A Checklist for Medication Compliance and Persistence Studies Using Retrospective Databases

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ABSTRACT

The increasing number of retrospective database studies related to medication compliance and persistence (C&P), and the inherent variability within each, has created a need for improvement in the quality and consistency of medication C&P research. This article stems from the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) efforts to develop a checklist of items that should be either included, or at least considered, when a retrospective database analysis of medication compliance or persistence is undertaken. This consensus document outlines a systematic approach to designing or reviewing retrospective database studies of medication C&P. Included in this article are discussions on data sources, measures of C&P, results reporting, and even conflict of interests. If followed, this checklist should improve the consistency and quality of C&P analyses, which in turn will help providers and payers understand the impact of C&P on health outcomes.

Keywords: compliance, guidelines, persistence, retrospective databases.

Purpose of this Article

Retrospective databases are increasingly being used to describe the incidence and prevalence of medication compliance and persistence (C&P) in a variety of disease states. The increasing number of studies reflects the growing concern surrounding medication C&P as well as the need to gain a better understanding of this widespread health and economic issue. The utility of these studies is in helping payers and providers see how medication C&P vary among patients and how that variation impacts health outcomes. Coupled with increased reports using retrospective databases is an expanding variability in the methods used to measure and analyze medication C&P. The numerous proxy measures of medication C&P used in these studies create a potential inconsistency that hampers the readers’ ability to apply such information to real-life practice.

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To help the readers and designers of such studies, the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) charged the ISPOR Medication Compliance and Persistence Special Interest Group (SIG) to develop a checklist of items that should be either included, or at least considered, when a retrospective database analysis of medication compliance or persistence is undertaken. The Analytic Methods Working Group of this SIG met frequently to define the appropriate elements for such a checklist. The members of this working group consist of researchers, academicians, and practitioners with a record of publication and interest in medication C&P and retrospective database analysis.

Some elements in this checklist were drawn from other ISPOR efforts related to retrospective databases and medication compliance. For example, the definitions of compliance and persistence were drawn from the ISPOR Compliance and Persistence SIG Definitions Working Group (http://www.ispor.org/sigs/medication.asp), and the broader discussion of retrospective database analyses was drawn from the Advisory Panel Report discussing methodological issues with retrospective and claims data studies [1]. Note that the terms “compliance” and “adherence” are considered synonyms, while both differ from “persistence.” Explicit definitions of compliance and persistence should, however, be provided by the researcher for individual studies (as noted later in this article).

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This document, and the accompanying checklist (Appendix A), can be used together or separately. The narrative portion reviews each of the sections of a medication C&P study and provides the reader with an explanation of the issues relative to that section. Within each section, we attempt to review the pertinent literature and provide the reader with sufficient information such that she or he would make an informed evaluation regarding the merits of a particular study. The accompanying checklist is designed to prompt the reviewer/reader about certain elements of a C&P study. (See Table 1 for an overview of the checklist framework.)

### How Should the Checklist Be Used?
This checklist should be used to aid in the evaluation of a study undergoing peer review or when a researcher is planning to develop a retrospective database study related to medication C&P. The purpose is to guide the reader/researcher through a systematic process to assure that they key issues related to retrospective database studies of medication C&P are addressed. Caution should be exercised, however, when applying this checklist. It is intended to be a guideline for either the researcher interested in conducting such a study or the reviewer of such studies to evaluate key elements of such a paper. The presence or absence of these elements is likely to affect the quality of the study; however, the absence of one or more of the checklist elements should not be interpreted as discrediting the quality of the study. It is up to the researcher and reviewer to use this checklist solely as a tool to aid them in their work, not judge it.

### Description of Checklist Elements

#### Title
The title of the study should be descriptive and reflect its purpose. Furthermore, the title should include the appropriate term(s) as represented by the study. This would include the retrospective nature of the study, the population(s) being examined, and the appropriate measure of compliance or persistence.

**Example.** Title: “A retrospective analysis of medication persistence among children taking stimulant medications for the treatment of attention deficit hyperactivity disorder (ADHD).”

#### Abstract
The title should be a short description of the study. The abstract, presented at the beginning of an article, should be a short summary of the objectives, methods, results, and conclusions. Structured abstracts require the author to follow a specific format. The purpose of the structure is to provide a systematic means of organization. Some journal editors request that the abstract be “the paper in miniature,” completely self-contained. The revised Consolidated Standards of Reporting Trials statement strongly encourages abstracts to be in a structured format to allow the reader to locate information more easily and potentially improve the quality of the abstract [2]. In this vein, the Methods section of the abstract should define the types of analyses used, and the Results section should describe the extent of the findings using those methods. The main results of the analyses should be stated numerically in the abstract. The Conclusion section should not overextrapolate the results and should only reflect the true findings of the study. Be aware that almost 5% of abstracts contain erroneous information [3]. Note that abstracts require great attention to accuracy because they are more widely available than full articles.

#### Introduction Section
The first part of the Introduction section should review the literature in the area of study. This scientific background should allow the reader to understand the rationale for the study being conducted and describe the nature of the problem or issue that the study intends to investigate. Furthermore, the scope and severity of the problem should be addressed using a clear review of the fundamental literature related to the topic being addressed, including appropriate clinical and health economic literature, along with the C&P literature.

#### Objectives and Definitions
The selection of an appropriate study objective is important because it drives the study design and variables being measured. These are important issues to address because the design and methods for the study should allow the researcher to measure appropriately the compliance or persistence variable and fulfill the objectives of the study.

Therefore, in this section of a study, the reader should find clearly stated objectives and an indication

### Table 1 Elements of the checklist

1. Title/Abstract
2. Introduction
3. Objectives/Definitions
4. Design and Methods
   a. Design
   b. Data Sources
   c. Inclusion/Exclusion criteria
   d. Measurement of Compliance
   e. Statistical Analyses
5. Presentation and Discussion of Findings
   a. Results
   b. Discussion/Conclusion
6. Disclosure of Potential Conflicts of Interest
of the primary outcome of interest. The author should indicate when compliance or persistence is the primary “outcome” of interest (the dependent variable), or being used as an explanatory or control variable to explain variance in an outcome. In either case, the author should provide explicit definitions of compliance or persistence based on a published definition with appropriate literature reference. Recommended definitions have been promulgated by the ISPOR Medication Compliance and Persistence Definitions Group and are available on the ISPOR Web site (http://www.ispor.org/sigs/medication.asp).

Data Sources
A well-described retrospective database analysis allows the reader to identify the population from which the sample is drawn. (For a full discussion of the key elements to defining the population and associated variables, the reader is referred to the ISPOR Advisory Panel Report on retrospective databases [1].) The methods for sampling need to be adequately described so the reader can infer whether the sample is representative of the population of interest. Also, a full description of the data source is important. The researcher should clearly indicate whether the data source is a public or a commercial database, or if it is not a prescription claims database (e.g., disease registry). The time frame for the data set needs to be described and the length of study should be clearly delineated so that an assessment of the appropriateness of the study period can be made in relation to the objectives.

To this end, the researcher should clearly state the inclusion and exclusion criteria for the study and describe the rationale for these criteria. To ensure that the sample represents the population of interest, the method by which the researcher verified subjects meeting the inclusion/exclusion criteria must be present and appropriate. For example, the continuous eligibility for a prescription benefit during the study period should be verified to determine whether patients had sufficient data to make a valid estimate of compliance or persistence (i.e., patients need at least two fillings of a medication to calculate a medication possession ratio). Furthermore, there should be a description of the pre-enrollment period and a determination of whether a subject was truly naive to the drug, if important to the study. The investigators should describe how the subjects were identified, including a prestudy period to determine prestudy medication use and diagnoses.

Other areas for consideration relate to the definitions used to select the subjects for inclusion. For example, did the researchers use diagnosis codes versus prescription claims to categorize patients as having diabetes? Also, if the researchers employed a matching process (if appropriate to the study design), did they describe it adequately and was it sufficient in detail to assure appropriate matching could occur? The purpose of the matching strategy is to minimize the potential for selection bias.

The researcher also needs to assure the reader that every effort was taken to protect the confidentiality of subjects, such as Institutional Review Board/Ethics Committee approval or meeting Health Insurance Portability and Accountability Act guidelines (for US studies). Coupled with this is evidence that the data
have been appropriately “cleaned” (entries that are clearly erroneous are eliminated or fixed) and that the researcher provided evidence for the reliability and accuracy of the data. The investigators should explain how cleaning/editing the data set affected eligibility, often by further excluding specific types of cases [1].

**Measurement of Compliance**

The transparency of the measurement of C&P is very important. The researcher simply stating that the method of calculating C&P is “proprietary” and cannot be disclosed is not conducive to scientific dialogue. Therefore, the methods for calculating the C&P variable should be clearly described. Every effort should be made to use standard methods for calculating C&P so that it is possible to interpret the findings of the study in context with other studies. It is important to note that the measure chosen as the C&P variable should be consistent with the objective of the study. For example, researchers interested in measuring compliance rates should not use a variable that actually measures persistence, or vice versa. There are several methods used to calculate C&P. The following are just a few. (The reader is also referred to Steiner et al. [4] or Farmer [5] for more examples.)

**Measures of compliance.** A variety of methods are used to estimate a patient's compliance using retrospective databases. One of the most common methods is to calculate the medication possession ratio (MPR). When this ratio is calculated across multiple refills, it may also be called the continuous measure of adherence (CMA) [6]. These measures are typically calculated using the basic formula noted below:

Number of Days of Medication Supplied within the Refill Interval/Number of Days in Refill Interval

This is usually calculated by summing the number of days supplied for all but the last refill, divided by the number of days between the first and the last refill. Therefore, at least two fill dates are required to calculate this ratio. Researchers, however, may choose a fixed time frame for the refill interval rather than using the last refill as the end point for the refill interval. Within most US-based prescription claims databases, the “days supply” is usually included as a data field within each prescription claim (e.g., 60 tablets of a medication that is taken twice daily would yield a 30-day supply), along with the dates that the prescription was filled or refilled. In some non-US databases, the researcher may need to estimate the days supply for each drug by applying the defined daily dose to the quantity dispensed.

Other methods include a continuous measure of medication gaps (CMG), in which the sum of the days in the gaps between refills in the observation period is divided by time between the first and last fills. This estimate provides an indication of the percentage of time the patient does not have the medication available for use. For example, the filling behavior of a cohort of patients being treated for congestive heart failure may be highly variable, resulting in numerous gaps in digoxin use. In some cases, the gaps can be negative (early fill) as well as positive (late fill). The CMG would require the analyst to add the positive and negative gaps for the period of observation. This measure provides an indication of the variability in refill behavior. An example of a study that used CMG in diabetes patients is Morningstar et al. [7].

**Measure of Persistence**

Persistence adds the dimension of time to the analysis and usually represents the time over which a patient continues to fill a prescription, or the time from the initial filling of the prescription until the patient discontinues refilling a prescription. The most common time unit is days, but could also be months or years. One means of calculating this is the estimated level of persistence (ELPT) method [8]. This calculation (below) allows the researcher to determine the percentage of individuals remaining on therapy (persistent) at a given time. ELPT may differentiate patients taking a medication sporadically during a defined time frame from those patients stopping the medication early during the same time frame [8]. The data can be displayed on a persistency curve, very similar to a Kaplan–Meier curve. The most common analysis is a Kaplan–Meier life table with discontinuation considered as elimination.

Proportion of patients refilling each subsequent prescription with (X*days supplied) from fill n.

Dezii used this measure to help differentiate patients taking a medication sporadically during a defined time frame versus those patients stopping the medication early during the same time frame.

**Proportion of days covered.** The proportion of days covered (PDC) is a measure of patient compliance that has been used with increasing frequency [9–13]. The PDC is calculated as the number of days with drug on-hand divided by the number of days in the specified time interval. The PDC may be multiplied by 100 to yield a percentage. The numerator of the PDC is not merely a sum of the “days supplied” by all prescriptions filled during the period. Rather, filled prescriptions are evaluated using a set of rules to avoid double-counting covered days. Thus, the PDC is always a value between 0 and 1. The denominator for the PDC is typically a clinically meaningful number of days that is the same for all intervals and patients (e.g., 90 days). The PDC can be analyzed as a continuous measure or divided into categories for use as an ordinal or dichotomous variable. When measured repeatedly
and analyzed using appropriate statistical methods for within-subject repeated measures, the PDC has the advantage of simultaneously reflecting both C&P. Data based on this approach are frequently described in a figure to illustrate time trends.

**Other measures of persistence.** Alternative analyses include number of days to discontinuation and number of prescription refills over a period of time. The days to discontinuation is a simple count of days from the index prescription to the date of the final dispensing, although some researchers include the days for which the final fill provided dosing (e.g., final 30 days). The number of refills, usually within 12 months of the index fill, could include patients who refill long after the allowed 30- or 60-day gap for being considered nonpersistent. This is a valuable calculation for drugs that may be used “as needed” without detriment to the clinical condition (e.g., treatments for seasonal allergy).

**Measurement issues.** The researcher needs to account for the how anomalous values were handled. Some measures of C&P allow for the calculation of “hypercompliant” values (e.g., MPR > 1 or negative gaps). The researcher should describe how and why these values were incorporated into the analysis. If an atypical method is used for calculating compliance, the researcher should report the rationale for the new method along with the formula for its calculation. Similarly, when the researcher collapses multiple medications into a single compliance estimate, the rationale and formula for this variable should be included. Examples of this are when the average MPR or gap across different medications is used to estimate overall compliance. If the researcher uses this strategy, then the analysis should also control for the influence that varying numbers of medications can have on the compliance variable itself.

The Methods section also should explain how the analysis handled patients who switched to another medication in the same class (e.g., another phenothiazine) or one that is used for the same diagnosis (e.g., an atypical antipsychotic) [14]. For example, did the researcher drop those patients who switched drugs within the same class, or did the researcher estimate the “equivalent” dose of the two drugs and allow the patient to remain in the analysis. Furthermore, there should be some estimation of whether the method used for handling this variable was appropriate for fulfilling the study objective. Some researchers have categorized a drug-therapy switch as nonpersistence because it involves discontinuation of the initially selected drug. Nevertheless, because the term “persistence” is typically used to describe a patient’s behavior, referring to a treatment switch as nonpersistence may suggest that the patient failed to take the product as directed even though the patient followed the directions appropriately.

If the drug is not an oral solid dosage form (e.g., capsules or tablets), alternative methods are needed. For example, the dose of liquid, powdered, injected, and inhaled drugs may be prescribed in a way that leaves the patient with an under- or oversupply of drug at the end of the month. An attempt should be made to calculate an adjustment for wastage from the dispensing container, particularly for inhaled and injected drugs. For example, insulin wastage was estimated to account for higher than expected compliance in one study [15].

**Statistical Analyses**

The distribution of the dependent variable must be considered when selecting an appropriate statistical test. The researcher should determine the best type of statistical test based on the type of data and their distribution. In general, parametric tests are preferred, but if the assumptions underlying a specific parametric test are violated, then a nonparametric equivalent should be employed. Nonparametric tests should be employed when

- the data are measured and/or analyzed using a nominal or ordinal scale of measurement;
- the probability distribution of the statistic is not normally distributed.

When there is a cap on the MPR (e.g., maximum = 1), there may be a violation of the normality assumption, and therefore a nonparametric test should be considered. Similarly, if all the gaps in a gap analysis are converted to “no gaps” or “0,” this also may violate the normality assumption. When subjects are categorized as “compliant” and “noncompliant” (e.g., when using a cutoff within the MPR to create the categories), a nonparametric test should also be used.

In general, it is not wise to convert continuous data to categorical data. Statistically, there is a loss of power because of a decrease in the number of degrees of freedom (ANOVA models). Conceptually, dividing the data into arbitrary categories limits the utility of the information. It may be appropriate to use categorical data for a logistic regression, but with caution about the definition. If continuous data are converted to categorical data, the rationale for selection of cutpoints should be provided and consistent with existing evidence for compliance in the selected population. The point at which discrimination is made for categorical definitions of compliance versus noncompliance should have been determined with a sensitivity analysis. An adequate discrimination of a cut-point has been made for few medications. One example is the need to take more than 95% of antiretroviral medication doses to avoid the development of resistance [16]. Few other
investigations have looked at outcomes above and below the postulated categories.

Researchers should be careful when using any categorical cut-point (commonly listed as 80%) unless they can document the clinical validity of the number as well as determine that that lower and higher values differ (sensitivity test). Selection of a cut-point usually requires information that patients taking more than this amount of medication have a clinically better outcome than patients taking less. This is not a statistical test but a clinical test of relevance. There are very few medications for which a cut-point has been determined.

If the researcher makes multiple comparisons using the same data, there should be an adjustment made to maintain the experiment-wise alpha error at the prespecified level. Examples of appropriate adjustments include Bonferroni adjustment for multiple comparisons or the use of a post hoc test (e.g., least significant difference, Tukey’s, Duncan’s, Scheffe’s) after determining a significant F-value in an ANOVA.

Realistic power and/or sample size calculations should be described. If the researcher did not achieve the prespecified sample size, a recalculation of the power based on the actual results might be appropriate. There is controversy, however, regarding this approach. Others suggest that confidence intervals be calculated so that the readers can interpret the results on their own [17].

Furthermore, the researchers should make an attempt to control for bias in the data set. Bias can come in a variety of forms, including selection bias and measurement bias. The research should address how the potential for bias was handled. For example, propensity scoring is a technique used to control for systematic differences between groups by reducing the differences between groups to a single variable [18]. The researchers should explain the variables they chose to generate the propensity score and the results of the scoring. The researchers should indicate whether the covariates used in the process were balanced between the two groups, and if not, what steps they took to produce balance.

If the researcher is evaluating an association between compliance and another variable, he or she should attempt to control for other variables that may confound the association being studied. To determine which variables directly affect compliance and which variables have mediating effects, the author should consider statistical techniques that facilitate answering the question. Such techniques include multivariate regression. To establish mediation, each variable is regressed in a hierarchical forward stepwise fashion on all other variables that precede it in the causal chain.

The risk of misleading results increases as the ratio of independent variables to the number of patients increases. Therefore, the researcher should consider what variables act as confounders and which variables are covariates and should be controlled for accordingly in an analysis. Typical variables that may confound the measure of compliance include cost of medication, comorbidities, severity of illness (as measured by the Charlson comorbidity index or the chronic disease score), sex, and other sociodemographic factors [19,20]. Before adjusting for any variables, it is suggested that the researcher undertake a thorough review of the literature to establish variables that are known confounders within the disease state being studied and which covariates may show trends but are not known confounders. Establishing this a priori will also help guide the analytical plan. The researcher should attempt to maintain an alpha at 0.05, recognizing that often we have to deal with small sample sizes in our studies and that sometimes the analysis is exploratory in nature.

**Presentation and Discussion of Findings**

**Results**

The results section should begin by stating the characteristics of the C&P variable. The reader should know the distribution of the variable (e.g., normally distributed) and whether the distribution matches the intended statistical tests. If not, the researchers should indicate what adjustments were made to transform it into a usable variable (e.g., log transformation to improve normality). The data should have the accompanying variability measure (e.g., mean for continuous data, medians for categorical data, or effect sizes/confidence intervals). If the data were subjected to statistical tests, the resulting statistic and associated P-values and/or confidence intervals should be appropriately displayed. The number of subjects (n) for each variable should be prominently displayed in all tables and graphs and the graphs should be constructed with appropriate scales to avoid misleading the reader.

**Discussion**

Within the discussion section, there should be a statement of the principal findings for the primary outcome, without excessive extrapolation beyond these results [21]. As such, this is the section of the report where the researchers place the results into context with the existing literature. The findings of this study should be compared with the findings of similar studies, and comparisons between populations, methods, and results should be made. Also within this section, the study limitations and their impact on the outcome of the study should be noted and discussed [2,21,22]. For example, the researchers should discuss the influence of the decision to retain values or cap values. Evidence of whether the final results are influenced heavily by retaining versus capping these values is valuable. Furthermore, this section should include a review of
the statistical power of the study, and the associated sample size should be mentioned as well as any source of bias.

The Discussion section should include an overview of the limitations of the analysis and interpretation of results from a retrospective database analysis. This includes a need to discuss the external validity of the results by taking into consideration the population of patients reviewed and how the inclusion/exclusion criteria may have impacted the results. In particular, the selection of patients, number of months to ascertain lack of previous use of medication, and number of months of follow-up should be defended. If the patients were selected by diagnostic codes, the accuracy of the codes should be supported. Most important is the need to explain the study design so that the reader does not perceive an intrinsic bias to favor a drug or class of drugs. This speaks to a need to address the internal validity of the study, and the researcher must openly discuss the limitations inherent in any retrospective analysis and how they apply to this particular situation.

Lastly, the researcher has the responsibility for placing the results of the research in context with the existing information. As such, this section should address, if appropriate, the implications of the findings as they may relate to health-care outcomes or health policy or how they support the need for further research.

Disclosure of Potential Conflicts of Interest

The study should include a statement regarding the researcher’s potential for conflict of interest. Conflict of interest refers to a self-interested financial benefit a researcher has in the product or technique being studied [23,24]. Notation of this is particularly important where the study has a commercial sponsor with a vested interest in finding the superiority of one product [23,24]. Although disclosure of this nature may not prevent the bias from being introduced, it allows the reader to assess the objectivity of the investigators and their research. Studies that are obviously biased in design to elicit the most favorable characteristics of the sponsor’s drug do a disservice to the community of health-outcomes researchers.

Conclusion

This report summarizes the consensus of international thought about how to perform retrospective analyses of administrative databases related to taking medication. This is a first step in the process undertaken by the ISPOR Medication Compliance and Persistence SIG. A key to understanding appropriate methodological approaches is the adoption of the definitions of medication compliance (synonym: adherence) and persistence developed by ISPOR, particularly to acknowledge that they are separate constructs. Working in coordination with other groups, additional methodological approaches will be prepared for prospective studies of medication C&P, as well as economic analyses of these issues. ISPOR will provide this checklist to journal editors with the expectation that future research will follow the standardized structure to allow a reasonable review of manuscripts as well as comparisons among published reports. Within time, the current heterogeneity of analyses will become a more uniform presentation of data to help providers and payers understand the impact of C&P on health outcomes.

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References


Appendix—Checklist for Assessing/Evaluating Medication Compliance and Persistence Studies Using Retrospective Databases

Title/Abstract
- The title is descriptive and reflective of the purpose of the study.
- The abstract is a short, concise description, commensurate with the journal’s standards.
- Abstract follows a structured format (as appropriate to the journal) and includes at least the following:
  - Objectives;
  - Methods;
  - Results;
  - Conclusions.
- The abstract accurately reflects the contents of the study and there are no discrepancies.

Introduction
- The author(s) clearly reviewed fundamental literature related to topic being addressed.
  - Appropriate clinical literature;
  - Appropriate compliance and persistence literature;
  - Appropriate health economic literature;
  - Other ____________ (specify).
- Objective of study clearly stated.

Objectives and Definitions
- The objective(s) of the study has been clearly stated and can be readily identified as one of the following:
  - Exploratory;
  - Descriptive;
  - Analytical.
- There is an explicit definition of the compliance and persistence variable and the definition used is based on a published, accepted definition.
- Compliance or persistence is the primary “outcome” of interest or
- Compliance or persistence is being used as an explanatory or control variable to explain variance in another outcome.

Design and Methods
Design
- The design is clearly stated.
- The design matches the objectives.

Data Sources
- All of the data sources have been described adequately.
- The time frame for data has been clearly stated.
- The methods for sampling the population are well described.
- The data have been appropriately “cleaned” (i.e., erroneous data were fixed or removed).
- There is evidence for the reliability/accuracy of the data.

Inclusion/Exclusion Criteria
- The inclusion and exclusion criteria for the study are clearly stated.
- The rationale for these criteria is described.
- The method by which the researchers verified subjects meeting the inclusion/exclusion criteria is stated and appropriate.
• Continuous eligibility for drug benefit during the study period was verified.
• Patients had sufficient data to make a valid estimate of compliance.
• For studies of patients who are newly initiated on a drug regimen, there was an examination of data from a sufficient pre-enrollment period to ensure that the subject was truly naive to the drug.
• The duration of the study period is appropriate to the objectives of the study.
• There is evidence for protecting the confidentiality of subjects.
• The matching process, if appropriate to the study design, is well described.
  ○ Matching strategy minimizes the potential for bias;
  ○ Propensity scores used to control for selection bias.

Measurement of Compliance
• The methods for calculating the compliance or persistence variable are clearly described.
• The measurement matches the operational definition provided earlier.
  ○ Do the objectives indicate that the study is to measure compliance but persistence is actually calculated?
• Standard methods are used for calculating compliance.
  ○ Continuous measure of medication availability/medication possession ratio (MPR).
    • The researchers explained how they handled values greater than 1.
      • Were the values retained or converted to 1?
  ○ Gaps methods (continuous measure of medication gaps).
    • The researchers explained how they handled negative gap values.
      • Were the values retained or converted to 0 (no gap)?
  ○ Proportion of days covered.

Standard Methods for Calculating Persistence
• If an atypical method is used for calculating compliance, the rationale/formula for the new method is provided.
• The researchers provided an appropriate explanation for how patients who switched drugs within, or between, therapeutic classes were handled.
• If multiple medications were included within a single compliance or persistence estimate, the researchers provided a rationale and/or a formula for this variable.
  ○ The average of the MPR/gap across the different medications was used.
  ○ The analysis controlled for the influence of how many medications were combined into a single variable.
    • Was another variable created to indicate whether the patient was on one drug for diabetes versus multiple drugs for diabetes?
    • Is there a logical argument for combining the MPRs? It may be more appropriate to combine the MPRs for drugs that treat the same condition (e.g., combining the MPR for two drugs for diabetes) as opposed to combining the MPRs for drugs used for different conditions.

Statistical Analyses
In general, the use of continuous data to measure compliance and persistence are encouraged.
• If continuous data are converted to categorical data, the rationale for the selection of cut-points should be provided and consistent with existing evidence for compliance in the selected population (e.g., cut-point of 95% may be most appropriate for antiretrovirals, but 80% may be appropriate for hypertension).
• The tests are appropriate given the objectives, design, and the nature of the data.
• Appropriate adjustments for multiple comparisons were conducted.
• Appropriate adjustments were made to the analyses if the data were not normally distributed.
• Power and/or sample size calculations are presented and appropriate.
• There was an attempt to control for selection bias (e.g., propensity scoring).
• If the researcher is evaluating an association between compliance or persistence and another variable, the researcher attempted to control for other variables that may confound the association being studied.

Presentation and Discussion of Findings
Results
• The distribution of the compliance or persistence variable is presented.
• Test statistics and confidence intervals are appropriately presented in addition to P-values.
• The number of subjects is clearly identified in tables and graphs.
• Graphs were constructed with an appropriate scale.

Discussion/Conclusion
• The limitations are appropriately noted and the implications of the limitations are discussed.
  ○ The influence of the decision to retain values or cap values is discussed.
• Power and sample size limitations are addressed.

• The findings of this study are placed in the context of our existing knowledge of the subject.

• Appropriate comparison of the current findings to that of similar studies is made.

• The findings and conclusions are related to the objectives of the study.

Disclosure of potential conflicts of interest

• Potential conflicts of interest are disclosed.