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# Proposal of Standardization to Assess Adherence With Medication Records: Methodology Matters

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## Abstract

**Background**: Medication adherence is the process by which patients take their medication as prescribed and is an umbrella term that encompasses all aspects of medication use patterns. Ambiguous terminology has emerged to describe a deviation from prescribed regimen, forcing the European ABC Project to define three phases of medication use: "Initiation, Implementation, and Discontinuation". However, different measures of medication adherence using medication records are currently available that do not always distinguish between these phases. The literature is lacking standardization and operationalization of the assessment methods. **Objective**: To propose a harmonization of standards as well as definitions of distinct measures and their operationalization to quantify adherence to medication from medication records. **Methods**: Group discussions and consensus process among all coauthors. The propositions were generated using the authors' experiences and views in the field of adherence, informed by theory. **Results**: The concepts of adherence measures within the new taxonomy were harmonized, and the standards necessary for the operationalization of adherence measures from medication records are proposed. Besides percentages and time-to values, the addition of a dichotomous value for the reinitiation of treatment is proposed. Methodological issues are listed that should be disclosed in studies on adherence. **Conclusions**: The possible impact of the measures in adherence research is discussed. By doing this, the results of future adherence research should gain in accuracy. Finally, studies will become more transparent, enabling comparison between studies.

## Keywords

adherence, medication, standards, measurements, operationalization

## Introduction

Medication records are increasingly collected worldwide and available from different sources such as prescribing, dispensing, or reimbursement databases. The ready availability of these records has stimulated widespread use of these data to study patterns of medication use and assess medication adherence in daily clinical practices. Medication records often contain several elements required to calculate the number of days' supply, such as the date of prescribing or dispensing, the quantity dispensed, and the prescribed daily dosage (PDD). Differences in information that is available may exist between Europe and the United States. As an example, the instructions to patients (ie, the daily dosage information, such as, "Take 1 tablet 2 times daily") are rarely contained in US prescription claims. Nevertheless, the US data set might

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have the days' supply included when the pharmacy staff has access to the dosing instructions and calculates the days' supply with its subsequent entry into the computer processing system. Nevertheless, calculations with medication records represent a simple approach to determine how much of the prescribed medications are being taken (ie, adherence) and for how long (ie, persistence). These measures have intuitive appeal, and their value in clinical research has been shown.[1,2] They are objective, noninvasive, and economical for use in large populations because they can be easily derived from data routinely collected for administrative or other purposes. The reported calculations of adherence from medication records are indubitably based on the above-mentioned elements, but specification of standards for these calculations is missing.[3-5] In the absence of any gold standard, no less than 11 different methods for calculating adherence were identified by Hess et al,[6] the most often used being the MPR (medication possession ratio) and the proportion of days covered (PDC).[7] When applying the 11 different calculation methods to the same set of pharmacy data, Hess et al[6] obtained adherence rates ranging from 63.5% to 104.8%, demonstrating the dramatic influence of the methods on the computed adherence values. Wilke et al[8] identified 47 publications with pharmacy claims using 12 different calculation methods. When applied to a simulation with reimbursement data of 113 108 patients, the adherence ranged between 15.7% and 97.0%. In fact, of the 47 publications, only 4 named all the elements that were included in the calculations.[8] Similarly, Caetano et al[3] identified 5 different methods for calculating persistence, which resulted in a wide range of values and interpretations when applied to a hypothetical patient. In some cases, 1 isolated refill beyond the 360 days following treatment start was sufficient to qualify a patient as persistent.[9] Authors publishing adherence rates mostly omit a description of the operationalization of the assessment methodology[5] – that is, how the adherence measures were calculated. This lack of transparency regarding the operationalization of adherence measures complicates the comparison of adherence results across studies[6,10,11] and the translation to real-world practice.[9]

In parallel, and almost inevitably, a proliferation of terms emerged in the literature to describe medication use.[12] They all describe a deviant behavior and are often used interchangeably but define different aspects such as seeking medical care, acquiring medication, or deviating from the prescribed therapeutic plan.[12] As a consequence, a European consortium defined a new taxonomy for the umbrella term *adherence to medications*, which is "the process by which patients take their medications as prescribed".[12] It is divided into 3 quantifiable phases: initiation, implementation, and discontinuation. Persistence represents one aspect of adherence and encompasses the time over which a patient remains on treatment. In this context, standards and definitions are needed to calculate the adherence measures according to the recently proposed taxonomy.[12]

**Aims and Objective**

The aims were (*a*) to harmonize the concepts of adherence measures from medication records within the new taxonomy; (*b*) to propose the standards necessary for the operationalization of these adherence measures; (*c*) to refine adherence calculation with medication data; and (*d*) to list the methodological issues that should be disclosed.

**Methods**

Six researchers with considerable expertise in medication adherence from Switzerland and the Netherlands - 2 leading European countries in the integration of adherence measurements from medication records into

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pharmacy systems - formed a panel in summer 2014. All members were researchers from academia and involved in governmental projects, and 2 members were doctoral candidates who worked on calculation methods. All are members of ESPACOMP (European Society for Patient Adherence, Compliance and Persistence); 2 are founding members, and 1 a former president. The leadership was taken by a member of the Special Interest Group on Adherence from the European Society of Clinical Pharmacy. Because the lack of standardization of adherence measures is a tenacious problem in adherence research, the panel decided to propose recommendations for future adherence research. A consensual nature of the process based on recent methodological articles[12,13] and discussion among experts was selected to generate first results in November 2014. Final consensus on the last version was obtained in July 2015. The concepts describing medication use behavior were harmonized; standards were set for the elements related to the (re)fill of a prescription; and the measures were refined, together with their basic calculations capable of quantifying the 3 phases of adherence.

## Results

### *Harmonization of Concepts and Proposed Measures Describing Adherence*

Because medical records contain variables that are mostly specific to their source – that is, quantity prescribed in prescription records versus quantity dispensed in dispensing records - some variable might be lacking for some calculation. The assumptions for adherence measurements with pharmacy dispensing records are listed in Box 1.

Initiation of the treatment occurs when the patient takes the first dose[12] and represents a dichotomous variable, based on first-fill data. With prescribing and dispensing records at disposal, sometimes, initiation is defined as the time from prescription until the first medication fill[14] – that is, a time-to-event variable. To reduce confusion, it should be named time-to-initiation. In any cases, the output is the number of primary nonadherers – that is, patients with a prescription that is not followed by a dispense.

Implementation is achieved when the patient's actual dosing is compared with the prescribed dosing regimen, from initiation until the last dose is taken.[12] For this phase, several measures are proposed.

Discontinuation and persistence are driven by the continuity of medication refilling. Discontinuation occurs when the next due dose is omitted and no more doses are taken thereafter. Discontinuation is, therefore, a dichotomous variable. Persistence describes the time from initiation until last dose[12] – that is, the end of therapy. Persistence is, therefore, a time-to-event variable. The dimension of time is an integral part of both terms.[4] Exceeding a maximal permissible length without supply (grace period) qualifies for discontinuation or nonpersistence. This maximal gap can range from zero to an infinite number of days. Between those 2 extremes, almost every gap length from 7 to 180 days has been proposed in the literature.[15] Setting the cutoff is equivalent to defining the sensitivity of the measure because the smaller the allowable gap, the higher the number of patients classified as having discontinued or being nonpersistent.[16] A 90-day allowable gap might be adequate to detect true nonpersistence because a study investigating the impact of several gap selections on persistence observed no major change with increasing gap days >90 days.[17] Ultimately, however, the length of the permissible gap should depend on the medication(s)/ condition(s) being studied.

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**Box 1.** Assumptions Underlying Adherence Measures With Pharmacy Medication Records.

- Medication records are complete, comprehensive, and accurate
- The first intake occurred on the day of the first fill
- The medication is taken as indicated (eg, tablet ingested)
- Lack of a refill equals a medication is not consumed after the oversupply is exhausted
- Medications are not purchased or borrowed from another person or venue
- No unknown treatment interruptions or dosing changes occurred during the observation period

Because patients may restart treatment at any point in time, the quantification of *reinitiation* of treatment is proposed as the proportion of patients with a dispensing after the maximal predefined gap length.

*Definition of Standards*

The definitions of the elements with standards and calculations are summarized in Table 1.

The observation period is defined as the length of time over which the adherence measures are assessed. The period should start at $t_1$ at the first (re)fill date, with the assumption that the patient starts medication intake that very day. The period should end either at the last refill date $t_n$ or at an arbitrary date $t_a$ (eg, a medication review date; $t_1$ + 360 days). The rationale for such variable end dates is that refills are time-dependent events.

The number of days' supply is defined as the quantity dispensed divided by the PDD. The latter equals the amount of medication to be consumed per day and is calculated with the dosing instruction as Unit(s) per dose x Dose(s) per day. Changes in dosage regimen according to medical prescription should be accounted for and should be exhaustively described. If the data set does not contain the quantity dispensed as a variable, it should not be used.

**Table 1.** Definitions of the Elements, With Standards and Calculation.[a]

| Element | Definition | Standards and calculation |
|---|---|---|
| Start and end points of the observation period | Period starts at $t_1$ and ends at $t_n$ or $t_a$ | $t_1$ = date of first (re)fill<br>$t_n$ = date of last refill[b]<br>$t_a$ = arbitrary date[b] |
| Observation period | Number of days of the entire period[b] | $t_n - t_1$ or $t_a - t_1$ |
| Quantity dispensed | Number of dispensed medication units (eg, tablets) | [quant_disp][c] |
| Prescribed daily dosage (PDD) | Amount of units to be consumed per day according to the dosing instructions | PDD = Number of units per dose x Number of doses per day[c] |
| Number of days' supply ($A_n$) | Number of days with medication available | [quant_disp]/[PDD] |
| Refill interval ($B_n$) | Number of days between 2 dispensations | (Refill date $t_n$) - (Refill date $t_{n-1}$) |
| Oversupply | Number of days' supply accumulated from previous dispensings (stockpile) | If ($A_n > B_n$), then oversupply = ($A_n - B_n$) |
| Gap | Number of days without medication supply | If ($A_n < B_n$), then gap = ($B_n - A_n$) |
| Maximal gap length | Number of days of the longest period of time without supply (after taking carryover of oversupply into consideration) | |

[a] See Figure 1 for graphical representation.
[b] a and n are integral numbers.
[c] Can be an integral or a fractional number.

With data sets that contain PDD as a variable, if the dosing instruction is missing, extrapolation from the following interval (for $t_1$) or from the previous interval (for all other t) should be allowed. A data set should be excluded if dosing instruction is missing for 2 intervals in a row or if the instruction changed over time and is unknown. With data sets

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that typically do not contain dosage instructions as a variable, noticeable differences may result from assumptions made.[18] Researchers should, thus, explicitly state what assumptions were made to estimate the numbers of days' supply.

Oversupply (or stockpiling) results from overlapping days' supply of subsequent refill intervals and equals to accumulated medications. Oversupply should be allowed, with the rationale that patients get supply before they have exhausted their drug supply and in a flexible manner according to their daily activities and duties. It should be carried forward to the next interval (carryover) or at the end of a period with a gap, with the rationale that this pattern reflects real life - patients exhausting previous supply before starting the new one. Retroactive compensation - that is, the use of an oversupply to compensate a gap that occurred earlier in the dosing history - should be forbidden. Results of a study with hypothetical dispensing patterns suggest that accounting for oversupply in adherence measurement (time-forward approach) performs better than other methods.[10] Oversupply beyond the observation period should not be permitted – that is, extra doses beyond the end of the observation period should be excluded. Oversupply beyond the end date was shown to overestimate adherence measures[6] by inflating the value of the quantity dispensed.

A gap may exist between refills when prior supply is depleted before refill supply is available. It should be compensated to the extent possible by any existing oversupply from a prior interval. Hospitalization or residence in a long-term care facility may lead to apparent gaps in pharmacy refills and are often interpreted as discontinuation, mostly because they remain unrecognized. If known, the hospitalization period should be subtracted from the denominator, assuming, first, complete adherence to hospital drugs during hospital stay and, second, that patients do not obtain medications at discharge, and with the rationale that the amount of previous medication at the disposal of the patients after discharge is identical to that before hospitalization. A similar approach was used in a study developing an adherence index with inhaled corticosteroid.[19] Unsurprisingly, adjusting for the time a patient was hospitalized by excluding the days of the hospitalization marginally influences the adherence rate – that is, the adherence value is approximately 0.5% lower than without accounting for hospitalization days.[7] If patients use their home medication in the hospital, no adaptation of the calculation is needed.

Switching is defined as one product being initially filled, then a different product in the same therapeutic class being filled at a latter point within the observation period, and the initial product is no longer filled. Generic switching is defined as switching between products with identical ATC code on level 5 (eg, C03EB01: Lasix 40 mg and Furosemide Actavis 40 mg). In this case, switch is considered as the possession of 2 products one after the other, and carryover is granted under the above-mentioned conditions. Therapeutic switching is defined as 2 different medications – that is, different ATC code on level 5 (eg, A02BC01: Omeprazole 40 mg and A02BC02: Pantoprazole 40 mg; switching within chemical group) or on level 4 (eg, A02BC: proton pump inhibitor and A02BA: $H_2$-antagonist; switching within pharmacological group). In this case, switch is considered as continuous use, and no overlap is granted – that is, a possible oversupply of one medication should be disregarded, with the rationale that a medical reason forced the physician to change medication (eg, lack of effectiveness, side effects, or intolerance).

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*Mandatory Information in Adherence Studies in Which Medication Records Are Used*

To facilitate formal comparison between adherence studies published in the literature, some information should be clearly disclosed (Box 2). The issues are related to the operationalization of the adherence measures, which could dramatically influence the above-mentioned results.

*Refinement of Calculation*

Implementation is best given by the cumulative proportion of time at which medications are available – that is, in the possession of the patient. For monotherapy, the basic algorithm of the MPR is proposed. It sums the number of days' supply (see calculation below), divided by the number of days in the observation period, multiplied by 100. Some researchers and guidelines include the days' supply for the last prescription dispensed (up to the end of the observation period) in adherence and persistence calculations.[20] However, oversupply beyond the observation should be excluded (see above), and the following calculation should be used:

If end date is $t_n$ (last refill date), then the numerator is [(Sum of days' supply) - (Days' supply obtained at $t_n$)].

If end date is $t_a$ (arbitrary date), then the numerator is [(Sum of days' supply without the last dispensing) + (Days' supply obtained at the last dispensing up to the end date of the period $t_a$).

The MPR ranges from 0% to 100%.

For polypharmacy, the basic algorithm of DPPR (daily polypharmacy possession ratio) is proposed. It has been described elsewhere.[13] The DPPR does not result from an equation but from the application of a stepwise algorithm. In brief, the number of all medications available is determined for each day separately over the observation period. A score between 0 (no medication available) and 1 (all medications available) is set. To obtain the proportion of all medications available for daily use, one has to sum the scores, divide by the number of days in the observation period, and multiply by 100. The DPPR ranges from 0% to 100%.

The basic algorithm for oversupply is (Number of days' supply $A_n$) - (Days in the refill interval $B_n$) if $A_n > B_n$ (Figure 1). The basic algorithm for gap is (Days in the refill interval $B_n$) - (Number of days' supply $A_n$) if $A_n < B_n$ (Figure 1). They are calculated simultaneously for each interval and summed up from one interval to the other. Because the use of an oversupply to compensate a gap that occurred earlier in the dosing history is forbidden (retroactive compensation), oversupply always has a value ≥0 (negative supply cannot exist).

**Box 2.** Issues to Clearly Disclose in Adherence Studies.

1. How was the data sample derived? (reimbursement, dispensing, prescribing data)
2. Was there a minimum number of fills and how was the minimum number of (re)fills defined?
3. Were all or only newly treated patients assessed? What was the definition of a newly treated patient?
4. Which adherence phase was assessed? (initiation, implementation, discontinuation)
5. How long was the observation period and how was it defined? (first vs last refill dates or first vs arbitrary end date)
6. How was the prescribed daily dose defined? (instructions for use, assumptions derived from treatment guidelines)
7. Was a single medication or polypharmacy analyzed?
8. How were hospitalization periods taken into account?
9. Which was the rationale for the use of threshold? (grace period, medication possession ratio)
10. How were missing values handled?
11. How were generic or therapeutic substitution handled?
12. How was dose switching handled?

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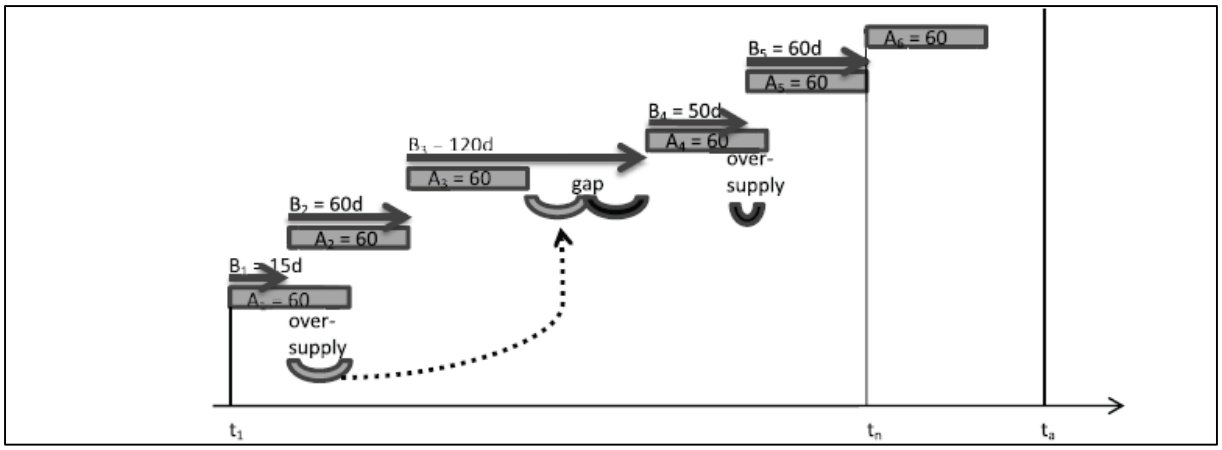


**Figure 1.** Graphical representation of the elements defined in Table 1. The observation period runs from the start day ($t_1$ at the first dispensing date) to the end day ($t_n$ at the last dispensing date, or $t_a$ at an arbitrary date); A is the number of days with medication available, and B is the number of days between 2 dispensings. Oversupply obtained from $A_1$ is carried forward to the next possible interval (arrow) at the end of $A_3$, which is likely to occur in the real world. Oversupply obtained from $A_4$ is disregarded if tn is the end date and added at the end of $A_6$ if $t_a$ is the end date.

Implementation is also depicted by the days without sufficient medication supply (gaps). The basic algorithm for the time without supply sums the number of days without supply after each interval (after taking oversupply from previous intervals into consideration; see Figure 1) divided by the number of days of the observation period, multiplied by 100. Last supply dispensed at the end of the observation period should be excluded. The value ranges from 0% to 100%. Because this value does not capture the dynamics of the gaps, further measures are proposed. The maximum gap length is the number of days of the longest period of time without supply (after taking carryover of oversupply into consideration). The mean gap value ± standard deviation can be an indicator of dispersion.

*Discontinuation and Persistence*

The maximum period without supply (gap) should be clearly defined. The clinical relevance of stopping therapy should guide the maximal allowed gap. Thus, with drugs with short half-lives or when outcome is linked to short-term drug effects such as cardiovascular or antidiabetic drugs, a shorter gap length can be justified, where patients are considered nonpersistent on the first day on which they would have exhausted their drug supply.[21] Similarly, shorter gaps might detect clinically meaningful ("true") nonpersistence, for example, for HIV or anticoagulants. After setting the allowable gap length, persistence is best summarized using a Kaplan Meier curve or as a percentage of patients who have discontinued treatment during a defined time period.[22] A cutoff at 3 to 6 months could be set to quantify the percentage of early discontinuers.

*Reinitiation*

Interruption of treatment and its subsequent reintroduction have been investigated, predominantly in HIV patients, where discontinuation(s) of treatment was shown to induce viral resistance[23,24] and, ultimately, morbidity and mortality.[21] In these studies, interruption was mostly self-reported[25] or was not defined.[26] In larger studies analyzing cohorts from national register, the probability of restarting a therapy with statin was estimated from gaps of different length

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– that is, after reinitiation of treatment.[27,28] The proportion of patients reinitiating therapy should be calculated by dividing the numbers of patients with a dispensing beyond the end of the allowable maximum gap by the number of patients defined as having discontinued therapy.

**Discussion**

Standards and their operationalization are proposed to quantify adherence to medication from medication records of various sources within the new taxonomy of the European ABC Group.[12] By doing this, this study builds on previous consensus-based work and links conceptual definitions to operational definitions.

Possession-related measures were selected (MPR for single medication and DPPR for multiple medication) to quantify the implementation phase of adherence because they are easy to calculate and interpret (the higher the value, the higher the medication possession). In addition, by integrating the last medication fill into the denominator, the MPR measures implementation over the time period that the patient was actually using the medication (from first fill to last fill). This deviates from the US standard for performance indicator-based reimbursement, which uses the PDC.[29] PDC uses a fixed denominator, often 365 days (based on a calendar year or a year's follow-up). Even more confusing, some researchers used the last medication refill as their end date in PDC calculations, and some others used a fixed end date in their MPR calculations, leading to inconsistencies in the literature. Thus, it could be helpful to use the last fill date exclusively for MPR measures and fixed end date for PDC measures. By doing this, the MPR value would indicate the quality of implementation in a single measure, whereas the PDC would be an indicator of both the quality and the length of implementation during a medication dosing history.

Some researchers have claimed that periods of under- or oversupply of medication may be obscured with possession rates.[15] This might be true because the usual method of calculation used so far does not account for duplication (simultaneous use of multiple agents from the same therapeutic class) and overlapping - the 2 parameters most frequently responsible for the general overestimation of adherence.[30] The proposed standards regulate duplication and overlapping and, thus, eliminate major elements that distort calculation results. A special emphasis was set to avoid mathematical equations that would depict impossible situations in the real world, such as including the supply left over beyond the end of the study period. On the other hand, medication oversupply through early refills (ie, stockpiling) is likely to occur in the real world and should be allowed. The most restrictive standard consists of forbidding the use of an oversupply to compensate a gap that occurred earlier in the dosing history (retroactive compensation). The proposed considerations reflect real-world situations because negative supply cannot exist. Patients either have supply (positive value) or they have not (zero value). Consequently, a stepwise algorithm along the intervals instead of an overall equation is needed. This algorithm is clearly more complicated, but it identifies more precisely periods of time where medication availability was unlikely.

The terms *discontinuation* and *nonpersistence* are used alternately to indicate the end of therapy. Confusion might occur when using nonpersistence as a dichotomous value because persistence is a time-to-event value. Choosing the term *discontinuation* might raise less doubts. Because medication records do not disclose what happens after the last dispense (ie, treatment stop or treatment holiday), uncertainty forces decisions to be made. Defining a cutoff value for the number of days without supply (grace period) beyond which

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treatment is discontinued – that is, end of therapy - determines nonpersistence. Part of the challenge is to set a limit that avoids misclassification of patients who restart treatment after a period of discontinuation and would otherwise be lost to calculation if the grace period is too small. As a consequence, the assessment of reinitiation is proposed as a further measure in adherence research. By doing this, the cutoff value for discontinuation can still be applied, and prolonged gaps between refills, which may not signify cessation of therapy, will still be detected. It is likely that repetitive stop-and-go patterns have dramatic influence on therapy, and they have seldom been evaluated properly.[31] With the setting of different cutoff values for discontinuation or nonpersistence, early discontinuers can be assessed, and new fields in adherence research are open for investigation. Generally, the allowable grace period is driven by the time between scheduled refills, and a pharmacologic rationale is lacking for the definition of the grace period or the threshold MPR. One study[32] defined an allowable interruption gap of 42 days in accordance with a previous clinical trial that reported a potential loss of efficacy of the drug of interest after an interruption of 6 weeks.[33] In most cases, the time between scheduled refills is an order of magnitude longer than the drug's therapeutic effect. Nevertheless, the grace period should depend on the drug forgiveness, which allows larger gaps between scheduled doses without noticeable loss of pharmacological effect. In any case, the search for a universal value set to separate adherence from nonadherence is doomed to failure and can only result in contradictory results.[34]

To reduce confusion and inconsistency, several terms are excluded from the proposed concepts, such as the *index date*. Although this term has been often used in recent literature as the date of first claim,[35] it also indicates the date of a drug-treated event in epidemiologic matched cohort studies. Furthermore, the simple measure of refill rates is excluded – that is, a measure based on the number of refills during a specified period of time (flexible or anniversary model) - because the length of time between refills is given no consideration. In addition, the refill rate is implicit in a gap-based measure. The number of refills may nevertheless be a valuable calculation for medications that may be used as needed without detriment to the clinical condition. It may further be appropriate for medications such as orally inhaled asthma drugs, where information on days' supply may be imprecise.

The way in which raw data are obtained (eg, by pillcount; prescribing; dispensing, or administrative data; electronic monitoring of single or multiple medication) determines the content of the database. However, mandatory information for calculations still includes drug name, drug dosage or dosing instructions, quantity of drug dispensed at each (re)fill, and date of each prescription (re)fill. In situations where the database contains the days' supply (as entered by the pharmacist, for example), calculations can be performed when drug name and refill dates are also known. Provided the records are complete, the proposed measures can be calculated indiscriminately with prescribing and dispensing databases. In this regard, it is interesting to see that, increasingly, nationwide personal electronic medicine profiles are stored online for electronic prescribing and electronic monitoring of medicine.[36] However, a recent evaluation of the Danish system showed that it was yet unable to accurately detect nonadherence,[36] predominantly because of incorrect prescription information and missing dosage information. Experiences from the United States after the introduction of the Medicare Improvements for Patients and Providers Act[37] in 2008 showed at least an increased use of e-prescribing in response to the

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incentive program.[38] Today and worldwide, the most accurate database remains the Dutch pharmacy dispensing system. It is worth noting that since January 1, 2014, Dutch physicians are obliged to use e-prescribing, and most of them send the prescription electronically to the pharmacy.

In future, the measures chosen by a researcher should be determined by the overall goals of the study – that is, clinical efficacy trials (eg, MPR of the study drug), selection of ambulatory patients at risk in order to initiate an intervention such as specific counseling (eg, nonpersistence with HIV medication), or conditions for reimbursement (eg, noninitiation). Much more, the study population should determine the cutoff values. As an example, the length of the observation period may vary depending on whether the study population is restricted to new or chronic users of the medications. Finally, because adherence is a complex behavior with several aspects, it cannot be caught in one number. In any case, a careful description of the definitions and operationalization used is crucial if comparisons between studies are to be made.

**Strengths and Limitations**

This study has several strengths. First, the proposed standards are close to a real-word setting and eliminate overestimation of adherence values. Second, the proposed measures build on the taxonomy established by the European ABC Project and pursue the work of promoting consistency for different experimental investigations. Third, the proposed measures take full advantage of the information available in many databases, which is not the case for most of the current measures of adherence or persistence.

This study has some limitations. First, as is true of any indirect method of adherence assessment, the proposed measures are unable to confirm ingestion of the dispensed medication. As a consequence, they function as surrogate measures of medication adherence. However, they provide an estimate of the highest possible level of medication possession and, thus, can identify those patients not able to consume the medication in sufficient quantity. In that sense, the measures can be considered to have a high sensitivity. Second, different assumptions must be made, the main one being that all medication will be taken at the days' supply indicated. However, a standardization of the assumptions will lead to comparable estimates of adherence across different studies.

**Conclusion**

By following the displayed propositions, results of future adherence research should gain in accuracy and in confidence, and results between studies should be comparable. Because the ultimate goal of adherence measurement is to improve patient care, the proposed measures could be used to set flags in electronic databases, based on which health professionals could select appropriate and effective interventions to move into practice. Researchers are invited to discuss this proposition of standards and to communicate their observations. Ultimately, generally approved standards are soon needed along with their operationalization, which could be endorsed by an umbrella society, so that health professionals, researchers, health authorities, and policy makers can make informed choices for the benefit of patients and society.

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