Characteristics of non-randomized studies of pharmacologic treatment: a cross-sectional study

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SUPPLEMENTAL MATERIAL

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Appendix 1. Search strategy for Ovid MEDLINE

1	exp Non-randomized controlled trials/ or (((Non random* or nonrandom*) adj3 (trial* or study or studies)) or NRSI).mp. or ((Non interven* or noninterven*) adj2 (trial* or study or studies)).mp. or ((cohort* or incidence) adj (study or studies or analys?s)).mp. or exp Control Groups/ or exp Matched-Pair Analysis/ or (case* adj2 (control* or comparison* or comparat* or compare* or referent* or compeer*)).mp. or ((match* or control*) adj (case* or group* or study or studies or pair* or control*)).mp. or (Interrupted Time Series or ITS study or ITS studies).mp. or ((CBA or Before after or "Before and after" or "pre and post" or pre post) adj (study or studies)).mp. or Comparative study/ or exp Epidemiologic studies/ or evaluation study/ or ((retrospective or prospective or longitudinal or follow up or followup or epidemiologic* or evaluation) adj1 (study or studies or analys?s or survey*)).mp. or ((comparat* or comparison* or continuing or observational) adj2 (study or studies or research or analys?s)).mp. or (population based adj1 (study or studies or analys?s)).mp. or (historic* adj2 (study or studies or analys?s)).mp. or Time factors/ or (time and factors).mp. or (Cross-section* or cross section* or Prevalence Studies or Prevalence study or prevalence analys?s or survey).mp. or ((emulat* or target or reference) adj2 (trial* or study or studies or experiment*)).mp. or exp Information Systems/ or exp Medical Records/ or Patient Discharge/ or Hospital Records/ or exp Health Services Research/ or exp insurance, health/ or exp Registries/ or (database* or registry or registries or register or registers or ehr* or emr* or secondary data* or big data).mp. or ((health or health care or healthcare or hospital* or patient* or physician* or medical or linked or surveillance or insurance or billing or admission or discharge or routine or routinely or claim* or administrative or registr* or real world or emergency department* or vigilance) adj2 (record* or claim* or data or file* or registr* or evidence or information system* or summar* or card* or study or studies)).mp.
2	exp drug therapy/ or drug therapy.fs. or (pharmacologic* or pharmacotherap* or pharmaco therap* or chemotherap* or chemo therap* or drug* or medication* or medicine* or dose* or dosing or intravenous* or oral or orally or subcutaneous* or subq or capsule* or tablet*or treatment* or pretreatment* or prescription* or agent* or regimen*).mp. or *pharmaceutical preparations/ or exp controlled substances/ or exp dosage forms/ or exp drugs, essential/ or exp drugs, generic/ or exp drugs, investigational/ or exp nonprescription drugs/ or exp prescription drugs/ or exp prodrugs/ or substandard drugs/ or synthetic drugs/ or exp designer drugs/ or exp "chemical actions and uses"/
3	1 and 2
4	exp Review/ or systematic review/ or Address/ or exp Biography/ or exp Bibliography/ or Case Reports/ or Clinical Conference/ or Comment/ or exp Congress/ or Editorial/ or Letter/ or exp Dictionary/ or Directory/ or exp Historical Article/ or exp Legal Case/ or exp Meta-Analysis/ or exp Guideline/ or News/ or Newspaper Article/ or Patient Education Handout/ or Legislation/ or Lecture/ or exp Video-Audio Media/ or Webcast/ or Portrait/ or Clinical Trial, Phase I/ or Clinical Trial, Phase ii/ or exp Randomized Controlled Trial/
5	exp animals/ not humans.sh.
6	3 not (4 or 5)
7	limit 6 to (english language and yr="2022")
8	limit 7 to dt=20220601-20220831

Appendix 2. Data extraction instruction sheet

Item	Explanation	Answer options
General characteristics		
Study ID		
Authors	Name of the first author	Open-ended
Title	Title of the article	Open-ended
Journal	Type of journal. E.g., General medical journal: The Lancet Specialized medical journal: The Lancet Oncology	1. General medical journal 2. Specialized medical journal 3. Non-medical journal
Region	Region of country of study	1. North America 2. Latin America and Caribbean 3. Middle East and North Africa 4. Sub-Saharan Africa 5. Europe 6. South Asia (Afghanistan, Pakistan, India, Nepal, Bangladesh, Sri Lanka) 7. Central and East Asia and Pacific 8. More than one: Specify
Setting	Healthcare setting of the study	1. Primary (Outpatient/Community), 2. Secondary (Inpatient/General hospital(s)), 3. Tertiary (Inpatient/Specialized or university hospital(s)), 4. Other: Specify 5. More than one: Specify 6. Not reported
Number of centers	Number of centers included in the study. In cases where the data is a regional/national registry, then it would not be applicable.	• [Continuous number] • Not reported • Not applicable
Sampling of centers or population	Is the sample representative of the population? i.e., there is a structured manner to sample the centers to obtain a representative sample of the population or the data source is representative of the population e.g., using a nationwide database of all health centers.	1. Yes: Specify 2. No

Medical area	Medical area in which the treatment is being evaluated based on the included population	1. Cardiology 2. Endocrinology 3. Infectious Disease 4. Obstetrics 5. Rheumatology 6. Oncology 7. Psychiatry/Psychology 8. Neurology 9. Respiratory 10. Hematology 11. Surgery 12. Gastroenterology 13. Other: Specify
Study design as reported	Study design as reported in the article, including all labels and terms used to describe it	Open-ended
Study design as judged	Study design as judged by reviewer according to the algorithm available at the end	1. Cohort 2. Case-control 3. Other: Specify
Study design diagram	Use of diagram to illustrate the study design including timepoints for eligibility, treatment assignment and follow-up	1. Yes 2. No
Flow diagram timepoints	The flow diagram of participants, if applicable, reports the dates for the timepoints for eligibility, treatment assignment and follow-up i.e., one is able to identify from the timepoints of eligibility, treatment assignment and follow-up from the flow diagram. Not applicable: when there is no flow diagram of participants.	1. Yes 2. No 3. Not applicable
Objective(s)	List the main objective of the study	Open-ended
Objective other than assessing treatment effect is included	In addition to the main objective of assessing treatment effect, do the authors report another objective? Objectives related to treatment effects are NOT considered as 'another objective', e.g., If an objective is to assess the factors associated with treatment success, then it is NOT another objective.	1. Yes: specify 2. No
Complementary or exploratory evidence	Is the study conducted to complement findings from previous studies or to explore the effect of the treatment?	1. Complementary of RCTs 2. Complementary of RCTs and/or NRS 3. Exploratory 4. Unclear
Data used	Type of data used, regardless of the purpose of the data used, i.e., for recruitment, for treatment evaluation, etc.	1. Routinely collected data 2. Standardized data collection from an existing cohort

	Routinely collected data is data collected without any research purpose, whereas standardized data collection is data collected with a specific research purpose, either an existing one or for the purpose of this study.	3. Standardized data collection from a cohort for the purpose of the study 4. More than one: Specify 5. Not reported
Source(s) of routinely collected data	Type(s) of data sources for all routinely collected data	1. Registry 2. Administrative data (Health administration data, Health insurance claims data, Pharmacy data) 3. Electronic health record 4. Wearable biometric monitoring device data 5. Health records (non-electronic, not specified) 6. Other: Specify 7. More than one: Specify 8. Not applicable 9. Not reported
Statistician/Methodologist	Statistician or methodologist included in the research team, as reported in the manuscript or included as an author with affiliation to a statistics, epidemiology or public health department, or mentioned in the acknowledgement.	1. Yes: author affiliation 2. Yes: explicitly reported 3. No
Research question	Explicit statement of research question or well-defined objective(s), from which the research question is identifiable.	1. Yes 2. No
Participants		
Eligibility criteria for participants	Eligibility criteria for participants is reported	1. Yes 2. No
Post-baseline/treatment events in the inclusion criteria	Post-baseline/treatment events included in the inclusion criteria. For example, use of treatment (“include only individuals who ever used therapy during the follow-up”), having an event (“include only those who ever had a specific event during the follow-up period”, or no follow-up data ("include only individuals who remain under follow-up" or “follow-up was at least 2 years”).	1. Yes: Use of treatment during FU 2. Yes: Having an outcome during FU 3. Yes: Specific duration of FU 4. Yes: More than one, specify: 5. No
Eligibility to any arm	Authors explicitly state whether participants can be eligible to any treatment arm i.e., patients should not have contraindications to any of the treatment arms.	1. Yes 2. No

Number of participants excluded due to post-baseline events	The number of participants that were excluded based on post-baseline events in the eligibility criteria*	• [continuous number] • Not reported • Not applicable
Sources for selection of participants reported	Sources for selection of participants are reported	1. Yes 2. No
Use of validation studies	Any validation studies of the codes or algorithms used to select the population. 'Not applicable' is when the study does not use routinely collected data.	1. Yes: validation studies 2. No: previous studies 3. No: not reported 4. Not applicable
Period of recruitment	Period of recruitment of participants is reported, e.g., a registry including patients registered in the 1 January 2014 to 1 January 2020. Include the day, month, year for the start and end of recruitment.*	• [Open-ended] • Not reported
Duration of recruitment	Duration of recruitment of participants is reported, e.g., the duration is 6 years (6x12=72 months) for a registry including patients registered in the 1 January 2014 to 1 January 2020 in months.*	• [Continuous number] • Not reported
Population	Define the population in which the treatment is being assessed	1. Chronic disease 2. Acute disease in chronic patients 3. Acute disease in healthy patients
Treatment		
Description of treatment	A description of the allocated treatment is reported, including the dosage form, dosage, and frequency	1. Yes 2. No
Comparator(s)	What is the pharmacologic treatment compared to?	1. Usual care/No treatment 2. Other active treatment 3. Different regimen of (target) treatment 4. More than one: Specify
Effect of active comparator	Do the authors explicitly state that the active comparator is expected to have no effect on the outcome of interest?	1. Yes 2. No 3. Not applicable
Pharmacologic family [If active comparator(s)]	If active comparator(s), is/are the comparator(s) in the same pharmacologic family as the (target) treatment? For studies with more than one comparator, if at least one of the comparators is from the same pharmacologic family, then select 'Yes: some comparator(s)'.	1. Yes: all comparators 2. Yes: some comparator(s) 3. No 4. Not applicable

Definition of treatment arms	How are the treatment arms defined? e.g., according to prescriptions, dispensing, adherence? Data from electronic health records are considered as prescriptions, unless reported otherwise. Data from pharmacy claims data or insurance claims are considered as dispensations, unless reported otherwise.	1. Prescriptions 2. Dispensations 3. Adherence 4. Other: Specify 5. Not reported 6. Not applicable
Description of actual treatment	A description of the actual treatment is reported, including, dosage form, dosage, frequency, duration	1. Yes 2. No
Initiation or continuation	The comparison is to assess the initiation of a treatment or to assess the continuation of a treatment (i.e., patients are starting the treatment, being already on the treatment, or having a combination of those starting the treatment and those on the treatment).*	1. Initiation of treatment 2. Continuation of treatment 3. Combination of initiation and continuation of treatment 4. Unclear
Inclusion of treatment users	Are the treatment users incident/new users or prevalent users? Incident users are 'new users', whereas prevalent users are patients who are already on the treatment.	1. Incident/New users 2. Prevalent users 3. Unclear 4. Both
Comparison in question	What is the comparison in question? Treatment initiation is a one-time decision (i.e., treatment exposure is not based on follow-up data [ITT analogue]). Static treatment strategy is when the treatment is given for a specific period of time, and needs follow-up data to identify/classify patients (per-protocol analogue). Dynamic treatment strategy is similar to static treatment but 'dynamic' e.g., treat to target strategy in rheumatoid arthritis.	1. Treatment initiation 2. Static treatment 3. Dynamic treatment 4. Delay of treatment 5. Discontinuation of treatment 6. Treatment duration 7. More than one: Specify 8. Other: Specify
Treatment over time	Did the distribution of the treatment change over time during the study period? i.e., Is there a 'time-issue'? This can be due to change in clinical practice, approval of drug, long duration of recruitment 'Addressed' time-issue is when authors accounted for the time-issue in their analysis, for example through matching.*	1. Yes: addressed 2. Yes: not addressed 3. No 4. Unclear
Treatment deviations defined	Treatment deviations are defined, i.e., cross-over, stopping treatment, non-compliance	1. Yes 2. No
Treatment deviations reported	Treatment deviations are reported, i.e., there was a difference between planned treatment and actual treatment	1. Yes 2. No

Addressing treatment deviations	Method for addressing treatment deviations	1. Excluded 2. Censored 3. Included in the allocated arm 4. Included in the treated arm 5. Other: Specify
Drug approval	When was the drug molecule approved? This is not dependent on the dosing regimen or indication. It is specific to the drug molecule.	1. Approved from a long time 2. Recently approved 3. Unapproved
Treatment assignment		
Grace period to start treatment or active comparator	A time window/delay to initiate the treatment (i.e., grace period) is reported	1. Yes 2. No
Grace period	If there is a grace period, specify period (with time unit) to initiate treatment or active comparator e.g., 7 days. If the grace period is a range, then report the upper end of the period e.g., the grace period reported in the study is 4-8 weeks, then the extracted grace period is 8 weeks.	Continuous number
Difference in grace period	Difference in the grace period to initiate treatment and to initiate active comparator is reported	1. There is a difference 2. There is NO difference 3. Not applicable 4. Not reported
Data during grace period	If the data during the grace period is available and aligned with sampling	1. Yes 2. No 3. Not applicable
Point-exposure or time-varying treatment	Treatment is at point-exposure (clearly defined irrespective of time), i.e., only chance to decide if treatment or not, for example, one administration of a treatment, e.g., injection) or treatment is time-varying (i.e., deciding to give a treatment or not based on time-varying factors e.g., (a) the treatment of interest is static but patients' treatment status may vary in the available observational data; or (b) the intervention of interest involves a strategy to vary treatment over time (time-varying treatment strategy).*	1. Point-exposure 2. Time-varying treatment 3. Unclear

Method to address time-varying treatment or point-exposure treatment	How did the authors address time-varying treatment?*	1. Randomly assign the individual to one of the strategies 2. Clone exact copies of individuals and assign each clone to one of strategies then censor clone when strategies are deviated from 3. Time-varying Cox model 4. Marginal structural model (MSM) 5. Structural nested mean models (SNMMs) 6. Other: Specify 7. Not reported
Statistical considerations		
Outcomes		
Primary outcome(s)	Authors first identify the primary outcomes, (i.e., list them), then define them, i.e., provide a detailed definition including details on method of assessment or on prespecified time point of primary interest, when relevant.	1. Identified only, not defined 2. Identified and defined 3. Not identified
Type of research question	The type of research question the study is addressing: efficacy, safety or both according to the *objective* and the *outcomes* reported in the *Methods section.* Mortality can be considered an efficacy and/or a safety outcome depending on the context. Adverse events are safety outcomes.	1. Effectiveness 2. Safety 3. Both
Confounders		
Confounders/Covariates reported	Confounders/confounders were clearly identified e.g., a list of confounders is reported	1. Yes 2. No
Identifying confounders/covariates	How were the confounders/covariates identified?	1. Literature 2. Statistical methods 3. Confounders/covariates are ONLY listed with no justification 4. Other: Specify 5. Not reported
Method of identifying confounders/covariates *[if they were identified through statistical methods]*	Method of identifying confounders/covariates through analysis. For example, authors use the backward or forward approach in the model, or they use a specific p-value cut-off. 'Not applicable' is when confounders/covariates where identified through methods other than 'analysis'	1. Select variables that are statistically significant in univariate analysis (p-value<0.05) 2. Select variables that have a p-value less than the chosen cut-off in the univariate analysis (other than 0.05) 3. Backward approach in the model

		4. Forward approach in the model 5. Other: Specify 6. Not applicable
Accounting for confounding	Method for accounting for confounding factors. G-computation is also referred to as parametric g-formula or g-standardization or regression-imputation	1. Matching 2. Stratification or regression 3. Inverse probability weighting 4. Standardization 5. Cloning and censoring 6. G-computation (i.e. regression-imputation) 7. Other: Specify 8. Not reported
Description of method to account for confounding	Describe the method used to account for confounding (e.g. regression with imputation, linear regression, logistic regression, time-varying cox model, etc)	[Open-ended]
Propensity score	Propensity score is used	1. Yes 2. No
E-value reported	E-value is reported. E-value is a new standardized approach for sensitivity analyses on confounding in observational studies. It is the minimum magnitude of association that an unmeasured confounder needs to have with both the exposure and the outcome to fully explain away the observed exposure-outcome association, conditional on the measured covariates.	1. Yes 2. No
Use of negative control reported	Use of negative control outcomes or exposures. A negative control outcome (NCO) is a variable known not to be causally affected by the treatment of interest. Likewise, a negative control exposure (NCE) is a variable known not to causally affect the outcome of interest. In prior literature, NCO has been referred to as falsification outcome/endpoint, control outcome, secondary outcome, supplementary response, and unaffected outcome. NCE has been referred to as control exposure and residual confounding	1. Negative control outcome(s) 2. Negative control exposure(s) 3. Not reported

	indicator. Both NCO and NCE have been referred to as proxies of unmeasured confounder.	
Patients included once or multiple times	Patients were allowed to enter the study population once or multiple times (i.e., new user study design)*	1. Once 2. Multiple times
Addressing multiple time zeros	Method to address having multiple eligibility timepoints*	1. Choose one of the multiple times 2. Take all eligibility times (sequence nested trials) 3. Choose eligible times and match person-time 4. No solution described 5. Not applicable
Study size		
Sample size determination	How was sample size determined is reported? Post-hoc power calculations are not relevant.	1. Yes: Specify 2. No
Participants considered eligible	Total number of participants considered eligible. If there are multiple cohorts in the study, report the number of participants of the largest one. If there are multiple analysis (ITT and PP), report the number of participants of the main analysis or ITT analysis if not specified. If there are different number of participants for different outcomes, report the one for the primary outcome. If there is more than one observation per patient, report the number of participants and not the number of observations. If there is matching or weighting, report the number of eligible participants before matching or weighting.	Continuous number
Participants analyzed	Total number of participants analyzed If there is matching or weighting, report the number of eligible participants after matching or weighting.	Continuous number
Analysis		
Analysis/Causal contrast of interest planned	Analysis or causal contrast of interest that is planned as reported	1. Per-protocol 2. Intention-to-treat 3. Both 4. Not reported
Analysis/Causal contrast of interest conducted	Analysis or causal contrast of interest that is conducted/done as judged by reviewer*	1. Per-protocol 2. Intention-to-treat 3. Both 4. Other: Specify
Follow-up		

Longest follow-up reported for an outcome (in months)	Longest follow-up time reported for an outcome (specifying the unit), e.g., median or mean of FU time reported or a specified time period e.g., 2-year mortality. If the outcome measured in unit of time e.g., 'length of stay', then report the median or mean for this outcome.	Continuous number
Target trial emulation		
Target trial	Did the author(s) specify a target trial?	1. Yes 2. No
Time points are clearly reported	Are the three timepoints clearly reported? The three timepoints are: 1. Eligibility: Time point of patients meeting complete eligibility criteria reported 2. Assignment: Time point of treatment initiation reported (treatment assignment) 3. Follow-up: Time point of the start of follow-up reported (baseline, time zero, T0)	1. Yes 2. No
Possible to identify the three time points *[If the three timepoints are not clearly reported]*	Is it possible to identify the three time points?	1. Yes 2. No 3. Not applicable
Key time points reported or identified are synchronized *[If the three timepoints are reported or identified]*	Are all three time points reported or identified are synchronized (i.e., eligibility, treatment assignment and start of follow-up)? 'Not applicable' is when NOT all of the three timepoints are reported	1. Yes 2. No 3. Unclear 4. Not applicable
Bias		
Relevant reported bias	Do the authors report presence of bias(es) (either accounted for or not) in the Methods or Discussion sections? Specify the bias reported, e.g., confounding bias, selection bias, etc	1. Yes: Specify 2. No
Bias due to inclusion of prevalent users	Was there a risk of bias due to inclusion of prevalent users as judged by reviewers? When (1) follow-up starts after eligibility criteria completion and treatment assignment OR (2) Follow-up starts at eligibility but after treatment assignment.	1. Yes 2. No 3. Unable to assess

	E.g., including individuals who initiated one of the treatment strategies of interest some time before the start of follow-up and who continue to follow the same strategy during the follow-up. Patients who experience early outcomes after starting the treatment are not captured.	
Bias in selection of participants due to post-treatment/baseline eligibility	Was there a risk of bias in selection in selection of participants due to post-treatment/baseline eligibility as judged by reviewers? When (2) follow-up starts at eligibility but after treatment assignment OR (3) Follow-up starts before treatment assignment and eligibility. E.g., including individuals to meet some eligibility criteria after treatment assignment (post-treatment criteria) In a target trial, there were several sequential eligibility criteria: having a diagnosis of colon cancer, undergoing surgery for colon cancer, surviving 1 month after surgery. Individuals who die between the times of first and last eligibility criterion –between colon cancer diagnosis and 1 month after surgery – were not included in the trial because they never complete eligibility into the study. Because treatment assignment predates eligibility, selection bias may arise. The same bias would arise if 'surviving 1 month after surgery' was instead, for example, 'receiving at least 2 consecutive prescriptions of treatment' where those who stopped the treatment after 1 prescription are excluded.	1. Yes 2. No 3. Unable to assess
Bias due to immortal time period	Was there a risk of bias due to immortal time period as judged by reviewers? When (3) follow-up starts before treatment assignment and eligibility OR (4) follow-up starts at eligibility but treatment is assigned later. E.g., taking the same example as the one before, immortal time bias exists because by definition nobody would die between treatment assignment and the completion of the eligibility criteria (surviving 1 month after surgery). Similarly, taking the other example 'receiving at least 2 consecutive prescriptions', patients who have an outcome between prescription 1 and prescription 2 are excluded from the analysis. Having a grace period would also lead to bias due to immortal time period.	1. Yes 2. No 3. Unable to assess

Bias in classification of treatment arms	Was there a risk of bias of classification of treatment arms as judged by reviewers? When (4) follow-up starts at eligibility but treatment is assigned later. When there is a grace period, assigning the treatment strategies based on a minimum or maximum number of prescriptions during a period after time zero (e.g., at least three prescriptions for active treatment and 0 prescriptions for no treatment) OR based on the mean number of treatment prescriptions after time zero. E.g., If there is a grace period where initiating treatment is within 6 days of diagnosis, if the patient has an outcome before day 6 without having started the treatment, it is uncertain whether to classify the patient in the treatment or no treatment arm. Assigning these patients to a single arm leads to bias due to classification of treatment arms.	1. Yes 2. No 3. Unable to assess
Strategy for addressing bias judged	What is the strategy to address the risk of bias identified by reviewers?	1. Selection of new users 2. An exact copy of the population was assigned to treatment and censored when deviation occurs 3. Exposure was considered as time-dependent variable in all analysis 4. Random assignment 5. Creating clone and assigning each clone to treatment arm 6. Series of analysis 7. Matching 8. Other: Specify 9. More than one: Specify 10. Not reported 11. Not applicable
Which bias was addressed	Specify which bias was addressed using the strategies specified in the previous question. If there is more than one strategy, then specify which strategy is used for which bias.	1. Prevalence user bias 2. Selection bias 3. Immortal time bias 4. Misclassification bias 5. More than one: Specify 6. Not applicable

Addressed bias due to inclusion of prevalent users	Was the bias due to inclusion of prevalent users addressed? Not applicable: When there is no bias	1. Yes 2. No 3. Not applicable
Addressed bias in selection of participants due to post-treatment/baseline eligibility	Was the bias in selection of participants due to post-treatment/baseline eligibility addressed? Not applicable: When there is no bias	1. Yes 2. No 3. Not applicable
Addressed bias due to immortal time periods	Was the bias due to immortal time periods addressed? Not applicable: When there is no bias	1. Yes 2. No 3. Not applicable
Addressed bias in classification of treatment arms	Was the bias in classification of treatment arms? Not applicable: When there is no bias	1. Yes 2. No 3. Not applicable
Open Science indicators		
Registration	Registration of the study in study registry	1. Yes 2. No
Protocol	Availability of (or accessibility to) the study protocol	1. Yes (open-access) 2. Yes (not open-access) 3. No
Changes reported	Important changes to protocol or statistical analysis plan with reasons are reported, e.g., the manuscript has a section on 'changes to protocol'	1. Yes 2. No
Data sharing statement	Data sharing statement	1. Data available in a public, open access repository 2. Data are available upon reasonable request 3. Data may be obtained from a third party and are not publicly available 4. All data relevant to the study are included in the article or uploaded as supplementary information 5. Data sharing not applicable as no datasets generated and/or analyzed for this study 6. Not reported
Access to the coding and algorithms	Code and algorithm provided, either as supplementary material or an accessible link to classify exposure and/or outcome	1. Code and algorithm used to classify exposures provided 2. Code and algorithm to classify outcomes provided 3. Both 4. None 5. Available upon request
Funding source	Funding source	1. Internal funding 2. Governmental 3. Intergovernmental

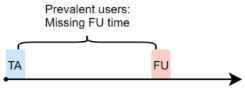
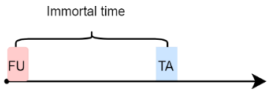
		4. Private-for-profit (companies/entities) 5. Private not-for-profit (organizations/philanthropies) 6. More than one: specify 7. Unclear 8. No funding 9. Not reported
Conflict of interest	Conflict of interests (COIs) of authors	1. None declared 2. Financial COI 3. Non-financial COI 4. Both types of COIs 5. Not reported
Ethical approval	Review of study by ethical/institutional review board	1. Approved 2. Waived 3. Not reviewed 4. Not reported
Adherence to reporting GL	Indication of adherence to reporting guideline	1. STROBE 2. RECORD 3. RECORD-PE 4. Other: Specify 5. Not reported
Use of causal language	Do authors conclude on the effect of the treatment using causal language in the **abstract.**	1. Yes 2. No
Conclusion in abstract	Authors' conclusion on the effect of the treatment is in favor, neutral or against the treatment in the **abstract.***	1. In favor of the treatment 2. Not in favor nor against the treatment (no clear preference) 3. Against the treatment 4. Unclear
Specific notes	Specific concepts, ideas, classifications to highlight for mapping of NRS	• Open-ended
General notes	General notes	• Open-ended

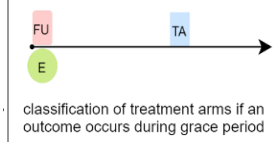
*Results are not presented.

Appendix 3. Study design

We considered the study as case-control when the participants were selected according to the outcome and then the treatment exposure was assessed. We considered the study design as cohort when the participants were selected according to the treatment exposure and the outcome was subsequently assessed.

Appendix 4. Summary table of possible biases related to time point misalignment

Bias	Illustration*	Explanation	Example	Methods to address it
Bias due to inclusion of prevalent users	 Time point of eligibility can be at treatment assignment or follow-up.	This occurs when follow-up starts after treatment initiation, therefore individuals who experience early outcomes after starting the treatment will not be included (if the outcome is death) or the outcome data may not be captured (if the outcome is different than death).	Hospitalized patients may already be taking DOACs prior to hospitalization although the follow-up in the study starts at hospitalization (eligibility). Individuals who die in the time-period between initiating DOACs and meeting eligibility (hospitalization)/start of follow-up will not be included in the study, or data on outcomes that occur during that time period will not be captured.	Only include new users
Bias due to post-treatment eligibility	 Time point of follow-up can be at treatment assignment or eligibility.	This occurs when eligibility is based on criteria that occurred after treatment initiation (e.g., specific duration of follow-up or having an event during follow-up).	1) Specific duration of follow-up: Only hospitalized patients who were followed up for one week would be included. 2) Having an event during follow-up: Hospitalized patients taking DOACs should have a specific level of international normalised ratio (INR) to be eligible, otherwise they would be excluded. Another example is if hospitalized patients on treatment with DOACs are excluded if major bleeding occurs, before the start of follow-up (i.e., follow-up start after treatment assignment).	Do not include participants based on post-treatment eligibility criteria
Bias due to immortal time periods	 The time point of eligibility can be at treatment assignment or at follow-up.	This occurs when treatment initiation is after the start of follow-up. There is 'immortal time', i.e., participants must survive long enough to receive the treatment being studied (they cannot experience the outcome during some period of follow-up time).	1) Sequential eligibility: to be included, patients should be hospitalized and survive for one week in hospitalization. Those who die in the first week will be excluded since they never fulfill the eligibility criteria. 2) Use of treatment during follow-up: Eligible hospitalized patients need to have at least two prescriptions to be assigned to the DOACs group. If they have received the two prescriptions, it implicitly means that they have survived through the two prescriptions.	- Clone exact copies of participants and assign each clone to one of strategies then censor the clone when strategies are deviated from - Randomly assign participants to one of the treatment strategies - Conducting a sequence of nested trial emulations where study eligibility criteria are applied and

			3) Grace period[a]: if eligible hospitalized patients can initiate DOACs within one week of hospitalization, it means that patients who initiate treatment at day 7 have survived an entire week.	treatment status is defined at different time points - Consider the exposure as a time-dependent variable
Bias due to classification of treatment arms	 classification of treatment arms if an outcome occurs during grace period	This occurs when there is uncertainty to which treatment arm the participant should be assigned to.	Eligible hospitalized patients can initiate DOACs within one week of hospitalization (i.e., 7-day grace period) and a major bleeding occurred at day 6 in patients who were not receiving DOACs, it is uncertain whether to classify the patient in the DOAC group or no prophylaxis group.	- Clone exact copies of participants and assign each clone to one of strategies then censor the clone when strategies are deviated from - Randomly assign participants to one of the treatment strategies

Abbreviations: FU: time point for start of follow-up, E: time point for eligibility, DOAC: direct oral anticoagulants, VTE: venous thromboembolism

[a]Grace period: a period between when participants meet eligibility to when they initiate the treatment. If not adequately addressed in the analysis, the presence of a grace period would impose risk of bias due to immortal time period and due to classification of treatment.

Appendix 5. Methods to address bias due to immortal time period and due to classification of treatment arms

- Clone-censor-weight approach (1): This method consists of cloning exact copies of participants and assigning each clone to one of strategies, then censoring the clone when strategies are deviated from, followed by using inverse-probability-of-censoring weights, where uncensored observations are up-weighted to represent censored observations with similar characteristics (n=1) [a,b]
- Randomly assigning participants to one of the treatment strategies (2-4): participants would be randomly assigned to one treatment strategy (n=2) [a]
- Conducting a sequence of nested trial emulations (2-4): several trial emulations are conducted where study eligibility criteria are applied and treatment status is defined at different time points (n=3)
- Consider the treatment as a time-dependent variable (2-4) and use an approach to address time-dependent confounding factors (n=10) [a]
- Landmark analysis (5): landmark time is selected and any participant who were lost to follow-up prior to that time is excluded from further analysis, while remaining participants who remain are classified based on their response at the landmark time (n=1) [c]

[a] More than one method was used in two reports: 1) clone-censor-weight approach with considering the treatment as time-dependent variable; and 2) randomly assigning participants with considering the treatment as time-dependent variable.

[b] The grace period introduced from clone-censor-weight approach was labeled as 'presence of grace period', but was considered as 'addressed' i.e., did not induce bias.

[c] May introduce prevalent user bias

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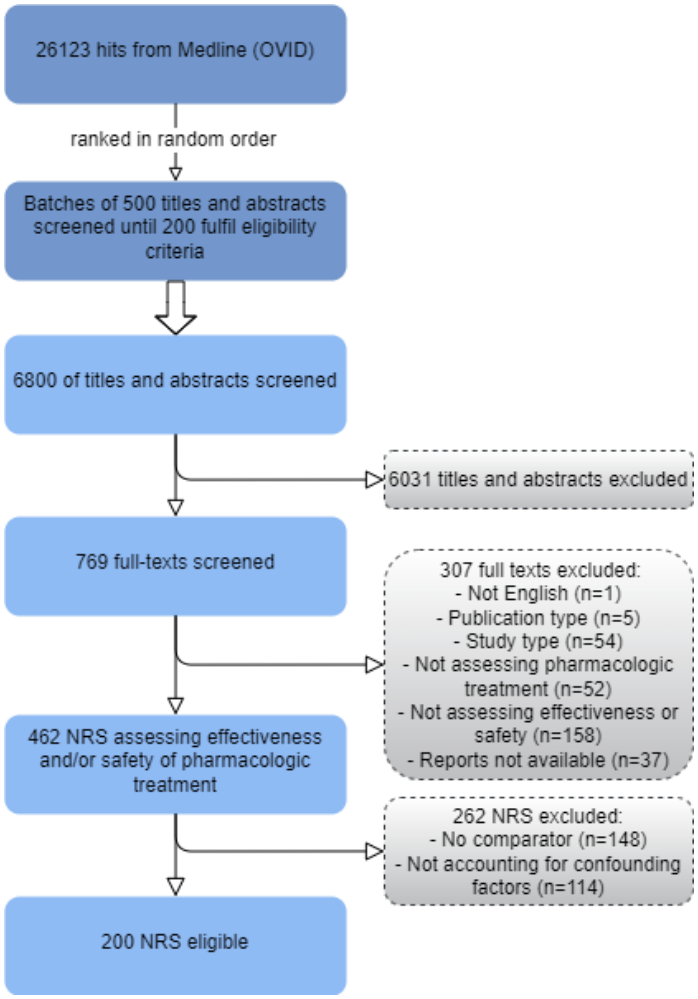
Appendix 6. Flowchart of included reports of non-randomized studies

Abbreviations: NRS: Non-randomized studies



Appendix 7. List of included reports of non-randomized studies

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Appendix 8. General characteristics of the included reports of non-randomized studies (N=200)

Characteristics*		**Frequency (%)**
Study characteristics		
Medical area†		
	Oncology	54 (27.0)
	Infectious Disease	41 (20.5)
	Cardiology	24 (12.0)
	Obstetrics and Gynecology	14 (7.0)
	Neurology	14 (7.0)
Region		
	Central and East Asia and Pacific	82 (41.0)
	Europe	59 (29.5)
	North America	50 (25.0)
	Middle East and North Africa	5 (2.5)
	More than one	4 (2.0)
Journal		
	Specialized medical journal	151 (75.5)
	General medical journal	45 (22.5)
	Non-medical journal	4 (2.0)
Statistician/Methodologist in authors or acknowledgements		94 (47.0)
	Author affiliation	83 (88.3)
	Explicitly reported	11 (11.7)
Research question		
Explicit statement		166 (83.0)
No effect of active comparator (N=112) reported		1 (0.9)
Study design and data		
Setting		189 (94.5)
	Primary	31 (16.4)
	Secondary	12 (6.3)
	Tertiary	102 (54.0)
	More than one	44 (23.3)
Centers (N=135)		
	Monocentric	72 (53.3)
	Number of centers	1.0 (1.0; 6.0)
Participants		
	Number of participants included	949 (288; 9 881)
	Number of participants analyzed	633 (216; 7 708)
Follow-up time (months) (N=175)		17.6 (3.0; 43.0)
Funding		168 (84.0)
	Internal funding	8 (4.8)
	Governmental	52 (31.0)
	Private-for-profit (companies/entities)	17 (10.1)

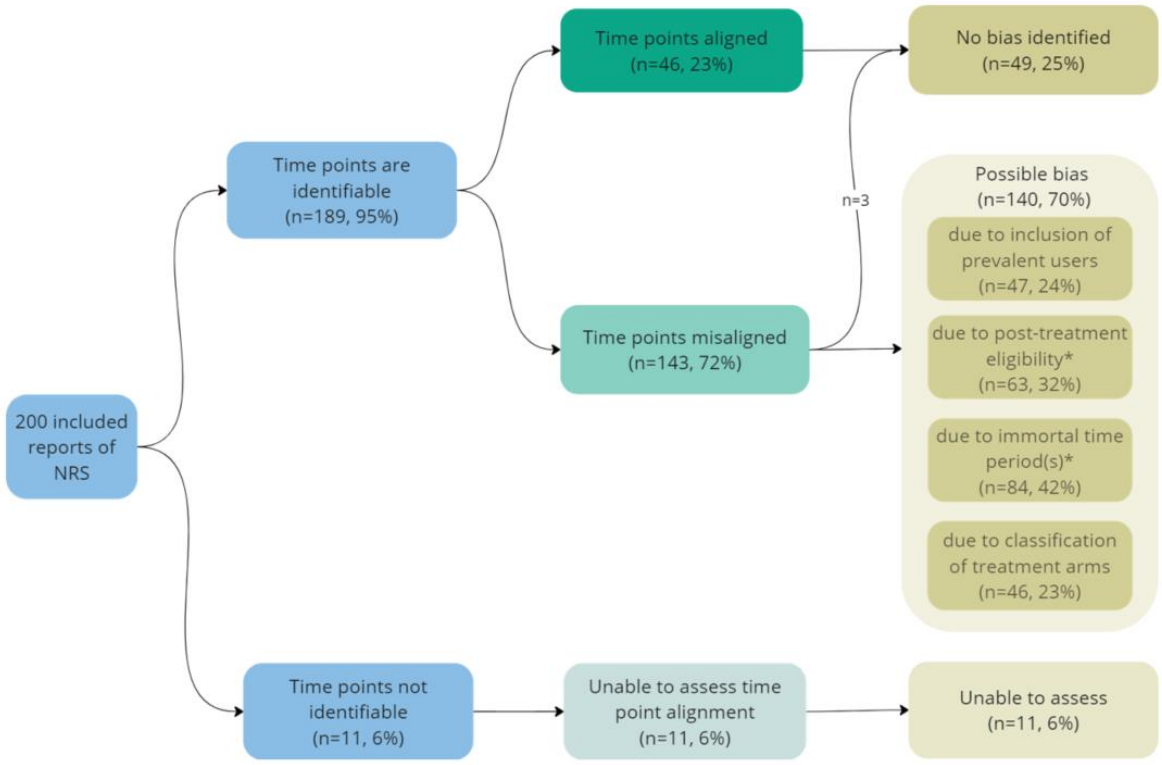
	Private not-for-profit (organizations/philanthropies)	17 (10.1)
	More than one	31 (18.4)
	Unclear	2 (1.2)
	No funding	41 (24.4)
Conflict of interest statement		196 (98.0)
	None declared	141 (72.0)
	Financial COI	24 (12.2)
	Non-financial COI	2 (1.0)
	Both types of COIs	29 (14.8)
Registration		14 (7.0)
Protocol		5 (2.5)
	Yes (open-access)	2 (40.0)
	Yes (not open-access)	3 (60.0)
Changes reported from protocol		0 (0.0)
Data sharing statement		123 (61.5)
	Data available in a public open-access repository	4 (3.3)
	Data are available upon reasonable request	61 (49.6)
	Data may be obtained from a third party	27 (21.9)
	All data relevant to the study are included	21 (17.1)
	Data sharing not available	10 (8.1)
Access to the codes and algorithms		9 (4.5)
	Available upon request	7 (77.8)
	Codes and algorithms provided	2 (22.2)
Ethical approval		190 (95.0)
	Approved	167 (87.9)
	Waived	13 (6.8)
	Not reviewed	10 (5.3)
Use of causal language in the abstract		
	Yes	69 (34.5)

COI: conflict of interest

*The median (25th percentile; 75th percentile) are reported for continuous outcomes.

†We only include the five most reported medical areas. Other areas include: Surgery (n=11), Endocrinology (n=10), Gastroenterology (n=7), Rheumatology (n=7), Psychiatry/Psychology (n=), Respiratory (n=4), Nephrology (n=4) and other (n=4).

Appendix 9. Time points for eligibility, treatment assignment and start of follow-up and possible related biases (N=200).

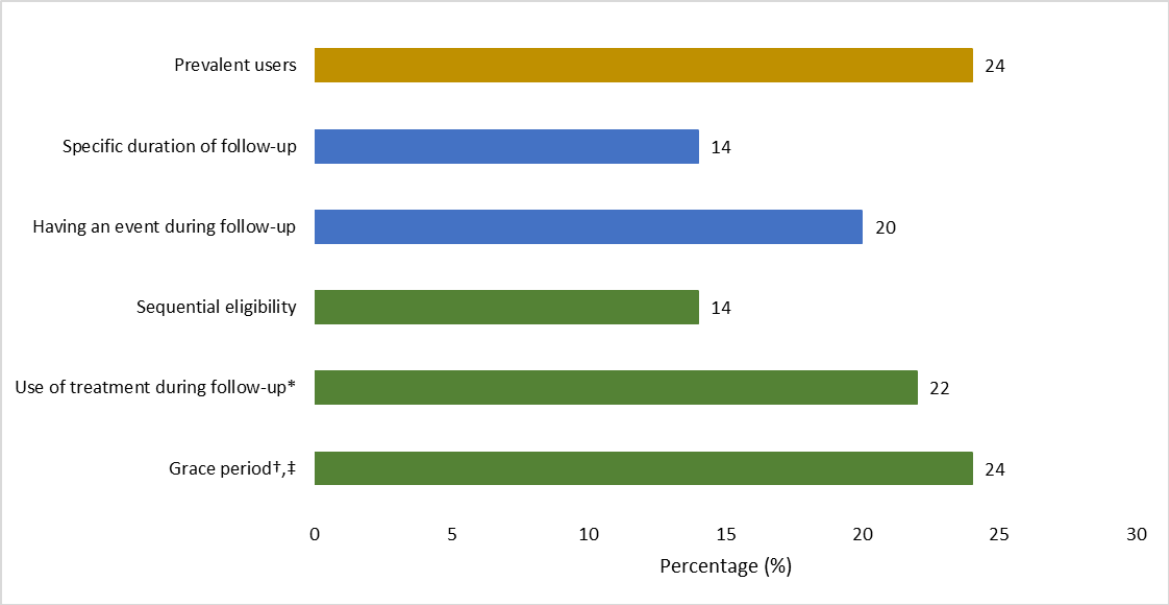


Abbreviations: NRS: non-randomized study

Note: Percentages might add up to more than a 100 due to rounding.

*Might have been underestimated due to the inadequate reporting of information (e.g., no reporting of eligibility criteria)

Appendix 10. Methodological characteristics that can lead to bias related to time point misalignment (N=200).



Brown: relevant to bias due to prevalent users; Blue: relevant to bias due to post-treatment eligibility; Green: relevant to bias due to immortal time periods.
*the requirement to use the treatment during follow-up was addressed in 5 reports
†relevant to bias due to classification of treatment arms
‡the grace period was addressed in 11 reports