PROTOCOL

Use of non-steroidal anti-inflammatory drugs and clinical outcome of COVID-19: a Danish nationwide cohort study

1 Introduction

In the early stages of the COVID-19 pandemic in Europe, case reports from southern France described young patients without comorbidities who developed severe COVID-19 after exposure to ibuprofen (1,2). This led to warnings against use of ibuprofen and other NSAIDs in patients with COVID-19 by multiple parties, including the world health organisation (WHO) and French health ministry (3). However, no data has been published regarding the safety of NSAIDs in COVID-19.

2 Aim

Hypothesizing that NSAIDs increase the risk of adverse clinical outcomes in COVID-19, we aimed to study the association between NSAID use and risk of death in patients with COVID-19. In secondary analyses, associations between NSAIDs and hospitalisation, ICU admission, mechanical ventilation and renal replacement therapy will be investigated.

3 Methods

Danish nationwide registry-based cohort study. All individuals tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will be followed from the date of positive test and 30 days onward for occurrence of death, and 14 days onward for occurrence of hospital admission, ICU admission, mechanical ventilation and renal replacement therapy.

3.1 Study population

Any Danish resident with a positive real-time reverse-transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 from 27th February 2020 and onwards. At the time of writing (21-04-2020), this includes 7,695 individuals of whom 370 died within 30 days after being tested positive. To ensure complete look-back for exposure and covariate ascertainment, all individuals are required to have resided in Denmark continuously the year preceding the positive test result.

3.2 Data sources

The Danish COVID-19 cohort contains prospectively collected information on all Danish residents tested positive for SARS-CoV-2 (4). All Danish RT-PCR tests for SARS-CoV-2 are reported to the Danish Microbiology Database, from which the study population will be identified (5). Data will be linked to the Danish Civil Registration system (6), the Danish National Prescription Registry (7), the Danish National Patient Registry (8), and the Danish Register of Causes of Death (9) by means of the unique personal identifier any Danish resident is assigned at birth or immigration.

3.3 Follow up

Follow-up will begin at the date of the first positive RT-PCR for SARS-CoV-2 (**Figure 1**). The outcome assessment window for death is 30 days. The 30-day follow-up window is chosen to increase the likelihood that the recorded outcomes are related to COVID-19 and since most deaths are expected to take place during this time window. The outcome assessment window for hospital admission, ICU admission, mechanical ventilation, and dialysis is 14 days to reduce the likelihood of the

secondary outcome not being related to the SARS-CoV-2 infection. Patients with an outcome of interest occurring in 30 days to one day before the test date is excluded.

3.4 Exposure

The exposure of interest is a filled prescription for any NSAID in the 30 days leading up to the date of positive SARS-CoV-2 test, representing current use. Use of NSAIDs is identified by the Danish Prescription Registry with information on all dispensed prescriptions at community pharmacies in Denmark since 1995 (10). All NSAIDs in Denmark except low-dose (200 mg) ibuprofen are available by prescription only and only prescription drugs are eligible for reimbursement. During the period 1999-2012, over-the-counter sales of ibuprofen accounted for less than 26% of total ibuprofen sales and an even smaller proportion of total NSAID sales (11). The comparison group will be no use of NSAIDs in the corresponding exposure assessment window, i.e. the 30 days leading up to the date of positive test.

3.5 Outcomes

3.5.1 Primary outcome

30-day mortality after positive RT-PCR for SARS-CoV-2 as identified using the Danish Register of Causes of Deaths (9).

3.5.2 Secondary outcomes

3.5.2.1 Hospitalisation

Hospital admission longer than 12 hours in the 14 days after a positive RT-PCR for SARS-CoV-2.

3.5.2.2 ICU admission

Intensive care unit admission in the14 days after a positive RT-PCR for SARS-CoV-2. Due to a transition to a new version of the Danish Patient Registry (LPR3), no

validation studies have been conducted yet. Validation studies conducted in the prior version of the database (LPR2) show the procedure codes for ICU admission to have a high positive predictive value (12).

3.5.2.3 Mechanical ventilation

Intubation and mechanical ventilation in the 14 days after a positive RT-PCR for SARS-CoV-2. Validation studies conducted in LPR2 show the procedure codes for mechanical ventilation to identify all individuals who have received this treatment (12).

3.5.2.4 Renal replacement therapy

Initiation of continuous or intermittent renal replacement therapy (dialysis) in the 14 days after a positive RT-PCR for SARS-CoV-2. The validity of acute dialysis as recorded in LRP2 has been validated previously (12).

3.6 Confounding

3.6.1 Propensity score methods

The propensity score (PS) is the probability of being treated with a drug of interest, given a set of selected patient characteristics. Propensity scores are used to increase comparability between two study cohorts (13), and thereby reduce confounding. The propensity to be a current user of NSAIDs at the time of cohort entry was estimated for the study population. Age, sex, calendar time (pre- and post-lockdown of Denmark), risk factors of death and relevant confounders were included in estimation of the PS, see the appendix for a full list of included characteristics. To reduce unmeasured confounding by removing the individuals treated most contrarily to the prediction made using the PS model (Stürmer trimming) (14). Individuals in the unexposed cohort will be matched to exposed individuals on PS in a variable 4:1 ratio (15) using a nearest neighbour algorithm (calliper 0.05) with

replacement, i.e. unexposed individuals can be matched to multiple exposed individuals.

3.6.2 **Unmeasured confounding**

Possible sources of unmeasured confounding in this study relate to the health and frailty of NSAID users. Due to the known adverse effects of NSAIDs on the cardiovascular and renal system NSAIDs are preferentially prescribed to younger, healthier individuals (16). Non-users of NSAIDs may be more frail than users. We try to address this by choosing appropriate frailty markers as covariates in the propensity score model, but frailty is notoriously difficult to estimate using register data and the control group may therefore have a higher risk of death, hospitalisation and ICU admission at baseline.

We do not expect significant selection or information bias, as all individuals who are tested positive for SARS-CoV-2 in Denmark will be captured and exposure to NSAIDs is not expected to influence the likelihood of being tested.

3.7 Descriptive analyses

First, the cumulative dose of NSAID for each user will be determined and the fraction of chronic users is identified. This fraction is expected to be very low and numerically too small to constitute a separate exposure definition.

Second, the number of individuals who initiated NSAIDs after a positive RT-PCR for SARS-CoV-2 will be identified. These individuals are not counted as being exposed in the main analysis to avoid measuring exposure after start of follow-up with the possibility of introducing immortal time bias.

Three, the timing of outcomes one month prior to and three months after a positive RT-PCR for SARS-CoV-2 will be explored. In case of a substantial fraction of

outcomes having occurred in the days leading up to a positive test, a post-hoc analysis with a larger follow up windows (pre- and post-test) will be conducted.

3.8 Statistical analysis and risk estimates

Risk, risk difference, risk ratio estimated using generalized linear models (binomial distribution).

Based on the number of COVID-19 confirmed cases in Denmark on April 21 (n=7,695), an expected case-fatality rate of 4.8% and exposure prevalence of 8%, we plan to have included 30 exposed individuals with the primary outcome at the date of analysis 01-06-2020. We assume this figure conforms to a Poisson distribution whose confidence interval is inherited by the effect estimate. Thereby, the expected ratio between upper and lower confidence limit of the effect estimate is 2.12, corresponding to a null effect estimate of 1.00 with a 95% confidence limit of 0.67 – 1.43.

3.9 Sensitivity analyses

3.9.1 Varying exposure assessment windows

To explore the effect of reverse causation, the following exposure definition will be used: Exposure to NSAIDs in the period 60 days to 14 days prior to a positive RT-PCR for SARS-CoV-2 and 14 days to 1 day prior to a positive test.
To explore the robustness of our exposure definition, exposure will also be assessed 60 days prior to a positive test.

3.9.2 Varying outcome assessment windows

To explore the effect of follow up duration on the effect estimates for secondary outcomes, these will be re-estimated using an extended follow of 30 days after a positive RT-PCR for SARS-CoV-2.

3.9.2 Nested analysis

All risks, risk differences and relative risks will be estimated (excluding risk of hospitalisation) within individuals hospitalised with COVID-19. Likewise, risk estimates will be obtained after exclusion of healthcare professionals younger than 65 years of age (the average retirement age in Denmark).

3.9.3 Effect modification

To explore effect modification by age, sex and cardiovascular disease (ischemic heart disease, arrythmia, or congestive heart failure), we will obtain stratified effect estimates for primary and secondary outcomes. Propensity scores will not be re-estimated for subgroup analyses according to Rassen et al (17).

3.10 Ethical aspects and data protection

According to Danish law, studies based entirely on registry data do not require approval from an ethics review board (18). Result will be published in a way, that it is impossible to identify individuals.

4 Timeline

4.1 Start of data collection

27-02-2020

4.2 End of data collection

Data collection is expected to end on 01-06-2020.

4.3 Start of data analysis

01-06-2020

4.3 Final report of study results

15-06-2020

5. Data management

Data management and statistical programming will be performed in the Danish Health Data Agency's protected computing environment. Data management will be performed by Martin Thomsen Ernst, Kasper Bruun Kristensen and Lars Christian Lund. Source code used for the analyses will be published on https://coderefinery.org/lcl.

6. Dissemination

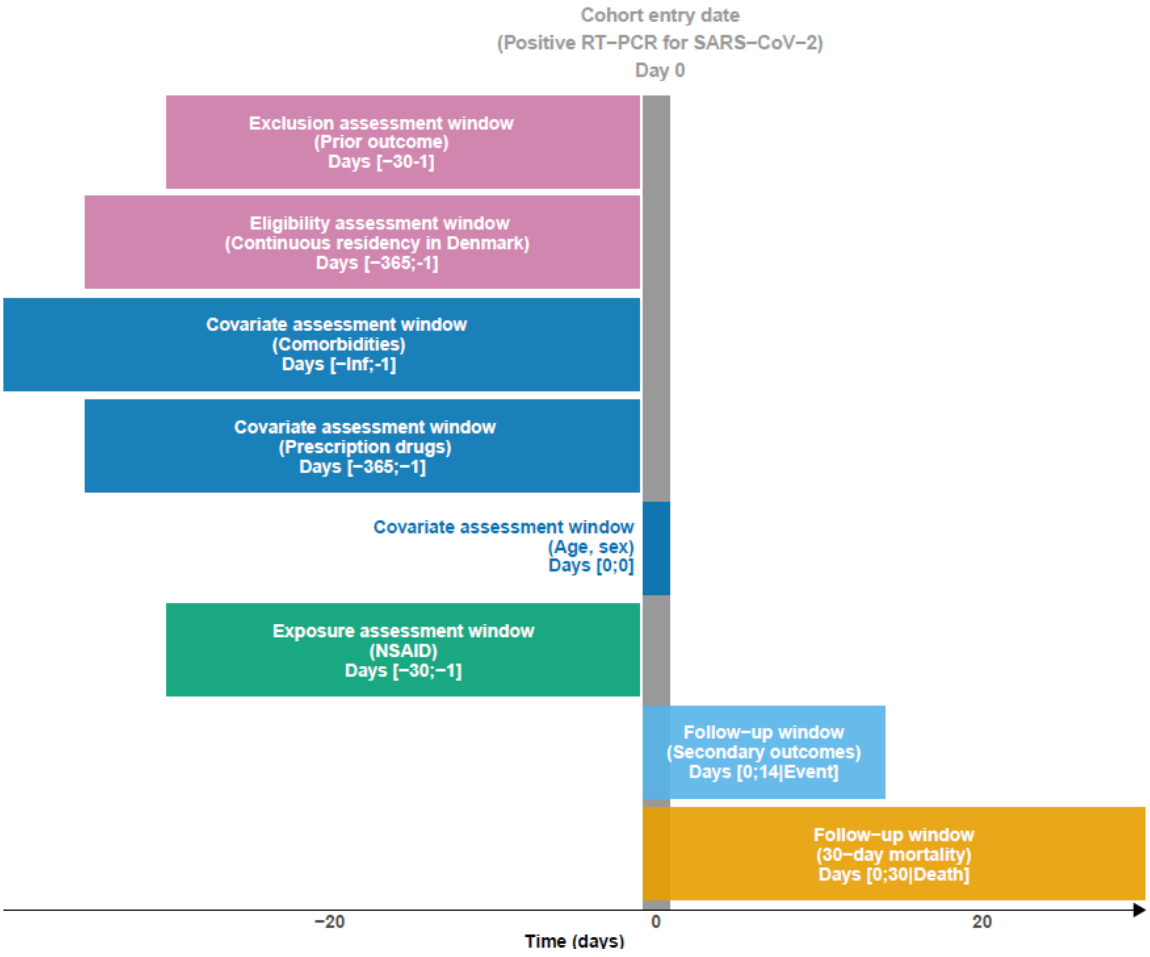
The study protocol will be registered in the EU-PAS registry. Results will be communicated in international peer-reviewed journals and the website of the Danish Medicines Agency. Results will be made available before peer-review on a preprint server, e.g. medrxiv.org. Any evidence of adverse events associated to ibuprofen and other NSAIDs will be communicated to the Danish Medicines Agency.

7. Amendments and deviations

Any future amendments or deviations will be recorded here.

Figures

Figure 1: Study design diagram



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7 Appendix

VARIABLE	CODING SYSTEM	CODE
Exposures		
NSAID	ATC	M01A (excluding M01AX)
Prescription drug use		
Antihypertensives	ATC	C08, C03CA, C07, C09
Antidiabetic drugs	ATC	A10
Low-dose aspirin	ATC	B01AC06, B01AC30, N02BA01
Immunosuppressants	ATC	L04
Opioids	ATC	N02A
Benzodiazepines	ATC	N05BA, N05CD
Non-benzodiazepine benzodiazepine receptor agonists	ATC	N05CF
1st gen. antipsychotics	ATC	N05AA, N05AB, N05AC, N05AD, N05AF, N05AG, N05AL01
2nd gen. antipsychotics	ATC	N05AE, N05AH, N05AX, N05AL05
Systemic glucocorticoids	ATC	H02AB
Inhaled corticosteroids	ATC	R03BA01-09, R03AK06-08, R03AK10, R03AK11
History of		
Asthma	ICD-10	J45, J46
Chronic obstructive pulmonary disease	ICD-10	J41-J44
Cardiovascular disease	ICD-10	I20-I25, I47-I50
Ischaemic stroke	ICD-10	I63, I64

Chronic kidney disease	ICD-10	N00, N01, N03-N06, N08.8, N14.1, N14.2, N16.8, N17, N25.1, N26, N27
Liver disease	ICD-10	B18, K70.0- K70.3, K709, K71, K73, K74, K76.0, B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Alcohol related disorders	ICD-10	F10, E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, Q86.0, Z50.2, Z71.4, Z72.1
Dementia	ICD-10	F01-F04
Cancer	ICD-10	C00-C97, excluding C44
Obesity	ICD-10	E66
Hemiplegia and paraplegia	ICD-10	G04.1, G11.4, G80.1, G80.2, G83.0-G83.4, G83.9
Osteoarthrosis	ICD-10	M15-19
Rheumatoid arthritis/collagen vascular disorders	ICD-10	L94.0, L94.1, L94.3, M05, M06, M08, M12.0, M12.3, M30, M31.0 - M31.3, M32-M35, M45, M46.1, M46.8, M46.9
Dysmenorrhoea	ICD-10	N94.4-94.6
Outcomes		
Admission to intensive care unit	SKS	NABB, NABE
Mechanical ventilation	SKS	BGDA
Acute renal replacement therapy	SKS	BJFD0

REGISTRY	CITATION	INFORMATION OBTAINED	VARIABLES
Danish National Prescription Registry (Lægemiddelmiddelstatistik registeret)	Pottegård et al (PMID: 27789670)	All redeemed prescriptions from community pharmacies in the period 1995-2018	ATC-code, fill date, number of DDDs redeemed
Danish National Patient Registry (Landspatientregisteret)	Schmidt et al (PMID: 26604824)	In- and outpatient hospital diagnoses in the period 1977-2018	ICD-10 code, admission date
Civil Registration System (CPR-registeret)	Schmidt et al (PMID: 31372058)	Age, sex, migration- and vital status	See "Information obtained"
The Danish Register of Causes of Death	Helweg-Larsen et al (PMID: 21775346)	Date of death	Date of death

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	X	☐	☐	4.1
1.1.2 End of data collection[2]	☐	☐	X	4.2
1.1.3 Progress report(s)	☐	X	☐	-
1.1.4 Interim report(s)	☐	X	☐	-
1.1.5 Registration in the EU PAS Register®	X	☐	☐	6
1.1.6 Final report of study results.	X	☐	☐	6

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	X	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	1
	2.1.2 The objective(s) of the study?	X	☐	☐	2
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	3.1
	2.1.4 Which hypothesis(-es) is (are) to be tested?	X	☐	☐	2
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	X	-

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	X	☐	☐	3
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	☐	☐	3.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X	☐	☐	3.8
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	X	☐	☐	3.8
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	X	☐	☐	6

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	X	☐	☐	3.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	X	☐	☐	3.2
	4.2.2 Age and sex	☐	X	☐	-

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	X	☐	☐	3.2
4.2.4 Disease/indication	X	☐	☐	3.2
4.2.5 Duration of follow-up	X	☐	☐	3.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	X	-

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	X	☐	☐	3.4
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	X	☐	☐	3.4
5.3 Is exposure categorised according to time windows?	X	☐	☐	3.4, 3.9.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	X	☐	-
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	X	☐	-
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	X	☐	-

Comments:

A recent study by the authors (manuscript under review) showed that paracetamol users are less comparable to NSAID users than non-users in individuals with an influenza diagnosis. Therefore, no active comparator was employed.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	X	☐	☐	3.5
6.2 Does the protocol describe how the outcomes are defined and measured?	X	☐	☐	3.5
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	X	☐	☐	3.5

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	X	☐	-

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	X	☐	☐	3.6, 3.9.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	X	☐	☐	3.6.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	X	☐	☐	3.6.2

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	X	☐	☐	3.9.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	X	☐	☐	3.4, appendix
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X	☐	☐	3.5, appendix
9.1.3 Covariates and other characteristics?	X	☐	☐	3.6, appendix
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	Appendix
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	Appendix
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X	☐	☐	Appendix
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	X	☐	☐	Appendix
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X	☐	☐	Appendix
9.3.3 Covariates and other characteristics?	X	☐	☐	Appendix
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	X	☐	☐	3.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	X	☐	☐	3.8
10.2 Is study size and/or statistical precision estimated?	X	☐	☐	3.1
10.3 Are descriptive analyses included?	X	☐	☐	3.7
10.4 Are stratified analyses included?	X	☐	☐	3.9.2
10.5 Does the plan describe methods for analytic control of confounding?	X	☐	☐	3.6
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	X	☐	-
10.7 Does the plan describe methods for handling missing data?	☐	X	☐	-
10.8 Are relevant sensitivity analyses described?	X	☐	☐	3.9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	3.10
11.2 Are methods of quality assurance described?	X	☐	☐	5

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	X	☐	☐	5-6

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	X	☐	☐	3.6.2
12.1.2 Information bias?	X	☐	☐	3.6.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	X	☐	☐	3.6.2
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	X	☐	☐	3.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	X	☐	☐	3.10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	3.10
13.3 Have data protection requirements been described?	X	☐	☐	3.10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	X	☐	☐	7

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X	☐	☐	6
15.2 Are plans described for disseminating study results externally, including publication?	X	☐	☐	6

Comments:

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Date: 21/April/2020

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