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Initial Medication Adherence—Review and Recommendations for Good Practices in Outcomes Research: An ISPOR Medication Adherence and Persistence Special Interest Group Report

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ABSTRACT

Background: Positive associations between medication adherence and beneficial outcomes primarily come from studying filling/consumption behaviors after therapy initiation. Few studies have focused on what happens before initiation, the point from prescribing to dispensing of an initial prescription. **Objective:** Our objective was to provide guidance and encourage high-quality research on the relationship between beneficial outcomes and initial medication adherence (IMA), the rate initially prescribed medication is dispensed. **Methods:** Using generic adherence terms, an international research panel identified IMA publications from 1966 to 2014. Their data sources were classified as to whether the primary source reflected the perspective of a prescriber, patient, or pharmacist or a combined perspective. Terminology and methodological differences were documented among core (essential elements of presented and unrepresented prescribing events and claimed and unclaimed dispensing events regardless of setting), supplemental (refined for accuracy), and contextual (setting-specific) design parameters. Recommendations were made to encourage and guide future research. **Results:** The 45 IMA

studies identified used multiple terms for IMA and operationalized measurements differently. Primary data sources reflecting a prescriber's and pharmacist's perspective potentially misclassified core parameters more often with shorter/nonexistent pre- and postperiods (1–14 days) than did a combined perspective. Only a few studies addressed supplemental issues, and minimal contextual information was provided. **Conclusions:** General recommendations are to use IMA as the standard nomenclature, rigorously identify all data sources, and delineate all design parameters. Specific methodological recommendations include providing convincing evidence that initial prescribing and dispensing events are identified, supplemental parameters incorporating perspective and substitution biases are addressed, and contextual parameters are included.

Keywords: good research methodology, initial compliance, initial medication adherence, medication adherence.

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Introduction

Medications are the most common treatment regimen used in ambulatory health care [1]. Yet, adhering to prescribed medications is a major issue affecting health care because nonadherence has been associated with worsening clinical symptoms and disease progression [2–10]. Furthermore, medication nonadherence has been linked to increased health care visits, services, and costs [11–15]. Studies linking nonadherence to these unfavorable outcomes have used various operational definitions for adherence—each with its own nomenclature (e.g., persistence), several representing similar if not exact components of medication adherence [2,13,16].

In two studies, taxonomic language has been developed to help researchers and clinicians understand subtle, yet powerful, differences among the processes inherent in adhering to prescribed medication regimens [16,17]. Although both taxonomies include an initiation point, which signifies the start of the medication adherence continuum, most of their focus is on what happens during implementation and discontinuation of medication therapy. We collectively refer to implementation and discontinuation of medication therapy as postinitiation medication adherence (PIMA) processes. The patient's intention to initiate the medication regimen is omitted [17] or given only limited attention [16]. Our focus is on this vital

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aspect of medication adherence, which we call initial medication adherence (IMA).

IMA is simply defined as the patient obtaining, for the first time, a new prescription medication. This is operationalized by two distinct events: a provider prescribing a medication for the first time, that is, a prescribing event, and a pharmacist dispensing this initial prescription, that is, a dispensing event. An initiation failure occurs whenever an initial prescription is not presented to a pharmacist or a presented prescription is not dispensed by a pharmacist. When this failure occurs, IMA is not achieved.

Although conceptually simple, IMA lacks the depth of exploration attributed to PIMA and suffers from a similar proliferation of terms. These issues are reflected in our recent systematic review in which only 24 of 865 selected publications examined IMA risk factors [18]. Disparity between the volume of published IMA and PIMA research may be due to the availability of data for measuring each in a cost-effective way. Information needed for measuring many aspects of PIMA is captured and readily available on a large scale in most US retrospective claim databases [19]. In contrast, the prescribing and dispensing events needed to measure IMA are seldom captured together, lack the necessary linkages, or are insufficient in quantity. Until recently, initial prescriptions were almost always handwritten and given to patients for filling at a pharmacy of their choice, though some health care systems do have pharmacy restrictions on that choice. In this environment, documenting filling behaviors has historically involved surveys, phone calls, data extraction, or other manually intensive techniques. The few health care systems that capture the information electronically have population sizes, privacy issues, and organizational resources that limit the production of disease-specific IMA rates. These are just some of the issues that contribute to the dearth in IMA research. Yet, IMA is the first step to realizing adherence benefits for both acute and chronic conditions. As such, increasing the body of IMA literature would provide baseline rates to support measuring the impact of interventions and additional insights into factors associated with initiation failures. Identification of this information can help to develop targeted interventions and lead to improved patient outcomes.

Building upon our past work on IMA [18], the purpose of this article was to assess the extent and means by which IMA has been operationally defined and provide guidance for future research in this area [16]. This article is not intended to be an exhaustive review with a meta-analysis of IMA research. Instead, the focus is on operational design to foster more coherent and standardized approaches to conducting, analyzing, and interpreting IMA research. As the body of IMA research grows, we expect that it will provide additional insights into achieving clinical, utilization, and cost benefits more commonly associated with PIMA [2].

Methods

An international panel of researchers with considerable expertise in medication adherence and research formed a leadership team on IMA as part of ISPOR's Medication Adherence Good Research Practices Working Group in July 2009. The leadership team divided into two groups to identify initial adherence rates and factors that influenced whether patients would fill their initial prescription. Finding insufficient IMA research to produce disease-specific rates with confidence, the two groups rejoined to publish findings on behavioral factors influencing the IMA goal [18]. Following this publication, we updated our earlier search and found that circumstances had not changed enough to identify initial condition-specific adherence rates. In short,

research was still fragmented, terminology and operational definitions were inconsistent, and methodologies were unclear. This finding is similar to that obtained in other recently published reviews [17]. To foster a proliferation of high-quality studies supporting the production of IMA condition-specific rates and solidifying the relationship between IMA and beneficial outcomes, the team decided to provide guidance for IMA research.

The key terms included initial, primary, first-fill, and early with adherence and compliance to search Medline (PubMed and Ovid), the Cochrane Library, PsycInfo, Scopus, Web of Science, Embase, and CINAHL databases [18]. The search extended from inception of the database to January 2014. We considered studies that measured IMA but did not have a link to behavioral factors. Selected studies had to conform to our definition of initial adherence, include primary data analysis, and have more than 10 patients. Articles presenting only conceptual or theoretical work or those dealing with adherence during the early treatment course or longitudinal persistence rather than the very first prescription were excluded. Two independent reviewers applied these criteria to review the titles, key words, and abstracts to determine which full-text publications would be reviewed and ultimately whether a study would be included. The reviewers documented information on study location, sample size, periods, and reference frame, which provide context for presenting and interpreting study differences.

The IMA Process

The study reference frames are categorized into whether the primary data source reflected a prescriber, patient, pharmacist, or combined approach to the IMA process. The IMA process begins with a prescriber and patient interaction in an emergency room/department, hospital, or other clinic setting (step 1) that results in a prescribing event (step 2)—the first of the two key events needed for an IMA measurement (Fig. 1). When a prescribing event occurs, data collected from the perspective of either a prescriber or a patient will capture it, whereas data collected from the perspective of a pharmacist will not. To qualify as IMA, however, the prescribing event must relate to a patient's first prescription within a therapeutic class (step 4). Otherwise, the dispensing event becomes part of a PIMA metric (step 5). Data from either the patient or the prescriber should be able to determine whether the prescribing event is an initial event.

The pharmacist becomes aware of prescribing events only when these events are communicated to the pharmacist for filling (step 6). Therefore, the pharmacist does not know how many prescribing events have occurred, only how many have been communicated. However, once the pharmacist receives the prescription (step 7) and fills it (step 8), the pharmacist must dispense the prescription to the patient (step 9). The dispensing event is the second key event needed for measuring IMA (step 10). With dispensing the medication to the patient, both the pharmacist and the patient know that the IMA is achieved, but the prescriber does not. If a pharmacist does not dispense a filled prescription, the prescription becomes abandoned to the pharmacist and is restocked (step 11). If an abandoned prescription is not transferred to another pharmacist (step 12) and subsequently dispensed, the patient will be initially nonadherent (step 13). Either the pharmacist or the prescriber may transfer the prescription from one pharmacy to another, but neither may know that the prescription has been dispensed. Thus, data from only a patient's perspective and the dispensing pharmacy can verify whether a dispensing event occurs.

For the purposes of this review, study design parameters were divided into core, supplemental, and contextual parameters. *Core parameters* are those that must be provided to calculate a valid

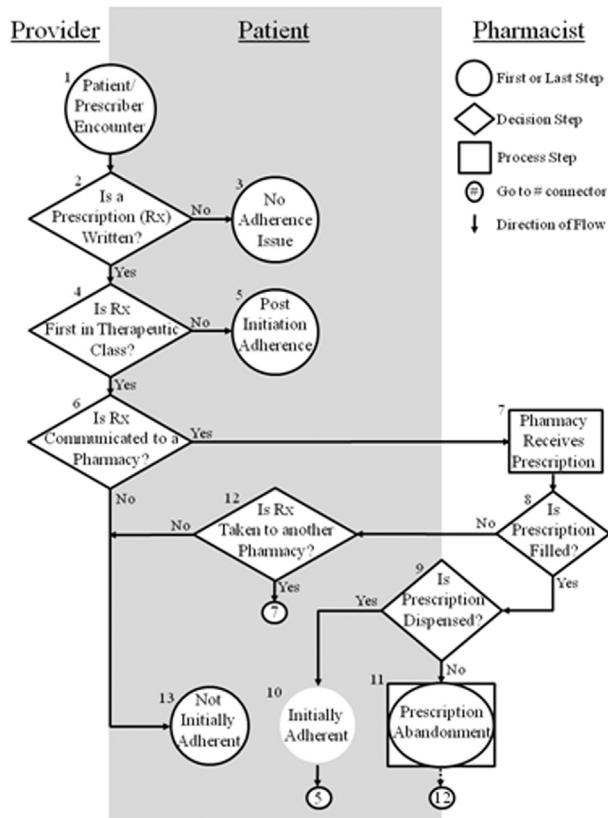


Fig. 1 – The Initial Medication Adherence Process and its Key Perspectives.

IMA measurement. Supplemental parameters help to refine the accuracy of the measurement, and contextual parameters are those factors that may influence the measurement. General and design parameter recommendations are made for improving the quantity and quality of IMA measurements. In addition, universal recommendations are made to improve documentation of IMA research.

Results

Characteristics of the 45 published IMA studies selected for inclusion are presented in Table 1. A total of 29 studies came from within the United States [8,9,12,19–45] and 16 from outside the United States [4,5,46–59]. The IMA publications were classified by primary data source into the following perspectives: 12, prescriber [23,26,32,33,38,46,47,49,51,52,57,58]; 3, patient [12,41,56]; 7, pharmacist [24,27,29,30,37,53,54]; and 23, combined [4,5,8,9,19–22,25,31,34–36,39,40,42,44,45,48,50,55,59,60].

The time frame used to identify prescribing and dispensing events for each study is also given in Table 1. The time frame consists of a preperiod and a follow-up period. The preperiod is the length of time before a prescribing event used to determine whether it was an initial prescribing event. The follow-up period is the length of time after the prescribing event researchers looked for a dispensing event. The influence that each perspective has on these time-frame components is presented in the Core Parameter section. Other differences among the studies and some techniques used to overcome inherent data limitations associated with using data captured from the perspectives of the primary data source are presented in Supplemental and Contextual Parameter sections.

Core Parameters

In general, studies measuring IMA provided details on the relevant medications, the means for capturing prescribing and dispensing event information, and the time frames used for the preperiods and the follow-up periods. The medication list identifies what dispensing and prescribing events are being tracked, whereas the preperiod is used to determine when a patient initiates pharmacotherapy for a new class and the length of the postperiod that is used to detect dispensing events. These details about the prescribing and dispensing events are the core parameters. Ideally, these details provide the information to determine precisely whether and when these key events occurred for numerous patients.

Although it may be impossible to have all the prescribing and dispensing information, there were differences among the studies related to their primary data source perspectives. In general, studies with data from a clinical (i.e., prescriber's or pharmacist's) perspective had relatively shorter time frames for detecting the prescribing and dispensing events and used fewer comprehensive information sources than did those that considered claims and other electronically captured sources (see Table 1). In addition to having nonexistent preperiods, many of these studies had relatively short follow-up periods ranging from 1 to 21 days [26,30,32,38,46,51,52,54,57]. Five had 1-month follow-up periods [23,29,33,47,49], four had 90- to 180-day follow-up periods [27,37,53,58], and two had variable follow-up periods up to a year [3,58]. Furthermore, although the prescriber generally had information on the prescribing event and the pharmacist generally had information on the dispensing event, only the prescriber's perspective studies incorporated study design parameters to capture the missing event information with manual direct patient or pharmacy contact. Thus, on the basis of evidence from these studies, the pharmacist was less likely to account for missed prescribing events and unrepresented/communicated prescriptions compared with the prescriber accounting for missed dispensing events. In addition, prescriber or pharmacist perspectives without a preperiod would likely be unable to distinguish between medication initiation and continuation. This lack of a preperiod would mean that it is difficult to separate IMA measurements from PIMA measurements.

Studies involving data on both key events from a combined perspective or a patient's perspective had mixed results. Almost all studies that used data sources from a combined perspective had at least a 6-month preperiod, with some having a year or more [4,5,8,9,19–22,25,28,34–36,39,40,44,45,50,55,60]. Similarly, most had at least a 28-day follow-up period, with several having 12 months or more. Prescribing event information was generally captured electronically through an electronic medical record or a system devoted exclusively to electronic prescribing in studies using a combined perspective. They also captured whether a medication had been filled through electronically maintained dispensing records within the pharmacies or by pharmacy benefit managers. In contrast, the length of the preperiods and follow-up periods was less defined in the three studies that approached the question from a patient's perspective. All three studies relied on a single question within a larger survey about whether the respondent had failed to fill a prescription in the last 3 months [56] or last 12 months [12,41]. The ambiguity of the question relating to the preperiods and follow-up periods likely led to variable period lengths, and in these studies there was no information on whether it was an initial prescription within a therapeutic class.

Supplemental Parameters

Supplemental design parameters provide details on how biases associated with perspective, substitution, and censoring—each

Table 1 – Key IMA characteristics of publications (n = 40).

Perspective*		Country	Sample size [†]		Study period [‡]	Prescribing event periods [§]	
Reference no.	Author (year)					Pre	Follow-up
Prescriber							
[46]	Arslan and Semin (2006)	Turkey	280	Patients	Feb 2003 to Jun 2003	0	5
[47]	Beardon et al. (1993)	Scotland	4,854	Patients	Jan 1989 to Apr 1989	0	30
[23]	Fernando et al. (2012)	United States	224	Patients	Jun 2010 to Dec 2010	0	7–31
[49]	Freeman and Guly (1985)	England	226	Prescriptions	Feb 1983	0	0–30
[26]	Ginde et al. (2003)	United States	31	Patients	Nov 2001 to Jun 2002	0	5–7
[51]	Jones and Britten (1998)	England	935	Patients	Jan 1996	0	21
[52]	Matsui et al. (2000)	Canada	1,014	Patients	Sep 1996 Jan 1997 to Mar 1997	0	2
[32]	Rosman et al. (2012)	United States	111	Families	Jan 2009 to Apr 2010	0	3
[33]	Saks et al. (2012)	United States	160	Patients	Jan 2009 to Mar 2010	1	30
[38]	Suffoletto et al. (2012)	United States	200	Patients	Jun 2011 to Sep 2011	365	1
[57]	Watts et al. (1997)	Australia	359	Prescriptions	3 mo in 1993	0	21
[58]	Wright et al. (2003)	Australia	65	Prescriptions	Apr 2000 to Jul 2000	NA	0–90
Patient							
[12]	Esposito et al. (2008)	United States	1,214	Patients	Jun 2003 to May 2004	0	1–365
[56]	Wamala et al. (2007)	Sweden	31,895	Patients	Mar 2004 to Jun 2004, Mar 2005 to Jun 2005	NA	0–90
[41]	Wroth and Pathman (2006)	United States	3,926	Patients	Nov 2002 to Jul 2003	NA	0–365
Pharmacist							
[27]	Gleason et al. (2009)	United States	10,104	Patients	Jul 2006 to Dec 2008	90	90
[24]	Fincham and Wertheimer (1986)	United States	32	Patients	4-mo period	0	14
[30]	McCaffrey et al. (1995)	United States	522	Pharmacies	8 wk	0	7
[29]	McCaffrey et al. (1998)	United States	128	Pharmacies	12 wk	0	30
[53]	Menckeberg et al. (2008)	The Netherlands	667	Patients	730	180	
[54]	Skutnik and Katsanis (1997)	Quebec	254	Prescriptions	4-wk period	0	14
[37]	Streeter et al. (2011)	United States	10,508	Patients	May 2007 to Jun 2009	120	90
Combined							
[20]	Berger et al. (2009)	United States	2,023	Patients	Jan 2002 to Dec 2006	180	30
[21]	Cheetham et al. (2013)	United States	19,826	Patients	Dec 2009 to May 2010	365	90
[22]	Deroose et al. (2013)	United States	2,606	Patients	Apr 2010 to Jun 2010	365	7–60
[48]	Ekedahl and Mansson (2004)	Sweden	91,704	Prescriptions	Mar 2000 to Sep 2000	0	120–210
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Table 1 – continued

Perspective*		Country	Sample size†		Study period‡	Prescribing event periods§	
Reference no.	Author (year)					Pre	Follow-up
[25]	Fischer et al. (2010)	United States	75,589	Patients	Apr 2004 to Mar 2005		180–365
0–365							
Fischer et al. (2011)	United States	280,081	Patients	Jul 2007 to Dec 2009	180	180	
[50]	Hansen et al. (2004)	Denmark	4,860	Patients	Jan 1998 to Jun 1999	1,825	180
[4]	Jackevicius et al. (2008)	Canada	4,591	Patients	2008	120	120
[42]	Karter et al. (2009)	United States	27,329	Patients	Jan 2004 to Jun 2008	730	30
[5]	Ko et al. (2009)	Canada	11,344	Patients	Dec 2003 to Mar 2007	90	365
[44]	Liberman et al. (2010)	United States	23,176	Prescriptions	Jan 2005 to Dec 2006	180	60
[19]	Raebel et al. (2011)	United States	15,147	Patients	Jan 2007 to Jul 2008	365	30
[31]	Raebel et al. (2011)	United States	16,173	Patients	Jan 2007 to Jul 2008	365	30
[9]	Shah et al. (2009)	United States	3,240	Patients	Jan 2002 to Dec 2006	365	30
[8]	Shah et al. (2009)	United States	1,132	Patients	Jan 2002 to Dec 2006	365	30
[34]	Shin et al. (2012)	United States	569,095	Prescriptions	Dec 2009 to Feb 2010	365	14
[35]	Shrank et al. (2010)	United States	5,249,380	Patients	Jul 2008 to Dec 2008	180	90
[36]	Solomon et al. (2009)	United States	17,183	Patients	1997–2002	365	0–1825
[55]	Storm et al. (2008)	Denmark	322	Patients	2006	180	28
[39]	Trinacty et al. (2009)	United States	1,906	Patients	1992–2001	365	365
[40]	Williams et al. (2007)	United States	1,064	Patients	Feb 2005 to May 2006	365	90
[59]	van Geffen et al. (2009)	The Netherlands	965	Patients	2001	180	30
[45]	Yood et al. (2008)	United States	236	Patients	At least 2.5 y	180	90

IMA, initial medication adherence; NA, not applicable/available.

* The data source perspective as reflected in the IMA process.

† The number of patients was reported unless it was not given; otherwise, prescriptions or pharmacies.

‡ Study period encompasses the look-back, dispensing event identification, and follow-up periods.

§ Some lengths were interpreted from provided statements such as from the prescribing event through the end of the study period. Months were interpreted as 30 days and a year as 365 days.

of which may introduce inaccuracies in the IMA metric—are to be addressed. *Perspective bias* occurs if prescribing or dispensing events are missed because data are limited to one perspective. For example, using data from only a pharmacist's perspective misses prescribing events, using data from only a prescriber's perspective misses dispensing events, and relying on a single administrative data source misses dispensing events if a patient opts out of using the covered benefit for another benefit source or for cash. *Substitution bias* occurs whenever the patient receives an alternative to the initially prescribed medication. Such substitutions may occur for various reasons, including insurance purposes, to minimize adverse drug reactions that might have been observed from a sample, in response to symptom improvements or negative test results, when an equivalent substitute is more readily available or less expensive, or when a newer medication with fewer adverse effects or with better therapeutic benefits is released. Any of these

substitutions qualify as a dispensing event for the initial medication and are the primary reasons that therapeutic classes rather than individual medications need to be a focus of IMA measurements. Finally, *censoring bias* occurs when events such as hospitalizations and death intervene to eliminate the possibility of capturing a dispensing event within the time frame of the research. The biases that a study addresses depend on the drugs and patient population being studied. For instance, censoring events such as rehospitalization and death may be more likely among patients discharged from the hospital after myocardial infarction. Likewise, patients prescribed therapies from certain medication classes, such as nonsteroidal anti-inflammatory drugs, may substitute prescribed medications for over-the-counter medicines without compromising medication intent or outcome. Finally, areas with a relatively transient population, such as a tourist location, may bias an IMA analysis if the patient returns home before filling the prescription.

A few studies have included supplemental parameters in their research design that addressed one or more of these three types of biases. Perspective bias has been addressed in several ways, including describing limits to the health care delivery system [48,50,57], determining from electronic health records whether prescriptions were transferred out of network [19,47], discovering erroneous transmittals to a pharmacy, and misidentifying PIMA as IMA [48]. Several more studies have applied criteria—such as system use and benefit eligibility—to ensure that dispensing event information would be captured [8,20–22,34]. Through surveys, studies have addressed substitution biases resulting from changing the prescribed medication before filling the original prescription [19], purchasing over-the-counter medication instead of the prescribed medication to reduce cost, and identifying instructions directing the patient to take the medication only if the symptoms persisted [51,53]. Others have addressed substitution bias by using a class coding system such as the Generic Product Indicator or the Anatomical Therapeutic Chemical classification rather than just the names of medications with the same active ingredients as those ordered in the original prescription [22,34,44,48,50,53,57,60,61]. Some researchers have even applied clinical criteria to ensure that medication substitutes were for the correct condition or diagnosis when multiple therapeutic possibilities existed for a medication. Furthermore, therapy changes made at the pharmacy could erroneously classify patients as nonadherent when they were actually switched to another class [8]. Death and emigration were two censoring events that Hansen et al. [50] used to exclude prescriptions from IMA calculations though the means used to identify the events were not presented. In other research, follow-up surveys/calls have been used to identify censoring events such as death and hospitalization [47,48].

Contextual Parameters

Although not central to the actual measurement of IMA, contextual parameters provide insight into the observed IMA rates and assist with understanding how the findings may be generalized across patient groups and health care environments. Contextual parameters comprise patient and nonpatient characteristics. Patient characteristics include demographic and behavioral factors such as age, sex, race, health beliefs, income, comorbidities, support network, and other patient-specific characteristics that might influence filling a prescription. Nonpatient characteristics include characteristics such as the health system, covered benefits, provider and pharmacy characteristics, and other factors that may influence the prescribing or dispensing events.

Research documenting a relationship between contextual parameters and PIMA is more prevalent than with IMA. Even some studies that purported to explore the relationships between IMA and contextual parameters actually studied PIMA instead, examining factors following a first prescription [62–64]. For those articles that examined IMA, associated factors included various patient and nonpatient factors, including demographic characteristics and socioeconomic status characteristics [35,56,59], specific medication or drug class [31,43], illness severity or medical comorbidities [5], and drug cost or pharmacy copayments [42,43]. In addition, health beliefs, concerns for adverse effects, and even receipt of medication counseling influenced the likelihood of IMA [4,45,53]. It should be noted that studies that expanded their goals to cover early implementation or persistence over 1 to 2 years revealed similar risk factors for poor adherence. When examining the role of patient characteristics or other behaviors associated with IMA, however, studies are needed to clearly document this goal through appropriate key words, abstract details, and Methods sections to identify their

objectives to the reader. This clarity distinguishes studies examining discontinuation or early implementation adherence from IMA.

Discussion/Recommendations for Good Practices

The ISPOR Medication Adherence Good Research Practices Working Group has developed a set of recommendations to guide future investigators into producing high-quality IMA research. Summarized in Table 2, these recommendations promote a standard of excellence for examining IMA. The recommendations should help researchers, health system practitioners, patients, and policymakers take advantage of this research and the implications arising from an increasingly important body of work.

General Recommendations

First among the general recommendations is to consistently use IMA when presenting research in this area. The IMA term was selected because it

1. reflects the position between prescribing and dispensing as the initial step along the medication adherence continuum [16].
2. fits well with PIMA as a means for describing the medication adherence continuum parts.
3. avoids some issues associated with the use of other terms.
 - a. “Abandoned” has been used almost exclusively from a pharmacist’s perspective to refer to prescriptions that were filled but not dispensed within their network. These studies miss dispensing events occurring outside their network and unrepresented prescribing events. In addition, these studies lack information on where a prescription belongs along the medication adherence continuum.
 - b. “Primary” has most often been used in prescriber’s perspective studies to reflect the filling of any new prescription regardless of where it occurs along the medication adherence continuum. Thus, it encompasses initial dispensing events associated with IMA and renewal dispensing events that often occur at least once a year. In Pharmacy Quality Alliance’s primary nonadherence metric, the term “primary” is limited to a pharmacist’s perspective (for pharmacy or pharmacy networks only), e-prescribed chronic medications, and a 30-day follow-up period that can detract from broader application [65]. The term primary also seems to imply that related terms, for example, secondary or tertiary, would be appropriate though they were not used in any medication adherence studies and do not appear as points along the medication adherence continuum.
 - c. “Acceptance” (and similar terms) has connotations that imply intentional patient motives for adherence that may not exist. For instance, patients may accept the need for the prescribed medication but lack the means to acquire it.
 - d. “Nonchronic,” an extension of referring to PIMA as chronic therapy, may be misconstrued to associate IMA only with acute or chronic medications though IMA applies to both.
 - e. “Early,” “first,” and other terms have been used for several PIMA metrics (e.g., early discontinuation, first-fill-drop off), contributing to the proliferation of terms and existing confusion.

By consistently using the IMA term throughout indexed key terms, abstracts, and within published articles, the identification of relevant research through search engine inquiries will become more systematized. This systemization will allow better

Table 2 – Recommendations for IMA research methodology.

Recommendations	Additional information/examples
General	
1 Use the term <i>initial medication adherence</i> .	Initial medication adherence describes the point along a treatment continuum being measured and should be used in titles, abstracts, key words, and throughout the manuscript.
2 State/define the specific research perspective taken.	Stating the data source perspectives—whether it be from the perspective of a patient, prescriber, or pharmacy, or a combined perspective—provides context for appropriately interpreting, finding, and identifying likely limitations to be addressed.
3 Delineate the core, supplemental, and contextual parameters that will be covered.	Core prescribing and dispensing event information must be provided or IMA cannot be measured. Supplemental parameters specific to the patient group and condition/symptoms being treated provide context for determining relevance, validity, and generalizability. Delineating the contextual factors enhances the salience of the research and improves the precision of the measurement.
Core	
4 Provide sufficient details on the prescribing event and the procedures for determining a new therapeutic class/initial Rx .	Ideally, prescribing event details include the following: <ul style="list-style-type: none"> • Scope of the data captured including data sources (e.g., provider charts and notes, patient surveys, medical records, and electronic medical or prescribing databases) and health care system within which patients are treated (e.g., closed, open but eligibility information verified). • Disease treated and the medications included in the therapeutic class covering possible adjunct or true initial therapy. • Actions taken to exclude renewed or other PIMA prescriptions, including length of time used to identify initiators. • Instructions the patient may have received that might impact filling behavior (e.g., PRN, or if symptoms persist).
5 Specify the dispensing event time frame for the dispensing event and justify selection .	Dispensing event details include the scope of the data captured, the fixed length of time after the prescribing event that a dispensing event was considered, how the length of time was determined, and any sensitivity analyses performed that support that the selected follow-up period for the therapeutic classes was long enough to not miss true dispensing events for the prescribing event, but short enough to not include other prescribing events.
Supplemental	
6 Address perspective bias by ensuring the comprehensiveness of information sources.	Address the limitation of the perspective taken, such as prescriptions being redeemed out of network, so that IMA rates will not be artificially low because of missed dispensing events.
7 Address substitution bias regardless of the source.	Address the bias that occurs from narrowly defining what constitutes a dispensing event by accounting for possible substitutions if multiple medications can be used to treat the same condition; benefit coverage favors lower costing alternatives including over-the-counter drugs.
Contextual	
8 Include patient characteristics information.	Patient characteristics such as treatment beliefs, insurance coverage, access barriers, disease severity, comorbidities, and support network provide additional context for interpreting and applying results to more relevant populations to the audience, particularly if the appropriate statistical test provide information on the relative association between individual characteristics and IMA.
9 Include nonpatient characteristics .	Nonpatient characteristics such as the health system (e.g., HMO or private family medicine clinic), provider, formularies, advocacy and other support groups, medications payment policies, connection among prescribing and dispensing units, and the pharmacy (e.g., onsite vs. community, paper vs. electronic prescription, HMO, and private family medicine clinic) can impact health policy, dissemination, generalizability, or quality improvement efforts made more salient if the associations have statistical significance.

Terms in bold highlight the key concepts that categorize the recommendations presented in the additional information/examples column and the term initial medication adherence was italicized to emphasize the importance of using the term. HMO, health maintenance organization; IMA, initial medication adherence; PIMA, postinitiation medication adherence; PRN, pro re nata (when necessary).

access to currently available information and reduce confusion and misunderstandings that impede comparisons across similar research.

The second recommendation requires specifying whether a patient, provider, pharmacy, or combined perspective is being taken to conduct the research. Each research perspective possesses its own advantages and disadvantages and therefore provides context as to the possible pitfalls in estimating IMA rates. These inherent pitfalls help determine which design parameters are most important to incorporate. The third recommendation is to delineate the specific elements or domains that the study addresses as the core, supplemental, and contextual study design parameters. These parameters provide vital information to the intended audiences by providing study context, details of the methodological approach, and information on the generalizability. All this information is useful for guiding interpretations and informing quality improvement efforts.

Core Recommendations

The core recommendations provide details on prescribing and dispensing events and on how the therapy was determined to be an initiation, including but not limited to

1. describing study design parameters that ensure
 - a. all the prescribing and dispensing events are being captured.
 - b. pre-prescribing and postprescribing event periods are long enough to account for common number of days supplied, possible substitutions, pharmacokinetics, pharmacodynamics, exhaustion of potential samples, return to stock, and similar issues related to the medication and data sources. For acute conditions, pre- and postprescribing periods may be as short as 7 to 10 days. For chronic conditions, pre-prescribing periods should be at least 6 months to a year and postprescribing, 15 to 30 days.
 - c. the same length of time is being used to determine whether a prescription in a prescribing event represents an initiation.
2. focusing on multiple medications rather than a single medication that can be used to treat the conditions/symptoms of the originally prescribed medication to ensure appropriate substitutions are considered.
3. explaining how the sample size was determined to be large enough to provide a valid measure.

Providing these details conveys information on the validity and reliability of the IMA calculations. At a minimum, these calculations should include an adherence rate (i.e., number of dispensing events divided by number of prescribing events), though calculating a time to initiation and metrics for multiple groups offers valuable insights and may have an association with clinical, financial, and utilization benefits. More research is needed to establish these associations.

Among the reviewed studies, those from a combined perspective are the only ones that consistently provided these core parameter details. Some of the other studies, however, do describe data sources they used to capture missing prescribing and dispensing event information. These data sources include medical charts, patient surveys, pharmacy records, claims databases, electronic prescribing databases, mobile phone “apps,” and other records. From our experiences, searching through paper-based records is time consuming and error prone, leading to misidentifying PIMA as IMA. Similarly, surveys can provide valuable information but they may be imprecise and are subject to patient recollection. Whether the effort and associated expenses to collect enough prescribing and dispensing events

from these sources is pursued may depend on the value those sources can provide for improving adherence. For instance, mobile phone applications might open direct communication lines between patients and providers that large electronic databases might not offer.

Electronic databases such as pharmacy records and claim databases can also have event capture issues. For instance, in the United States, \$4 generics being paid for with cash rather than being paid out by their pharmacy benefit manager as a usual and customary price may be missed and therefore requires steps to ensure that these gaps are addressed in the design. Studies that do not examine a patient's prescription history before a prescribing event long enough will include PIMA patients in an IMA measurement, likely overinflating the IMA estimate. This risk diminishes as the preperiod gets longer until it is long enough to cover all previous dispensing events. Determining the appropriate length for an acute or chronic condition requires considering supplemental factors presented later.

Conveying how well the core recommendations are met can be challenging depending on the data source perspective. A patient's perspective should have the most prescribing and dispensing event information, but the challenge is designing an efficient methodology to extract enough specific and detailed information to make it practical. A pharmacist's perspective may have dispensing information, but how completely dispensing events are captured, how prescribing events are captured, and how therapy initiation was determined are challenges that must be addressed. Research from a prescriber's perspective should have prescribing information, but it must describe how therapy initiations are determined and dispensing events are captured. In contrast, using electronic medical and claim records for a combined perspective provides a broader capture of prescribing and dispensing events information and leads to longer preperiods and follow-up periods. Longer periods can be and were sometimes used to determine their appropriate lengths. This may not, however, be an easy or practical option for many, and it faces challenges associated with complete capture of dispensing events. Regardless, any characteristics that may influence the timing or capture of the prescribing and dispensing events should be presented, as reflected in our Supplemental and Contextual Recommendations sections.

Supplemental Recommendations

Supplemental recommendations are intended to address the biases that may arise when measuring IMA. The first recommendation is to address perspective bias by ensuring the comprehensiveness of information sources. IMA rates will be artificially low if dispensing events occur outside of the perspective where they can be observed, such as when a patient has more than one health insurance system or pays with cash. For instance, in the United States, the extent to which a pharmacy benefit manager uses usual and customary pricing and deductible accumulation to increase the capture of \$4 generics would be valuable as context for assessing dispensing events in the claim database. The second recommendation is to address substitution bias, regardless of the source. Depending on the type of medication and available information, researchers should consider the possibility of substitution at the pharmacy, which may not qualify as nonadherent behavior. This may require a mechanism to identify filling within a therapeutic class as potential adherent behavior or consideration of potential over-the-counter substitution. Ideally, the focus should be ensuring that a patient starts recommended pharmacotherapy within a fixed time window, even if the therapy requires revision before receipt. Many studies do not report a procedure for identifying successful fills of revised prescriptions, and therefore may underestimate IMA.

In general, apparent nonadherent behavior based on available dispensing event information should rule out any instance in which a patient may actually be following instructions (e.g., *pro re nata* [when necessary], substitutions, and censoring events). One solution may involve a survey of nonadherent patients on the reasons for their nonadherence. Because a survey may not be feasible for every study, a review of the findings of similar studies noted within this article can identify possible alternative explanations for not filling a prescription. These explanations include filling the prescription outside the normal health benefit network, substituting therapeutically equivalent medications, not wanting any more medications, prescribing instructions to redeem a prescription if another criterion is met (e.g., symptoms persist/do not improve), or censoring due to emigration, uncaptured physician/pharmacist events, hospitalization, or death. The extent to which these can be addressed in the design should be clearly noted, and if not, the potential impact of this limitation is to be noted in the Discussion section. Overall, the researcher should recognize the limitations of the data and that most may not cover all physicians, pharmacists, or insurers.

Contextual Recommendations

Contextual recommendations are to include patient and non-patient characteristics within the study design. This information is crucial to understanding how observed IMA rates may apply or be adjusted to specific populations, thus impacting generalizability. Patient characteristics include health beliefs, insurance coverage, barriers to obtaining care, illness severity, and other medical or mental health comorbidities. These provide a better understanding of the importance of medication to the patient, and thus IMA. Investigating from the patient's perspective requires careful attention to the research design to elicit meaningful information. Some of the nonpatient characteristics include a description of the organization (e.g., health maintenance organization and private family medicine clinic), pharmacy formulary or medication co-payment policies, the pharmacy itself (onsite vs. community, paper vs. electronic prescription), and other nonpatient factors that can support health policy, dissemination, generalizability, or further quality improvement efforts.

Universal Recommendations

In addition to the IMA recommendation presented in Table 2, there are a few universal recommendations that apply to most, if not all, research. The objective of measuring IMA, research significance, and clinical implications should be presented clearly and concisely. In the Methods section, researchers should define the population, inclusion and exclusion criteria, and statistical analyses to be performed. The Methods section should also describe how the analyses will be performed and summarized, and tables for presenting the analyses should include multiple outcomes that present raw descriptive sample numbers, means, confidence intervals, and ranges, in addition to multivariable models as pertinent. The outcomes and explanatory variables should be clearly defined, including the rationale for all statistical tests undertaken—there should be a priori justification for associations. The Discussion section should tie results to stated objectives explaining how they relate to past research and openly acknowledge the strengths and limitations of the research methods, such as the potential for overstating adherence rates using medication possession ratios from administrative claim databases and surveys being subject to patient recall.

We strongly believe that observing and incorporating these recommendations into IMA research will foster better research, enhance documentation of key findings, and enable a broader

audience to understand and incorporate relevant findings into their clinical processes and patient outcomes improvement efforts. Much work lies ahead to fully understand the role of IMA in acute and chronic care, the health system, and provider and patient factors that collectively influence the treatment trajectory outlined here. Regardless of the perspective's data source limitation, IMA can be measured from any perspective if the research includes core, supplemental, and contextual design parameters.

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