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|  | Statistical Analysis Plan |
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| **Title of Proposed Research (with subtitle specifying the design, e.g., case-control)** |
| Two-dose Covid-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong KongRetrospective cohort studyThis Statistical Analysis Plan describes definitions and outcomes in this study, which will investigate the relationship between Covid-19 full vaccination and possible arthritis flare among rheumatoid arthritis receipts of two doses (complete immunization) of BioNTech or Sinovac between Feb 23 to June 30, 2021 in Hong Kong. |

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| title page |
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| Publicly available on CSMPR website? | Yes [x]  Date:  | May 30, 2022 | No [ ]  |

List Of Abbreviations

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| **Abbreviation or special term** | **Explanation** |
| CDARS | Clinical Data Analysis and Reporting System |
| ICD-9-CM | International Classification of Diseases, Ninth Revision, Coding Manual |
| IRR | Incidence rate ratio |
| PICO | Population, Intervention (or exposure), comparator, and Outcome |
| STROBE | STrengthening the Reporting of OBservational studies in Epidemiology |

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| 1. | BACKGROUND |
|  | Patients with rheumatoid arthritis (RA) are two-fold more vulnerable to infections that result in hospitalisation and impaired quality of life.1 With consideration to the benefits of vaccination outweighing the risks, the European Alliance of Associations for Rheumatology (EULAR)2 recommends that patients with RA should receive Covid-19 vaccines without needing major adjustment to their ongoing treatment regimens. However, one of the major barriers to vaccine uptake among patients with RA is the fear of arthritis flare despite non-relevant evidence from landmark trials and few case reports in the post marketing.3Understanding the association between arthritis flare and vaccination is important to overcome vaccine hesitancy. Currently, the Hong Kong (HK) Government Vaccination Program provides two authorised Covid-19 vaccines: CoronaVac (inactivated virus vaccine; recommended vaccination interval 28 days) and BNT162b2 (mRNA vaccine; recommended vaccination interval 21 days). Since the launch of the vaccination programme on February 23, 2021, more than 8 million doses have been administered with close safety monitoring. In this study, we analysed the territory-wide electronic medical records (EMRs) database and aimed to investigate the population-level risk of possible arthritis flare following full vaccination based on two technology platforms. |
| 2. | [OBJECTIVES](#_Toc351646345) |
|  | To investigate the relationship between Covid-19 full vaccination (two completed doses) and possible arthritis flare. |
| 3. | [STUDY](#_Toc351646344) DESIGN |
| 3a | Design: Retrospective cohort study. |
| 3b | Data source: Population-based electronic medical records (EHRs) from the Hospital Authority (HA) with linked vaccination records from the Department of Health (DH) of the Hong Kong Government.4 The EMRs database managed by the HA holds centralised medical records from 42 public hospitals with high population coverage, representativeness, and coding accuracy.5 The EHRs records demographics, date of registered death and cause, date of hospital admission and discharge, prescriptions, diagnoses, and immunization history in the centralised CDARS, which is routinely used for research and audit purposes. All records are anonymised to protect patient confidentiality and identity. |
| 3c | Details of data handling: Index date: Vaccination date of the 2nd dose of Covid-19 vaccine.Censor: outcome, death, “2021-07-31”whichever is the earliest. |
| 4. | STUDY POPULATION |
|  | Adult active Hospital Authority service users between 2018/01/01-2021/07/31 living with rheumatoid arthritis.  |
| 4a | Inclusion criteria:Aged ≥16; ICD-9-CM 714 ever recorded before 1st dose of vaccination |
| 4b | Exclusion criteria: Diagnosis of neoplasm (ICD-9-CM 140-149, 150-159, 160-165, 170-172, 174-176, 179-189, 190- 195, 200-209) Diagnosis of other autoimmune diseases [Systemic lupus erythematosus (710.0); Psoriasis (696); Spondyloarthritis (720.0); Inflammatory Bowel Disease (555, 556); Multiple sclerosis (340)] ever recorded before index dateSummary of ICD-9-CM codes for diseases identification are listed in **Appendix 1**. |
| 5 | STUDY OUTCOME |
| 5a | Primary outcome: Diagnosis of rheumatoid arthritis/reactive arthritis (ICD-9-CM, 714/099.3, 711.1, 711.3, 716.4, 716.5, 716.6, 716.9, 719.4) from In-patient or Out-patient settings, whichever earlier. |
| 5b | Secondary outcomes: Inpatient primary diagnosis of rheumatoid arthritis/reactive arthritis. |
| 6 | EXPOSURE |
| 6a | Primary exposure: vaccination of BNT162b2 or CoronaVac |
| 6b | Secondary exposure: / |
| 7 | CONFOUNDERS/COVARIATES |
|  | 1. Age, Sex,
2. Medical History since 2018 (Asthma, Cerebrovascular disease, Chronic obstructive pulmonary disease, Congestive heart failure, Chronic renal failure, Dementia, Diabetes, Mild liver disease, Moderate-severe liver disease, Myocardial infarction, Peripheral vascular disease, Paralysis, Respiratory infections, Stroke or systemic embolism, Ulcers, Viral infections), ICD-9-CM codes are listed in **Appendix 2**;
3. Health service utilisation. Health service utilisation will be assessed by records of emergency attendance or hospital admission and outpatient clinical visit since 2018 (binary outcome).
4. Medication use within 90 days (Immunosuppressants, NSAIDs, Corticosteroids, b/tsDMARDs, csDMARDs, Drugs for gout, details are listed in **Appendix 3**).
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| 8 | EFFECT MODIFICATION/STRATIFICATION |
|  | / |
| 9 | ANALYSIS |
| 9a | Main analysis: Multi-group Inverse Probability of Treatment Weighting (IPTW) method will be used to balance the patient characteristics among two exposure groups and unexposed groups, using R package ‘WeightIt’ (version 1.2-9). Poisson regression will be used to estimate the adjusted incidence rate ratio (IRR) with 95% Confidence Interval (CI) using the non-vaccination group as reference. Over-dispersion of the Poisson Regression model will be tested using R package ‘AER’ (version 1.2-9). |
| 9b | Sub-group analysis: / |
| 9c | Sensitivity analysis: Supplementary analysis: Weekly prescription pattern (number of prescriptions per-patient and proportion of each drug category) of rheumatoid drugs between Feb 23 and Jul 31, 2021 will be compared using Kruskal-Wallis test to further test whether there would be increased medication use associated possible arthritis flare. |
| 10 | SAMPLE SIZE CONSIDERATION |
|  | Sample size estimation is not applicable and this study will use all the available data from the record-linked cohort between February 23, 2021 and July 31, 2021. |
| 11 | ANTICIPATED PITFALLS |
|  | Any possible ways the results could fail to achieve one or more of the study objectives.1. Potential violation of assumptions of Poisson Regression;
2. Modest sample size anticipated;
3. Arthritis flare-up was defined by ICD-9 diagnostic codes but not direct measurement of disease activity assessment or patient-reported symptoms.
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| 12 | RELEVANT RESEARCH CHECKLIST |
|  | STROBE for cohort study. |

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| **REFERENCES:** |

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5. Lau WC, Chan EW, Cheung CL, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. *JAMA* 2017;317(11):1151-58. doi: 10.1001/jama.2017.1363 [published Online First: 2017/03/23]

Appendix 1. ICD-9 Clinical Modification (CM) Codes used for disease identification

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| Diseases | ICD-9 CM Codes |
| Rheumatoid arthritis | 714 |
| Reactive arthritis1 | 099.3,711.1,711.3,716.4,716.5,716.6,716.9,719.4 |
| Systemic lupus erythematosus | 710.0 |
| Spondyloarthritis | 720.0 |
| Psoriasis | 696 |
| Multiple sclerosis | 340 |
| Inflammatory Bowel Disease | 555; 556 |
| Neoplasm | 140-149, 150-159, 160-165, 170-172, 174-176, 179-189, 190-195, 200-209 |

1 Curry JA, Riddle MS, Gormley RP, Tribble DR, Porter CK. The epidemiology of infectious gastroenteritis related reactive arthritis in U.S. military personnel: a case-control study. BMC Infectious Diseases 2010; 10(1): 266.

Appendix 2. ICD-9 Clinical Modification (CM) Codes used for baseline characteristics

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| Diseases | ICD-9 CM Codes |
| Asthma | 493 |
| Cerebrovascular disease | 430-438 |
| Chronic obstructive pulmonary disease | 490-496,500-505,506.4 |
| Congestive heart failure | 398.91, 402.01,402.11,402.91,404.01,404.11,404.91,404.03,404.13,404.93,428 |
| Chronic renal failure | 582, 585, 586, 588, 583.0, 583.1, 583.2. 583.4, 583.6, 583.7 |
| Dementia | 290 |
| Diabetes  | 250 |
| Mild liver disease | 571.2, 571.4, 571.5, 571.6 |
| Moderate-severe liver disease | 456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8 |
| Myocardial infarction | 410 |
| Peripheral vascular disease | 441, 443.9, 785.4, V43.4 |
| Paralysis | 342, 344.1 |
| Respiratory infections | 460-466, 480-488 |
| Stroke or systemic embolism | 433.01,433.11,433.21,433.31, 433.81,433.91, 434,436,437.0,437.1,444,445 |
| Ulcers | 531-534 |

Appendix 3. BNF codes used for medication

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|  | BNF code | Notes |
| Immunosuppressant | 8.2 |  |
| NSAIDs | 10.1.1 |  |
| Corticosteroids | 10.1.2 |  |
| b/tsDMARDs | 10.1.3 | Drug item codes in HK EMR:ABAT01/03, ABT-03, ADAL05/08/10/13/15/16, ANAK01, BARI15-18, BELI01/02/05, CERT01/02,ETAN01/04-06/08-10,FILG07/08/10, GOLI02/04-06,INFL03/04/31/33, IXEK01/02, LEFL01-03, S01257, S01311, S01315, SARI03-06, SECU02/03, TOCI01/03-09, TOFA01-05 |
| csDMARDs | 10.1.3 | Drug item codes in HK EMR: HYDR21;METH10, METH1D, METH1E, METH1G, METH1L; PENI04,PENI06,PENI07;SULP23  |
| Drugs for gout | 10.1.4 |  |

**Abbreviation:** BNF: British National Formulary;NSAIDs: Non-steroidal anti-inflammatory drugs; b/tsDMARDs: biological/target synthetic disease-modifying antirheumatic drugs; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; HK EMR: Hong Kong electronic medical records