

# Comparison of adherence measures using claims data in the South African private health sector

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**Background.** Medication adherence measurement is becoming increasingly important. Biological assays and markers, directly observed therapy, self-reports, pill counts and surveys have been successfully used to assess adherence under various circumstances, but may be limited by cost, ethical concerns and self-reported bias. Administrative claims data, in addition to offering a solution to these limitations, provide access to large study populations under real clinical practice situations, and in a timely and effective manner. With the wide range of adherence measures determined from claims data available – some of which have been found to be mathematically equivalent – researchers are often faced with the decision of choosing which is appropriate. An assessment of the various measures is therefore important for better understanding and to facilitate future adherence studies using administrative data.

**Objectives.** To compare different adherence measures using data from a medicines claims database in South Africa (SA), employing montelukast for the purpose of illustration.

**Methods.** This retrospective, cross-sectional research used data from 1 January 2006 to 31 December 2015 from a privately owned pharmaceutical benefits management (PBM) company in SA. Claims for montelukast were identified and adherence was determined using the continuous multiple-interval measure of oversupply (CMOS), compliance ratio (CR), modified medication possession ratio (MPR<sub>m</sub>), refill compliance rate (RCR), continuous single-interval measure of medication acquisition (CSA) and proportion of days covered (PDC) capped at 1. The measures were compared with the medication possession ratio (MPR) as the reference.

**Results.** The MPR, CMOS and CR were equivalent, each yielding an adherence value of 86%. The MPR<sub>m</sub>, RCR and average CSA yielded higher adherence values of 96.9%, 117.2% and 129.0%, respectively, whereas the PDC produced a lower adherence value of 76.0%. The measures that used the entire study period as the denominator produced consistent results compared with the measures that used the difference between claims dates as denominator.

**Conclusions.** The MPR is considered the most widely used metric to measure adherence using administrative data, but it may not always be applicable owing to the type of data available. Adherence computed using the CR, CMOS and PDC capped was found to be comparable to the MPR, and they may therefore be used as alternatives.

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Adherence to medication is the degree to which the drug-taking behaviours of patients agree with recommendations by the prescriber.<sup>[1]</sup> The measurement of adherence is becoming increasingly important, as it is critical to the success of pharmacotherapy.<sup>[2-5]</sup> There are several methods of computing adherence, and these include, *inter alia*, the use of biological assays and markers, directly observed therapy, self-reports, pill counts, use of surveys, questionnaires and electronic medication packaging.<sup>[2,4,6-11]</sup> These methods, although beneficial, may be limited by cost,<sup>[6,10,11]</sup> ethical concerns<sup>[11]</sup> and self-reported bias.<sup>[6,7,10]</sup> Administrative claims data offer an inexpensive, efficient and non-invasive means by which adherence can be measured.<sup>[2,4,9]</sup>

In addition, administrative claims databases provide access to large populations for study under real clinical practice situations, and in a timely and effective manner.<sup>[12-15]</sup> Compared with other sources of data for health research, data obtained from such databases are less susceptible to recall and interviewer bias and can be linked to other databases,<sup>[14]</sup> such as medical records databases, to facilitate the determination of adherence. However, the use of administrative databases for measuring adherence has some inherent disadvantages. Administrative datasets estimate adherence based on medication possession and not consumption,<sup>[4]</sup> since they are unable to determine patients' intake of prescribed and dispensed medications.<sup>[2]</sup> Grégoire

and Moisan<sup>[1]</sup> add that dispensing data depend on conditions of reimbursement and will therefore not measure adherence to medications purchased over the counter and those not covered by a healthcare scheme. Adherence determined solely by claims data may mask periods of over- and under-utilisation of medications.<sup>[11]</sup> Successful use of administrative claims data for estimating adherence requires that all relevant information is recorded accurately, and patients are eligible for the medication of interest during the period of study to allow for valid conclusions to be made.<sup>[9]</sup>

Although several measures have been proposed to estimate adherence using medicines claims data and validated using other methods such as patient reports and pill counts, there are no specifications for their mathematical calculation.<sup>[16]</sup> With the wide range of adherence measures available, researchers are often faced with the decision of choosing which is appropriate.<sup>[16,17]</sup> Some adherence measures have been identified to be mathematically equivalent, yielding similar adherence values.<sup>[16]</sup> Hess *et al.*<sup>[4]</sup> suggest that it may not be necessary to have a variety of measures currently employed to assess adherence when administrative claims are used. An assessment of the various methods is therefore important for better understanding and to facilitate future adherence studies using administrative data.

## Objectives

To the best of our knowledge, no study has been published on the use of secondary data for the comparison of different adherence measures in South Africa (SA). This study aimed to use claims data from a medicines claims database in SA to illustrate the comparison of different adherence measures. Montelukast was employed for the purpose of illustration.

## Methods

### Study design

We performed a quantitative cross-sectional study analysing medicines claims data that are nationally representative for a 10-year period (1 January 2006 - 31 December 2015).

### Data source and study population

We employed nationally representative medicines claims data obtained from a privately owned SA pharmaceutical benefit management (PBM) company. This PBM is a large independent company that has been providing medicine claims processing services to about 1.6 million beneficiaries of about 42 medical schemes in South Africa for over 25 years. The data obtained represent about one-third of the SA patients registered with private medical aid schemes.<sup>[18]</sup>

We employed information on prescribed medications dispensed to patients, including the active pharmaceutical ingredient, quantities dispensed, number of days' supply and the prescription fill date, as well as *International Classification of Diseases*, 10th revision (ICD-10) codes for diagnoses.

All patients who had a diagnosis code (ICD-10 code J45) for asthma in conjunction with at least two consecutive claims for montelukast based on the National Pharmaceutical Product Index (NAPPI) code 10.4.2, provided by the MIMS,<sup>[19]</sup> during the study period were included in the research. Patients had to be enrolled

continuously with the PBM throughout the study period. A total of 9 141 claims for montelukast were analysed.

## Study measurements

### Measuring adherence

The medication possession ratio (MPR) is one of the most extensively used measures of adherence based on claims data.<sup>[2,17,20,21]</sup> Karve *et al.*<sup>[21]</sup> proposed that researchers consider the MPR first for the calculation of adherence, since several studies have discovered it to be valuable as an adherence measure.<sup>[2,17,22]</sup> Although the MPR is easy to compute and interpret, it may mask periods of oversupply.<sup>[2,17]</sup> There is currently no perfect adherence measure using claims data,<sup>[23]</sup> but the MPR serves as an acceptable standard against which other measures can be assessed. For this study, the MPR was used as a reference to which other measures of adherence were compared.

Six adherence measures,<sup>[4]</sup> namely the proportion of days covered (PDC) capped at 1, refill compliance rate (RCR), compliance ratio (CR), modified medication possession ratio (MPRm), continuous multiple-interval measurement of oversupply (CMOS) and continuous single-interval measure of medication acquisition (CSA) averaged over the period of observation were determined, three of which (capped PDC, MPRm and average CSA) were compared with the MPR using Bland-Altman plots. In interpreting the results, smaller bias levels together with narrow limits of agreements were considered representative of more equivalent measures than larger wide values with wider margins. The mathematical formulae for the determination of these adherence measures are described in Table 1.

### Statistical analysis

SAS system version 9.4 (SAS Institute Inc., USA) was used to compute the means and standard deviations of the various measures. Bland-Altman plots, plotted using SPSS version 25 (IBM Corp.,

**Table 1. Mathematical formulae for adherence measures**

Adherence measure	Formula
MPR	$\frac{\text{Number of days' supply in index period}}{\text{Number of days in the study period}}$
PDC capped	$\frac{\text{Number of days' supply in index period}}{\text{Number of days in the study period}}$ , whereby oversupply is truncated so that the adherence value obtained does not exceed 1
RCR	$\frac{\text{Number of days' supply}}{\text{Last claim date}} \times 100$
CR	$\frac{\text{Number of days' supply in index period} - \text{last refill's supply}}{\text{Last claim date} - \text{index date}}$
MPRm	$\frac{\text{Number of days' supply}}{\text{Last claim date} - \text{index date} + \text{last refill's supply}} \times 100$
CMOS	$\frac{\text{Total days of treatment gaps (+) or surplus (-)}}{\text{Total days to next fill or end of observation period}}$
Average CSA	$\frac{\text{Days' supply obtained at the beginning of the interval}}{\text{Days in the interval}}$

MPR = medication possession ratio; PDC capped = proportion of days covered, capped; RCR = refill compliance rate; CR = compliance ratio; MPRm = medication possession ratio, modified; CMOS = continuous multiple-interval measure of oversupply; Average CSA = continuous single-interval measure of medication acquisition, average; Last refill's supply = the amount supplied at the last prescription/claim (30 or 60 tablets, etc., i.e. 1 month's supply of medicine).

USA), were used to compare selected adherence measures against the medication possession ratio as reference category.

**Ethical considerations**

The study was approved by the Health Research Ethics Committee of North-West University (ref. no. NWU-00179-14-A1-06) and the board of directors of the PBM.

**Results**

Table 2 depicts the values for each adherence measure. The MPR and CR resulted in an adherence of 86.4%. Adherence values for PDC, modified MPR, RCR and CSA, averaged, were 74.0%, 96.6%, 117.2% and 129.1%, respectively. The value for CMOS, the gap measure evaluated, was 0.136.

Results from Bland-Altman plots for MPR as reference category against MPRm, average CSA and PDC are presented in Table 3. Varying degrees of equivalence were observed between MPR and each of the measures to which it was compared. Against PDC capped, there was a stronger agreement as evidenced by the small bias value (0.02) as well as narrow limits of agreement (-0.11 - 0.15). However, this was not the case with the MPRm, for which there was a wide limit of agreement (-42.97 - 2.06).

**Discussion**

This large cross-sectional study produced four key findings. Firstly, the study showed that two measures (CR and CMOS) produced equivalent mean adherence to the MPR. The observation confirms the results of the study by Hess *et al.*<sup>[4]</sup> in which CMOS and MPR produced the same mean values, but is contrary to the same study's finding of significant difference between the CR and MPR. This variation in findings can be attributed to the different ways in which the variables were defined for computing the measures. The formulae by which the MPR, CMOS and CR were calculated were almost the same, requiring the same variables and therefore resulting in adherence values that were equivalent. The CMOS, being a gap measure, produced a value of 0.14, which is equivalent to adherence levels of 0.86 in non-gap methods. For gap measures, adherence values closer to zero represent better adherence levels.<sup>[21]</sup>

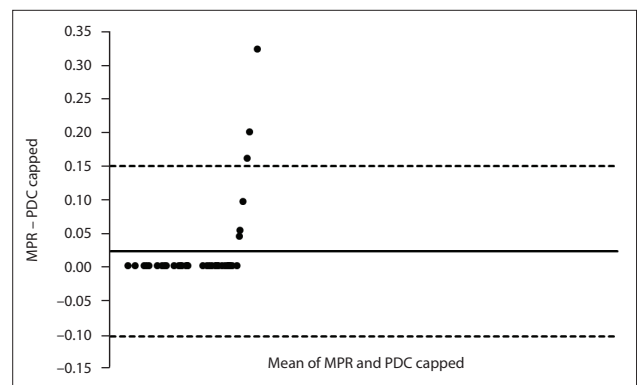
**Table 2. Adherence values for the cohort (N=9 141)**

Adherence measure	Mean (SD)
MPR	0.86 (1.44)
PDC capped	0.76 (0.25)
RCR, %	117.15 (281.08)
CR	0.86 (1.44)
MPRm, %	96.60 (35.61)
CMOS	0.14 (1.44)
Average CSA	1.29 (2.11)

SD = standard deviation; MPR = medication possession ratio; PDC capped = proportion of days covered, capped; RCR = refill compliance rate; CR = compliance ratio; MPRm = medication possession ratio, modified; CMOS = continuous multiple-interval measure of oversupply; Average CSA = continuous single-interval measure of medication acquisition, average.

Secondly, it was also observed that besides the capped PDC, which produced adherence values lower than the MPR, all the other measures (Table 3) resulted in adherence values greater than the MPR (average CSA>>>RCR>>MPRm>MPR), a trend consistent with results of earlier studies.<sup>[4,20]</sup> The PDC capped resulted in adherence values lower than those from the MPR because this measure uses the total study period and does not consider excess medication on hand at the termination of the study. We observed a strong agreement between MPR and PDC capped for adherence values <1 (Fig. 1), as most of the data points that correspond with mean values <1 showed zero difference between these measures. This is also evidenced by a small bias value of 0.02 and the narrow range between the limits of agreement (-0.11 - 0.15). Consequently, our results show that MPR and PDC capped are equivalent when adherence is <1, where there is no oversupply or excess medication on hand. In the event of adherence values >1 (oversupply) as shown in Fig. 2, however, there is an increasing difference with increasing mean. MPR therefore consistently produces values higher than PDC capped with increasing adherence. The presence of patients with some degree of medication oversupply in our investigation may therefore be the reason for the higher mean MPR value relative to the mean value of capped PDC.

The RCR evaluates the time period between dispensations instead of the entire study period, leading to a denominator which is smaller compared with that for measures that consider the entire period. This results in an overestimation of adherence reflected by the high mean RCR value. To overcome the drawback of RCR in overestimating adherence, the MPRm, which also assesses the period between fills, includes number of days equal to the number of days' supply of medication acquired at the last dispensation. This addition of days assumes that the patient is completely adherent during the period to be covered by the last dispensation, accounting for its relatively high



*Fig. 1. Bland-Altman plot of MPR v. PDC capped, showing good agreement in the adherence determined using the two measures. The plot depicts data from 40 patients randomly selected from the study population. The mean of the adherence values determined using both MPR and PDC capped for each patient (x-axis) was plotted against the difference between these same adherence values (y-axis). Solid lines represent bias, while the dashed lines represent the lower and upper limits of agreement. (MPR = medication possession ratio; PDC capped = proportion of days covered, capped.)*

**Table 3. Comparison of adherence measures**

	Bias (SD)	Lower limit of agreement	Upper limit of agreement
MPRm	-20.46 (11.49)	-42.97	2.06
PDC capped	0.02 (0.07)	-0.11	0.15
Average CSA	-0.59 (1.26)	-3.06	1.88

SD = standard deviation; MPRm = medication possession ratio, modified; Average CSA = continuous single-interval measure of medication acquisition, average.

value compared with the MPR. There is some degree of agreement between MPR and MPRm, as most data points fall within the limits of agreement (Fig. 2). A bias of  $-20.46$  together with the wide range of limits of agreement between  $-42.97$  and  $2.06$ , however, suggests that the MPR and MPRm are not equivalent. The difference between the MPRm and MPR can be attributed to their difference in denominator and the consideration of the last dispensation in the computation of the MPRm.

In the calculation of the CSA, adherence for each dispensation period is calculated independently and averaged. The number of refills affects the weight of adherence in the cumulative analysis, so patients with single refills will not have the same weight as those with multiple refills. Patients' receipt of medications close to the end of the study period leads to bias, as this is reflected as an oversupply and accounts for the measure's high adherence values. This measure does not allow a carryover of excess medication from one refill interval to another, a very likely event in practical settings.<sup>[4,21]</sup> The MPR and average CSA also exhibit an agreement, as most data points fall within the limits of agreement (Fig. 3). With a bias of  $-0.59$  and a range of limits of agreement between  $-3.06$  and  $1.88$ , the two measures can be said to be fairly equivalent. For mean adherence  $>2$ , it can be noticed that there is decreasing difference with increasing mean, the MPR consistently producing smaller values than the average CSA.

Thirdly, it was interesting to note that the definition of the denominator was critical to the results obtained from measure computations. Similar to what has been found by Hess *et al.*<sup>[4]</sup> and Karve *et al.*,<sup>[21]</sup> adherence measures that presented the entire study period as the denominator (MPR, PDC capped and CMOS) in our study ensured uniformity and consistency, as opposed to measures that used the time between dispensations as the denominator. The measures that estimated the denominator as the difference between refills do not provide a uniform denominator. These measures may overestimate adherence since they may not be able to account for patients who discontinued medications early, resulting in overestimation of adherence for such patients.<sup>[21]</sup>

Finally, it was observed that an appropriate choice of adherence measure depends largely on the data available to the researchers. The variables required as well as the complexity of calculations are features that also need to be considered. Determination of the variables for computation of adherence is critical to the accuracy of results in assessing adherence using these measures.<sup>[3,4,24]</sup> Days' supply must be cautiously estimated. Depending on the available data, this can be determined as the quotient of the prescribed dose and the number of units of the drug dispensed.<sup>[3,4]</sup> The number of evaluation days is also essential in the calculation of adherence measures. It is therefore important to determine *a priori* the time frame for the evaluation of adherence to obtain consistent values.

### Study limitations

A notable limitation of this study was that the data used were intended for reimbursement purposes and not for research purposes, and may therefore lack certain data fields that would be relevant for the calculation of adherence methods, such as the exact number of days for which drugs were supplied. However, this limitation can be overcome by appropriate determination of variables for the computation of adherence and cautious estimation of supply and evaluation days based on the available data. Again, the use of administrative claims data limits the ability to draw definitive

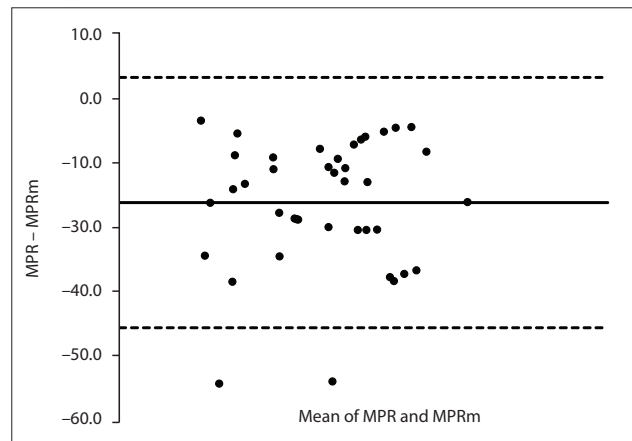


Fig. 2. Bland-Altman plot of MPR v. MPRm, showing poor agreement in adherence values determined using the two measures. The plot depicts data from 40 patients randomly selected from the study population. The mean of the adherence values determined using both MPR and MPRm for each patient (x-axis) was plotted against the difference between these same adherence values (y-axis). Solid lines represent bias, while the dashed lines represent the lower and upper limits of agreement. (MPR = medication possession ratio; MPRm = medication possession ratio, modified.)

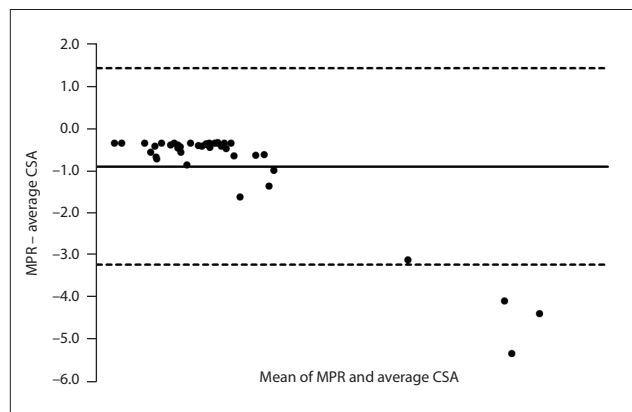


Fig. 3. Bland-Altman plot showing agreement in adherence computed using the MPR and average CSA. Data from 40 patients randomly selected from the study population were employed in this plot. The mean of the adherence values determined using both MPR and average CSA for each patient (x-axis) was plotted against the difference between these same adherence values (y-axis). Solid lines represent bias, while the dashed lines represent the lower and upper limits of agreement. (MPR = medication possession ratio; CSA = continuous single-interval measure of medication acquisition.)

conclusions from such methods. Careful considerations must therefore be made in making inferences about results of studies that utilise administrative claims data, and these must be made in the context of the data sample used.

### Conclusions

Data extracted from administrative databases ultimately determine the adherence measures that can be used. The most extensively used measure is the MPR. From this study, we found that adherence computed using CR, CMOS and PDC capped was equivalent to that obtained from MPR. Researchers can therefore consider the use of these measures when the MPR cannot be appropriately used.

**Declaration.** The research for this study was done in partial fulfilment of the requirements for MO-K's Master of Pharmacy in Pharmacy Practice degree at North-West University.

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**Author contributions.** JRB and MSL conceptualised the research; MC and MSL conducted the data and statistical analyses; and MO-K was responsible for data interpretation and manuscript write-up under the supervision of JRB, MSL and MC.

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**Conflicts of interest.** None.

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