pre-prints. The scope of the output is to be confirmed pending the details above being agreed and the timeline for the output being agreed. This workplan will be shared and agreed between the Wales Con-Cov group including representatives from Public Health Wales (PHW) and other invited members to comment on, as well as members of DaCVaP, and prior to submission the final draft output will be shared with group members as per the authorship agreement.<br><br>Results will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected Data (RECORD) (via the COVID-19 extension) guidelines. |

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| **Links:** | 1. Farrington P, Whitaker H. Mortality and the self-controlled case series method: letter to the editor. *Pharmacoepidemiol Drug Saf*. 2012;21(8):906-906. doi:10.1002/PDS.3273<br>2. Farrington P. Censoring on outcome is not valid in self-controlled case series studies. *J Clin Epidemiol*. 2013;66(12):1428-1429. doi:10.1016/J.JCLINEPI.2013.06.010<br>3. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Stat Methods Med Res*. 2009;18(1):7-26. doi:10.1177/0962280208092342<br>4. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ*. 2016;354:i4515. doi:10.1136/BMJ.I4515 |

**Appendix I**

The list of READ and ICD-10 codes used in this workplan can be found on the SharePoint folder in:


READ_CD_thrombosis.xlsx


Read-ICD10-Thrombosis.xlsx


ICD10_positive_controls.xlsx

**Appendix II**

Mild-to-moderate AEFI are likely to be systematically under-ascertained, especially those that are already known since patients won't seek healthcare if it's an already known adverse event. Similarly, issues of increased reporting may occur in response to publicity around vaccines and also due to higher clinician awareness and guidance on coding.

A list of candidate AEFIs is available here but need to make sure this list is updated as the vaccination programme is rolled out and as any concerns are identified within the UK and internationally:

**Adverse Events Following Immunisation (AEFI) reported in pre-licensure COVID-19 vaccine trials**

| Adverse event | Pfizer-BioNTech | Oxford-AstraZeneca |
|---|---|---|
| Abdominal pain | | Uncommon |
| Acute peripheral facial paralysis (/palsy) | Rare (37 days after dose 1, 3-48 days after dose 2) | |
| Anaphylaxis* | Not known | |
| Arthralgia | Very common | Very common |
| Chills | Very common | Very common |
| Decreased appetite | | Uncommon |
| Dizziness | | Uncommon |
| Facial swelling | | |
| Fatigue | Very common | Very common |
| Headache | Very common | Very common |
| Hyperhidrosis | | Uncommon |
| Hypersensitivity | Not known | |
| Influenza-like illness | | Common |
| Injection site bruising** | | Very common |
| Injection site erythema | | Very common |
| Injection site induration | | Common |
| Injection site pain | Very common | Very common |
| Injection site pruritus | Uncommon | Very common |
| Injection site rash | | |
| Injection site redness | Common | |
| Injection site swelling | Very common | Very common |

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| Injection site tenderness | | Very common |
| Injection site urticaria | | |
| Injection site warmth | | Very common |
| Insomnia | Uncommon | |
| Lymphadenopathy*** | Uncommon | Uncommon |
| Malaise | Uncommon | Very common |
| Myalgia | Very common | Very common |
| Nausea**** | Common | Very common |
| Neuroinflammatory disorders***** | | Very rare |
| Pain in extremity | Uncommon | |
| Pruritus | | Uncommon |
| Pyrexia****** | Very common | Very common |
| Rash | | Uncommon |
| Vomiting | | Common |

** Injection site bruising includes injections site haematoma
**** A higher frequency of pyrexia observed after dose 2 for the Pfizer BioNTech vaccine.
***** Very rare events of neuroinflammatory disorders and increased risk of blood clots (thromboembolic events) have been reported following vaccination with the Oxford AstraZeneca vaccine, but a causal relationship has not been established.
****** Pyrexia includes feverishness

Note. Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated).

**List of AEFI for influenza vaccines**

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| Anaphylactic reactions |
| Arthropathy |
| Bell’s palsy |
| Conjunctivitis |

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| Coryza |
| Cough |
| Decreased appetite |
| Diarrhoea |
| Drowsiness |
| Epistaxis |
| Facial oedema |
| Fatigue |
| Fever / pyrexia |
| Guillain-Barré syndrome |
| Headache |
| Hoarseness |
| Hypersensitivity reactions |
| Irritability |
| Local symptoms (i.e. local erythema) |
| Malaise |
| Muscle aches / myalgia |
| Nasal congestion |
| Nausea |
| Oropharyngeal pain |
| Peripheral tremor |
| Rash |
| Rhinorrhoea |
| Seizure / febrile convulsions |
| Vomiting |
| Wheezing |