QUALITY CRITERIA

This tool is intended to evaluate the quality of observational studies examining the outcomes of metformin use in patients with contraindications/precautions. Use this risk of bias tool for the following study designs: nonrandomized controlled trial, cohort studies, and case-control studies. Each item that is marked "C" applies to nonrandomized trials and cohort studies, "CC" to case-control studies, and "CS" to case-series.

Instructions for use:
1. Items are organized by risk of bias domains (selection, performance, attrition, detection and reporting bias). Rate each question using the response categories listed. Focus on study design and conduct, not quality of reporting.

2. Two questions: basic study design, sample size/power are not used in the overall ratings but are collected for descriptive purposes.

3. After answering each item, rate the study overall as "low risk of bias," "moderate risk of bias," or "high risk of bias" based on the following definitions. This overall rating is specific to the basic study design used. For example, if the basic study design was a cohort study, then the risk of bias rating would be interpreted as "For a cohort study, the risk of bias is _____."

- "**Low Risk of Bias**" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses recruitment and eligibility criteria that minimizes selection bias; has a low attrition rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. These studies will meet the majority of items in each domain.

- "**Moderate Risk of bias**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid. These studies will meet the majority of items in most but not all domains.

- "**High Risk of Bias**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

1. Basic Design

Is the study design prospective, retrospective, or mixed? *[Abstractor: Prospective design requires that the investigator plans a study before any data are collected. Mixed design includes case-control, nested case-control, or cohort studies in which one group is studied prospectively and the other retrospectively.]*

Prospective Mixed Retrospective Cannot determine

2. Selection Bias

2.1 Inclusion/exclusion criteria [C, CC, CS]

a. Are the inclusion/exclusion criteria clearly stated (does not require the reader to infer)? *[Key eligibility criteria are: age, diabetes type/level of control, use of metformin and/or other hypoglycemic medication, presence of metformin contraindication/precaution, certain comorbidities. Abstractor: use "Partial" if only some criteria are stated or if some criteria are not clearly stated.]*

Yes Partial No

b. Did the study apply valid and reliable measures to determine inclusion/exclusion criteria that were applied criteria uniformly to all comparison groups i.e., the group on metformin and the group not on metformin? *[C, CC] Pay particular attention to determination of DM2 and precaution. Measures accepted:*

T2D: ICD codes or medical record diagnosis; ≥ 2 HbA1c measures with values ≥ 6.5, **FBS values > 126 mg/dl**

Use of metformin: prescription, pharmacy database, medical record. If reported, please note whether it is incident use of metformin or prevalence of metformin use or NR in the text box.

Precautions: Age – take whatever is given; Liver disease – biopsy, imaging (fibrscan or CT), ICD codes, medical record diagnosis; CHF – echo or other cardiac imaging, ICD codes, medical record IF structured criteria (*eg*, BNP, list of symptoms, PE findings); CKD – eGFR <60, 90 days apart, ICD codes or medical record diagnosis

Yes Partial No Not applicable (no comparator)

***2.2*. Recruitment (prospective studies only)**: [Prospective Cohort]

Did the strategy for recruiting/entering participants into the study differ across study groups?

Yes No Cannot determine NA (retrospective)

2.3 Baseline characteristics similar or appropriate adjusted analysis [C]

Are key characteristics of study participants *[age, race, gender, diabetes severity, metformin contraindications/precautions, etc.]* similar between intervention and comparator groups? If not similar, did the analyses appropriately adjust for important differences *[Design: stratification, matching; Analysis: multiple regression, propensity score adjustment, etc.]*? Pay particular attention to whether the metformin precautions are

similar between groups, i.e., rates of CHF, levels of kidney function, and prevalence of liver disease.

Yes PartialNo NA (no comparison group)

2.4 Comparison Group (KQ1b/2 only) [C, CC]

Is the selection of the comparison group appropriate? *[Comparison group must include DM2 patients with a precaution of interest – then, less importantly, other DM treatment, eg, exposed to one or more non-metformin hypoglycemic medications.]*

Yes No Cannot determine NA (KQ1a)

Box given on form for comments on Selection bias:

3. Performance Bias [C, CC, CS]

Were metformin and comparison group patients treated **similarly?** Or was there a difference that might affect outcomes? If so, in selecting the population or analyzing the data, did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? For example:

a. for MALA, are there other likely causes of LA?
b. for hypoglycemia, consider use of other hypoglycemics, especially insulin, when metformin use is not the only difference between groups,
c. for A1c, are there differences in treatment other than metformin, especially insulin or very intense lifestyle intervention program?
d. for mortality or CV mortality, was overall management of other disease states comparable – HTN treatment, use of statins, etc.,
e. For MACE (major adverse cardiovascular events, *eg*, MI, hospitalization, CHF) consider that same concern about equitable treatment for other disease states between groups.

Yes Partial No Unclear NA

Box given on form for comments on Performance bias:

4. Attrition Bias

4.1 Equality of length of follow-up for participants [C, CC]

In cohort studies, is the length of follow-up similar between the groups, or appropriately accounted for using statistical techniques? For case-control studies, is the time period between the intervention/exposure and outcome the same for cases and controls?*[Abstractor: Where follow-up was the same for all study patients the answer is yes. If different lengths of follow-up were adjusted by statistical techniques, for example,*

survival analysis, the answer is yes. Studies where meaningful differences in follow-up are ignored should be answered no. A meaningful difference is more than 3 months.]

Yes **No** **Unclear** **NA**

4.2 Completeness of follow-up [C, CC]

Was there **a low rate** of differential or overall attrition? *[Attrition is measured in relation to the time between baseline (allocation in some instances) and outcome measurement. Standard for overall attrition is <20 percent for <1 year f/u and <30 percent for longer term ≥ 1 year). Standard for differential attrition is ≥ 10% absolute difference.* ***Pay particular attention it this is a KQ1 study on LA or MALA as differential drop-out is more problematic in these studies****.]*

Yes **No** **Unclear** **NA**

4.3 Attrition affecting Participant Composition [C]

Was attrition small enough that it did not result in a difference in group characteristics between baseline and follow-up?

Yes **No** **Unclear** **NA**

Box given on form for comments on Attrition bias:

5. Detection Bias

5.1 Blind outcomes assessment [C, CC, CS; doesn't apply to MALA or mortality]

Were the outcome assessors blinded to the intervention or exposure status of participants? [If outcomes based on clinical codes, then "No" unless additional review because they are determined clinically]

Yes **No** **NA (not an intervention study)**

5.2 Source of information: Outcomes

Are primary outcomes (*eg*, LA, MACE, mortality) assessed using valid and reliable measures and implemented consistently across all study participants**?**

[*LA is defined typically as blood lactate concentration >45mg/dl or 5.0mEq/L, decreased blood pH, and electrolyte disturbances with an increased anion gap**.***

***MALA is defined** as meeting the definition for LA plus either (a) elevated metformin level or (b) investigator judgment that LA is metformin-induced.*]

Yes **No** **Cannot determine (measurement not reported)**

5.3 . Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? *[Major potential confounders include: age, race, gender, diabetes severity (i.e. glycemic control and complications), comorbidities, metformin contraindications/precautions, etc.]*

Yes **Partial** **No** **Cannot determine**

Box given on form for comments on Detection bias:

6. Reporting Bias

Are findings for all primary outcomes reported? [Abstractor needs to identify all pre-specified, primary outcomes that should be reported in the study.]

Yes **Partially (some outcomes NR)** **No (Primary outcomes not pre-specified)**

Box given on form for comments on Detection bias:

7. Other Risk of Bias Issues [C, CC, CS]

No (no other concerns present) **Yes (other concerns present)**