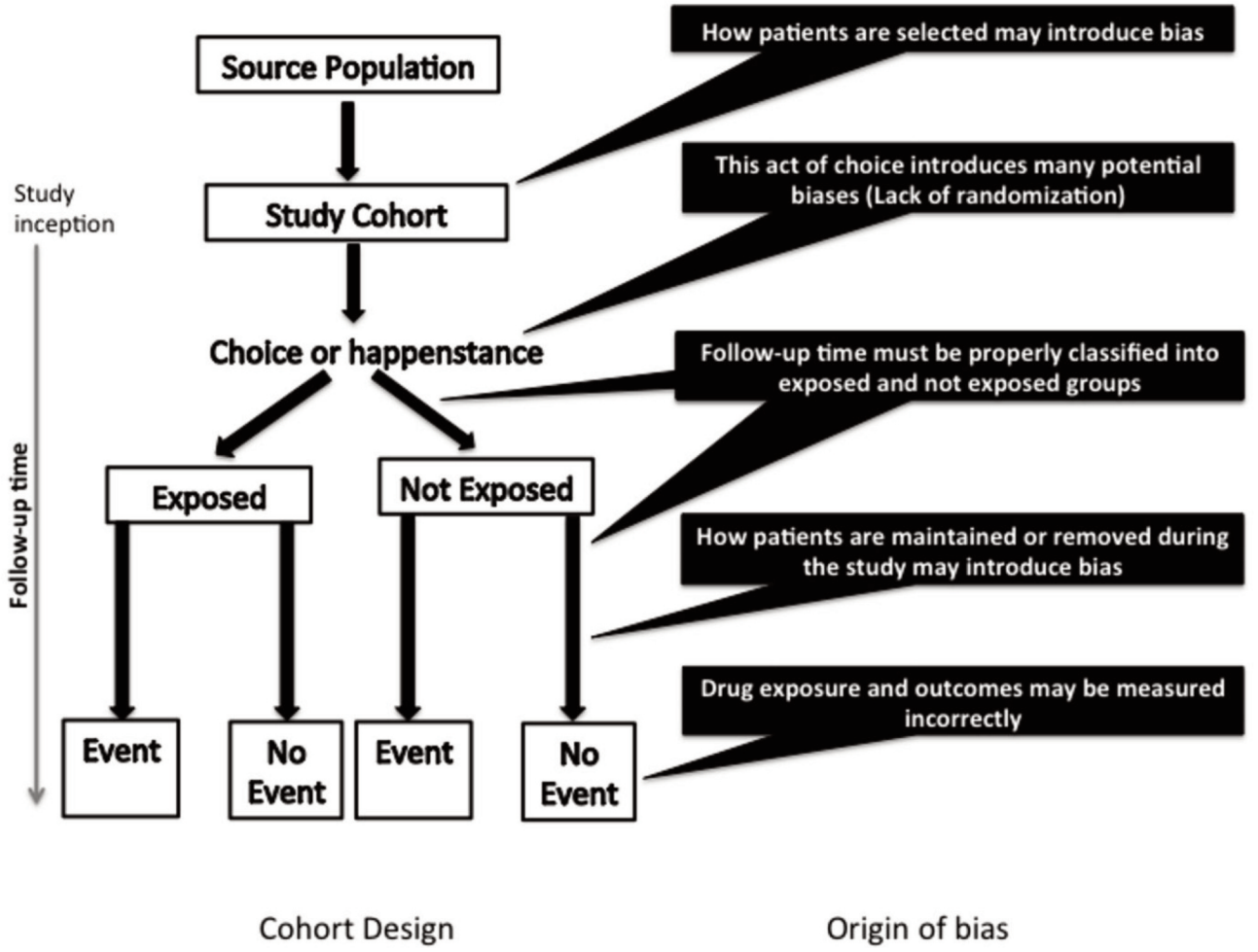
Appendix 1. Potential design and analytic solutions to selection bias, information bias, and confounding in cohort and case–control studies evaluating drug–outcome associations

Type of Bias	Potential Design or Analytic Solutions
Selection bias (systematic error due to how patients are selected or maintained in the study)	- Use a population-based data source - Apply random sampling from the source population - Adopt a well-codified accrual procedure - Select incident users of a medication when defining the cohort - Minimize losses to follow-up and implement a tracking procedure for those who drop out - Select incident cases for case–control study
Information bias (systematic error due to misclassification of exposure or outcome status)	- Standardize measurement process - Use standardized definitions for exposure and outcome measurement - Blind outcome assessors, especially for subjective outcomes - Select data source with accurately measured exposures and outcomes (consult validity studies)
Confounding (distortion or confusion of a drug–outcome association because of one or more variables associated with the exposure and outcome of interest)	Design techniques: - Restriction - Matching - Active comparator Analytic techniques: - Direct or indirect standardization - Stratification - Multivariable regression modelling - Propensity score adjustment - Disease risk scores - Instrumental variables - Marginal structural models

Supplementary material for Gamble JM. An introduction to the fundamentals of cohort and case–control studies. *Can J Hosp Pharm*. 2014;67(5):366-72.

Appendix 2. Schematic showing origin of major biases in cohort studies



Supplementary material for Gamble JM. An introduction to the fundamentals of cohort and case–control studies. *Can J Hosp Pharm*. 2014;67(5):366-72.

Appendix 3. Common types of bias and confounding in cohort and case–control studies of drug effects

Type of Bias or Confounding	Mechanism of Bias
Selection bias	
Referral bias	Occurs when the patients are referred to a health care provider or setting because of their drug exposure status.
Self-selection (volunteer) bias	Occurs when patients decide to participate in or drop out of a study because of their drug status or health status.
Prevalence bias	In cohort studies, bias is introduced when prevalent drug users are studied because early outcome events are missed and certain confounders are improperly adjusted for. In case–control studies, prevalent cases may be spuriously related to exposure because prevalence is proportional to the duration of disease.
Protopathic bias	Occurs when the first symptoms of the outcome of interest are the reasons for starting or stopping the exposure of interest.
Loss to follow-up bias	Patients who do not respond or are lost to follow-up may introduce bias if their reason for nonresponse or loss to follow-up is related to their exposure and outcome status.
Immortal time bias	Exclusion of the period of follow-up time whereby a patient cannot experience the outcome of interest (immortal time), which creates a false survival advantage to the exposed group.
Healthy user/adherer bias	Occurs when patients who seek preventive therapy or are more adherent to therapy also participate in other preventive and health behaviours that are related to the outcome of interest.
Information bias	
Exposure ascertainment bias	Occurs when exposure status is misclassified because of errors in measurement. This may occur in cohort studies if exposure status is incorrectly measured because of missing information (e.g., only formulary medications captured) or because of how person-time is classified; specifically, misclassification of immortal time creates a false survival advantage for the exposed group. In case–control studies, interviewers aware of a patient's outcome status may change how they ascertain exposure status. Moreover, cases remember or forget exposure status more frequently than do controls.
Outcome ascertainment bias	Occurs when outcome status is misclassified because of errors in measurement. In cohort studies, information bias may occur if the procedure for detecting outcomes is related to the exposure status either via knowledge of exposure status or more intensive follow-up due to a certain drug exposure.

Supplementary material for Gamble JM. An introduction to the fundamentals of cohort and case–control studies. *Can J Hosp Pharm*. 2014;67(5):366-72.