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Systematic Review of Outcomes for Assessment of Medication Adherence Enhancing Interventions

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ISPOR Report

Systematic Review of Outcomes for Assessment of Medication Adherence Enhancing Interventions: An ISPOR Special Interest Group Report



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ABSTRACT

Objectives: The lack of universal guidance on outcome measures for evaluating medication adherence enhancing interventions (MAEIs) poses a challenge for assessing their effectiveness. This literature review aimed to provide a systematic overview of outcome measures currently used for the value assessment of MAEIs.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and searched MEDLINE, PsycINFO, Scopus, CINAHL, and Academic Search Complete for randomized and nonrandomized clinical trials, prospective cohort studies, model-based economic evaluations, and value frameworks published in English between January 2010 and September 2020. Two independent reviewers screened all titles and abstracts, followed by a full-text review. Due to the large number of relevant studies, data extraction was limited to articles published between January 2018 and September 2020. We collected data on the general characteristics of the study, the type of intervention, and the outcomes measured.

Results: We screened 14 685 records and identified 308 articles for data extraction. Behavioral interventions were the most common (n = 143), followed by educational interventions (n = 110) and mixed-method interventions (n = 73). Outcomes were clustered into 7 categories with medication adherence (n = 286) being the most frequently measured, followed by clinical outcomes (n = 155), health-related quality of life (n = 57), resource use (n = 43), patient satisfaction (n = 31), economic outcomes (n = 18), and other outcomes (n = 76).

Conclusions: Various outcomes measures have been used to evaluate MAEIs, with only a small number of studies exploring economic and patient-reported outcomes. Future research is warranted to develop a consensus-based set of criteria for assessing MAEIs to facilitate the comparison of interventions and enable informed decision making.

Keywords: medication adherence, medication adherence enhancing intervention, outcome measure, systematic literature review, value assessment.

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Introduction

Medication nonadherence is prevalent across all disease areas causing serious negative impact on clinical and economic outcomes.^{1–3} Although several medication adherence enhancing interventions (MAEIs) have been developed in recent years,^{4–6} only a few of them have been implemented in routine healthcare practice.^{7,8} An important obstacle to the implementation of MAEIs is the lack of evidence regarding their long-term impact on medication adherence and clinical outcomes.^{9,10} Moreover, existing data on the cost-effectiveness of MAEIs come mostly from low-quality studies. Consequently, health policy decisions about adherence interventions are based on poor and inadequate evidence.^{11,12}

In health technology assessment, the development and utilization of value frameworks have been increasingly popular.

Although they are primarily used for assessing pharmaceutical therapies (eg, medicines in general,¹³ orphan drugs,¹⁴ off-patent medicines¹⁵), they can also serve as effective tools to evaluate healthcare interventions (eg, integrated care delivery models,¹⁶ palliative care programs¹⁷). In these frameworks, value is often defined as a multidimensional concept comprising various perspectives, including benefits for patients (eg, improved symptoms, functioning, or prognosis), caregivers (eg, reduced burden of care), healthcare systems (eg, improved efficiency and quality of care), and society (eg, improved productivity).^{18,19} Key elements of value may depend on whose perspective the analysis is being undertaken, but patient health is central to the definition of value in these frameworks.^{19,20} Nevertheless, most current measurement efforts of healthcare interventions often fail to capture such comprehensive sets of outcomes needed to fully describe their impact.²¹

To understand the specific outcomes relevant to evaluating MAEIs, we need to determine the core elements of value by considering perspectives of different stakeholder groups, including patients, payers, healthcare providers, and the pharmaceutical industry. To facilitate this process, this study aimed to provide a systematic review of outcome measures currently used for assessing MAEIs in randomized and nonrandomized clinical trials, prospective cohort studies, and model-based economic evaluations and identified in published value frameworks of pharmaceutical and healthcare interventions. To the best of our knowledge, no previous systematic review has been performed on this topic.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement was followed for conducting and reporting this systematic literature review.²² The review protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42021242934).

Research Questions

First, the scope of the review was translated into clear and focused research questions according to the PICOS (population, intervention, comparison, outcome, and study) framework that enabled the literature search to be planned efficiently (Table 1).²³

This review was conducted based on the following research questions: (1) “Which outcomes are considered for the assessment of MAEIs in randomized and nonrandomized clinical trials, prospective observational studies, and model-based economic evaluations?” and (2) “Which criteria of published value frameworks could be considered for the assessment of MAEIs?”

Literature Search

The literature search covered 5 databases, that is, MEDLINE (via Ovid), APA PsycINFO (via Ovid), Scopus, CINAHL (via EBSCO), and Academic Search Complete (via EBSCO). The search strategy was developed collaboratively with a librarian, incorporating a combination of search strings related to medication adherence intervention, value assessment, study design, value framework, and pharmaceutical and healthcare intervention, allowing the capture of all relevant keywords and synonyms that may appear in the articles. The literature search was limited to studies published in the English language between January 2010 and September 2020. The exact search strategies for each database, along with the

number of search hits, are presented in Appendix 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.10.016>. Citation data of all identified search hits were imported into EndNoteX9 (Clarivate, London, United Kingdom) reference management software for creating a merged database.

Selection of Studies

The literature screening was conducted in 2 steps by 2 independent reviewers: step 1, title and abstract screening of all identified records; step 2, full-text screening of potentially eligible articles identified in step 1. To ensure a standardized approach and enhance the reviewers' understanding of the inclusion and exclusion criteria, a comprehensive online workshop was organized before the literature screening. This workshop aimed to equip the reviewers with the necessary skills and knowledge for the screening process. Given the high number of identified records, 12 pairs of reviewers were involved. Disagreements between the initial pair of reviewers on inclusion/exclusion were resolved by a third reviewer. Title and abstract screening were performed in Rayyan, a web-based tool for systematic reviews.²⁴

In our review, we included randomized and nonrandomized clinical trials, prospective observational studies, and model-based economic evaluations (eg, cost-effectiveness analysis) evaluating MAEIs and value frameworks related to medication adherence. Exclusion criteria were the following: (1) the presence of duplicate records; (2) the article did not have an abstract or an English abstract; (3) the article did not report original data (eg, letter, editorial, comment, review, guideline); (4) the presence of a study protocol; (5) the research was not a clinical trial, prospective observational study (observational studies that analyzed pre-existing data were excluded), model-based economic evaluation, or a value framework; (6) the study did not evaluate an MAEI or a value framework related to medication adherence; and (7) the presence of a systematic literature review or meta-analysis. The selection process was documented by a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. Risk of bias or quality assessment of included studies was not performed because this review aimed to describe the literature on outcomes and value criteria relevant for assessing adherence interventions and not for determining the comparative effectiveness of different MAEIs.

Data Extraction and Analysis

A pilot data extraction Microsoft Excel (Microsoft, Redmond, WA) spreadsheet was developed by 2 researchers (T.A., I.J.) and was circulated to all reviewers, together with an example extraction of a study. Each reviewer performed a pilot extraction of a study that was selected at random. After the pilot extraction, the data extraction grid was finalized according to comments of the research team. Data from the included studies were initially extracted by one reviewer, and subsequently, the extracted data were carefully reviewed by another independent reviewer to ensure accuracy.

The following data elements were extracted from the included studies: general characteristics of the study (ie, study type, number of participants, disease category, country, and number of assessed MAEIs), data on the type of intervention and value framework, and data on relevant outcomes and value criteria. Regarding the assessment of medication adherence or persistence outcomes, we did not collect data on the specific phase of the medication adherence process (ie, initiation, implementation, or discontinuation) to which it corresponded. Disease categories were defined according to the International Classification of Diseases 10th Revision.²⁵ MAEIs were clustered as behavioral,

Table 1. Review questions according to the PICOS framework.

P (population)	Patients receiving pharmacotherapy
I (intervention)	MAEIs
C (comparison)	NA
O (outcome of interest)	Outcomes or criteria for the value assessment of MAEIs
S (study design)	<ul style="list-style-type: none"> A) Clinical trials: randomized or non-randomized, controlled or single-arm trials B) Prospective observational studies C) Economic evaluations D) Value frameworks on pharmaceuticals and healthcare interventions

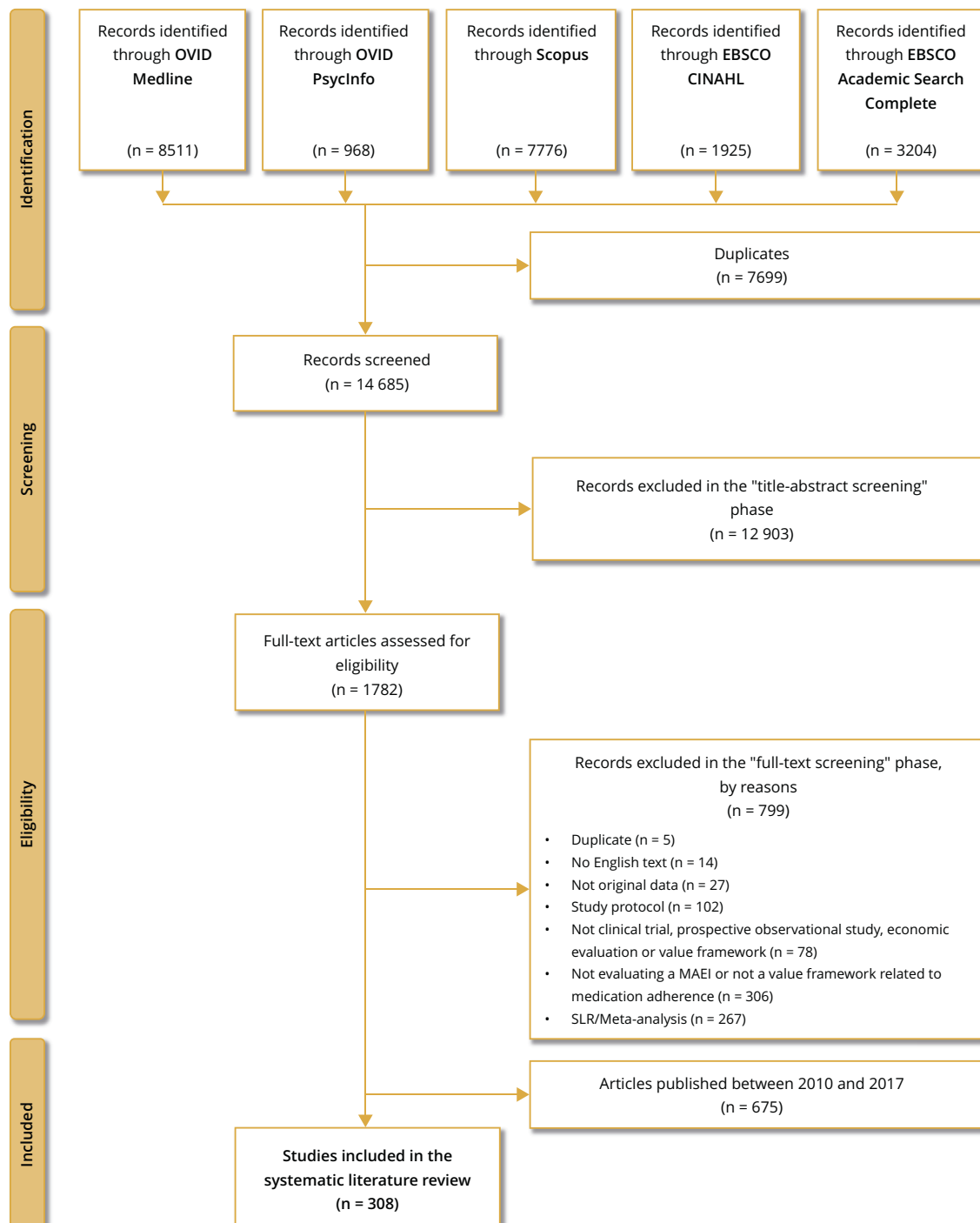
MAEI indicates medication adherence enhancing intervention; NA, not applicable.

educational, or mixed behavioral and educational interventions according to the framework applied by Cross et al.⁴

Initially, data extraction was performed on studies published between January 2018 and September 2020. However, because of data saturation and a significant volume of potentially relevant studies, we opted to limit the data extraction process to articles specifically published within this specified time frame.

After this, a narrative synthesis of the extracted data was performed. The researchers (T.A., M.H., B.B., C.B., A.T.S.) responsible for data analysis organized all identified outcomes into 7 distinct groups through a process of clustering: medication adherence or persistence, clinical, health-related quality of life (QOL), resource use, patient satisfaction, economic, and other outcomes. Where appropriate, they further divided these groups

Figure 1. Flowchart of the selection of studies for the systematic review.



into suboutcomes based on similarities, using an iterative process. Descriptions of these groups and subgroups can be found in [Appendix 2 in Supplemental Materials](#) found at <https://doi.org/10.1016/j.jval.2023.10.016>.

As a final step, we used the Pearson's chi-square test to examine associations between outcome groups and both geographical regions of studies and their publication years. All analyses were conducted using R version 4.1.2. (R Foundation, Vienna, Austria), with a significance level set at 0.05.

Results

After removing duplicates, the literature search resulted in 14 685 records between 2010 and 2020. The titles and abstract screening identified 1782 potentially eligible articles; 799 records were excluded during full-text screening. Finally, of the 983 relevant articles, we restricted data extraction to articles published between 2018 and 2020 ([Fig. 1](#)). The list of included articles is available in [Appendix 3 in Supplemental Materials](#) found at <https://doi.org/10.1016/j.jval.2023.10.016>.

The general characteristics of studies included in the literature review are presented in [Table 2](#). There were 218 clinical trials, 79 prospective cohort studies, and 11 economic evaluations. No relevant value framework studies were identified. The articles originated from 59 countries with most being conducted in the United States ($n = 105$). The mean study sample size was 702 participants, whereas the range of participants was from 4²⁶ to 60 232.²⁷ In the studies included, the most frequent medical conditions were diseases of the circulatory system ($n = 67$) and certain infectious diseases ($n = 58$; eg, HIV or AIDS).

Types of Interventions

Most studies evaluated 1 MAEI ($n = 291$). The total number of identified interventions was 326 whereby 143 were behavioral interventions, 110 were educational interventions, and 73 were mixed-method interventions ([Table 3](#)). Reminder-based interventions ($n = 48$) were the most common type of behavioral interventions; educational interventions were group or individual education provided by pharmacists, physicians, nurses, or other healthcare providers.

Types of Outcomes

The most frequently assessed outcomes in included studies were medication adherence or persistence ($n = 286$) and clinical outcomes ($n = 155$) ([Fig. 2](#)). The mean number of outcomes per study was 3.17, ranging from 1 to 11. The distribution of outcome groups showed no significant variation by geographical regions or years of publication ([Appendix 4 in Supplemental Materials](#) found at <https://doi.org/10.1016/j.jval.2023.10.016>).

Identified outcomes are presented in [Table 4](#). Under the medication adherence or persistence outcome group, 9 sub-outcome groups were created according to the different measurements methods applied, such as self-reported methods (eg, 4- or 8-item Morisky Medication Adherence Scale), methods using medical or pharmacy claims or prescription refills data, or methods using electronic medication monitoring devices (eg, Medication Event Monitoring System). Among studies that assessed medication adherence using medical or pharmacy claims or prescription refill data, the medication possession ratio (in general, calculated as the total number of days of medication supplied within a specific time frame divided by the number of days in that time frame) was used in 30% of studies ($n = 16$). Meanwhile, the proportion of days covered (in general, the proportion of days a patient has medication coverage for a specific

Table 2. General characteristics of the included studies.

Characteristic	n of studies (%)
Total number of included studies	308 (100)
Year of publication	
2018	107 (35)
2019	123 (40)
2020*	78 (25)
Study type	
Clinical trial	218 (71)
Prospective cohort study	79 (26)
Economic evaluation	3 (1)
Economic evaluation and clinical trial	5 (1)
Economic evaluation and prospective cohort study	3 (1)
Study country	
United States	105 (34)
China	17 (6)
The Netherlands	16 (5)
Iran	11 (4)
India	10 (3)
Other	149 (48)
Number of participants	
<100 participants	121 (39)
100-1000 participants	161 (53)
>1000 participants	23 (7)
NA [†]	3 (1)
Disease category (ICD-10)	
Disease of the circulatory system	67 (22)
Certain infectious or parasitic disease	58 (19)
Endocrine, nutritional, or metabolic disease	32 (10)
Disease of the respiratory system	27 (9)
Mental or behavioral disorder	23 (7)
Other	101 (33)
Number of assessed MAEIs per study	
1 intervention	291 (94.5)
2 interventions	16 (5.2)
3 interventions	1 (0.3)

ICD-10 indicates International Classification of Diseases 10th Revision; MAEI, medication adherence enhancing intervention; NA, not applicable.
*Articles published until September 2020.
[†]Economic evaluations.

time frame) method was used in 20% ($n = 11$). These 2 adherence calculation methods were the most frequently applied in studies using medical or pharmacy claims or prescription refills data. For monitoring medication adherence or persistence, some studies ($n = 66$) used multiple measurement methods in parallel.

Most of clinical outcome measures were related to disease control (eg, blood pressure in hypertension), and the effect of MAEIs on mortality was assessed in 7 studies. Resource use and economic outcomes were grouped into 3 categories (ie, in- or outpatient care, nurse visit or emergency room visit, use of intervention, and medication utilization) and 4 categories (ie, cost-effectiveness or cost-utility, direct medical cost, productivity loss, and indirect medical cost), according to the measured endpoints, respectively. Health-related QOL and patient satisfaction outcomes were evaluated by different patient-reported outcome measurements (eg, health-related QOL, EQ-5D; patient satisfaction, System Usability Scale). In addition, we also identified 43 further outcomes that could not be classified in any of the abovementioned outcome categories (eg, disease knowledge, self-efficacy, medication beliefs, and coping).

Table 3. Type of interventions assessed in the included studies.

Intervention type	n of MAEIs (%)
Behavioral intervention	143 (44)
Reminders (eg, mail, telephone, email)	48 (15)
Adherence monitoring with or without feedback	18 (6)
Follow-up (eg, home visit, scheduled clinic visit)	12 (4)
Tailoring (routinization)	10 (3)
Skill building (supervised, group)	8 (2)
Multicompartment pillbox or calendar pack or compliance aid	5 (1.5)
Reminder chart or medication list	5 (1.5)
Other	37 (11)
Educational intervention	110 (34)
Mixed behavioral and educational intervention	73 (22)

MAEI indicates medication adherence enhancing intervention.

Discussion

This study provides a systematic overview of the scientific evidence on key outcome measures used to assess MAEIs. Previous literature reviews have mainly investigated the type and effectiveness of interventions for improving medication adherence in different age cohorts and certain medical conditions,^{4,28-33} but no previously published systematic literature review has focused specifically on study outcomes.

We identified a range of MAEIs being conducted in different patient populations. Of the 308 studies analyzed, most interventions were behavioral (44%), including reminders (eg, mail, telephone, email) and adherence monitoring technologies. Although mixed methods—behavioral and educational—interventions are considered the most effective to improve medication adherence,^{34,35} only 22% of studies applied mixed MAEIs. It is important to note that our review did not aim to draw any definitive conclusions regarding the most effective interventions.

Previous reviews have highlighted the challenge of comparing MAEIs because of heterogeneity in study methods and variations in outcome measures.^{9,10} However, high-quality evidence on the effectiveness of interventions is crucial for decision making regarding their implementation. Recommendations of core outcomes relevant to the assessment of MAEIs and their validated measures could help to address this issue and improve the overall quality of clinical research for interventions aimed at addressing medication adherence.

There is no “gold standard” for measuring medication adherence in research settings; each method has advantages and disadvantages. In the studies we reviewed, various outcomes were used to measure medication adherence. The most used method was self-reported adherence measures, although there are concerns about their accuracy.^{36,37} Self-report questionnaires, even validated ones, tend to overestimate medication adherence because of social desirability and memory biases. However, self-report measures can provide valuable information on determinants and reasons for nonadherence.³⁸ Electronic medication monitoring was applied in only 17% of studies but it has the advantage of assessing the timing and patterns of dose taking. To overcome the shortcomings of various adherence measures, it is recommended to combine multiple methods. The selection of specific approaches to be combined should be determined according to the clinical or research context. Although combining multiple methods can improve the accuracy of measuring adherence, only 21% of studies have used this approach. In addition, there is a lack of consensus on an appropriate cutoff point for determining nonadherence, which also limits the comparability of results across studies. The use of standardized terminology, measurement, and analysis methods, such as the ESPACOMP ABC Taxonomy and the Medication Adherence Reporting Guideline, can greatly enhance consistency in reporting medication adherence research, facilitating better comparability and synthesis of research findings.³⁹⁻⁴¹ According to the ABC Taxonomy,⁴⁰ the process of medication adherence can be divided into 3 phases: initiation, implementation, and discontinuation. These phases represent distinct aspects of adherence behavior. Group-based

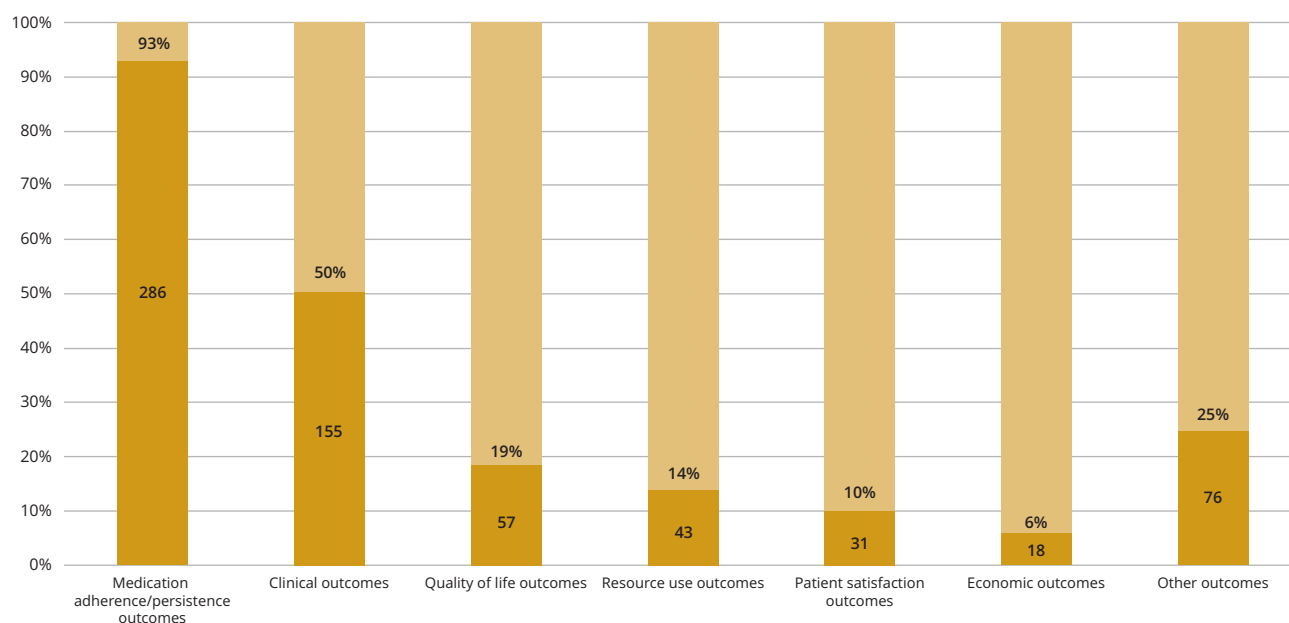
Figure 2. Percentage and number of studies per outcome category (n = 308).

Table 4. Outcomes identified in the included studies.

Outcome group	Suboutcome group	n of studies (%)
Medication adherence or persistence outcomes	Self-report method	178 (57.8)
	Medical or pharmacy claims or prescription refills data	54 (17.5)
	Electronic medication monitoring	51 (16.6)
	Pill count	20 (6.5)
	Clinical drug testing measure	7 (2.3)
	Caregiver-reported adherence	3 (1.0)
	Clinician-reported adherence	3 (1.0)
	Direct observation	1 (0.3)
	Method not reported	6 (1.9)
Clinical outcomes	Disease control	129 (41.9)
	Disease burden	17 (5.5)
	Laboratory parameter	13 (4.2)
	Lifestyle	11 (3.6)
	Safety or adverse event	11 (3.6)
	Body weight or abdominal perimeter	7 (2.3)
	Mortality	7 (2.3)
Resource use outcomes	Inpatient, outpatient care, nurse visit, or emergency room visit	32 (10.4)
	Use of intervention	11 (3.6)
	Medication utilization	4 (1.3)
Health-related quality of life outcomes	Health-related quality of life	57 (18.5)
Economic outcome	Cost-effectiveness or cost-utility	10 (3.2)
	Direct medical cost	7 (2.3)
	Productivity loss	2 (0.6)
	Indirect medical cost	1 (0.3)
Patient satisfaction outcomes	Patient satisfaction	31 (10.1)
Other outcomes	Disease knowledge	16 (5.2)
	Beliefs about medicines	12 (3.9)
	Self-efficacy	10 (3.2)
	Disease management	7 (2.3)
	Stigma related to the disease or medication	5 (1.6)
	Communication	4 (1.3)
	Inhalation technique	4 (1.3)
	Coping	3 (1.0)
	Medication knowledge	3 (1.0)
	Self-care	3 (1.0)
	Barriers of adherence	3 (1.0)
	Social support	2 (0.6)
	Perceived support	2 (0.6)
	Intention to adhere	2 (0.6)
	Health literacy	2 (0.6)
	Motivation	2 (0.6)
	Absence from school	2 (0.6)
	Perception	1 (0.3)
	Behavioral control	1 (0.3)
	Caregiver burden	1 (0.3)
Concerns	1 (0.3)	
Decisional conflict	1 (0.3)	

continued on next page

Table 4. Continued

Outcome group	Suboutcome group	n of studies (%)
	Emotional stress	1 (0.3)
	Engagement with healthcare provider	1 (0.3)
	Expectancy	1 (0.3)
	Habit strength for taking medication	1 (0.3)
	Implementation	1 (0.3)
	Infection transmission risk	1 (0.3)
	Loss to follow-up	1 (0.3)
	Medication administration errors	1 (0.3)
	Medication appropriateness	1 (0.3)
	Medication intake-related skills	1 (0.3)
	Medication management	1 (0.3)
	Nurse satisfaction	1 (0.3)
	Patient's behavior	1 (0.3)
	Problem-solving ability	1 (0.3)
	Problems with using medications	1 (0.3)
	Risk reduction behavior	1 (0.3)
	Self-esteem	1 (0.3)
	Self-regulation	1 (0.3)
	Social desirability	1 (0.3)
	Social functioning	1 (0.3)
	Subjective norms toward medication adherence	1 (0.3)

trajectory models can provide valuable insights into the dynamic nature of adherence behavior over time.⁴² By considering both the quantity and timing of medication availability, these models enable the identification of patients with unique adherence patterns. Moreover, these trajectory models have the potential to deepen our understanding of intervention effectiveness in different phases of adherence. They can help determine the effect of MAEIs at specific phases and may assist in identifying outcome measures that effectively capture their impact.

The second group of most commonly investigated outcomes was clinical outcomes (50%), which were primarily assessed using standardized clinical measures for disease and symptom control. However, only very few studies evaluated the impact of MAEIs on mortality (2.3%). Especially in the case of interventions aimed to improve adherence to chronic pharmacotherapies, future studies should examine not only the short-term but also the long-term clinical consequences of MAEIs on morbidity and mortality (eg, progression-free survival, overall survival). Such studies would be necessary to fully understand the benefits of these interventions on patients' health outcomes.

This review has revealed that only a small number of studies investigated resource use (14%) and economic outcomes (6%). The number of economic analyses was even lower, with only 4% of studies performing an economic evaluation. A recent study conducted in Europe identified a very limited number of reimbursed MAEIs (13 reimbursed interventions in 39 countries), which can be partly attributed to the low and poor quality of existing evidence on the economic aspects of adherence interventions.⁷ Clinical outcomes associated with MAEIs alone are insufficient for proper decision making regarding implementation and reimbursement.⁴³ When evaluating the economic impact of these

interventions, it is crucial to consider all relevant cost elements, which can be influenced by the perspective of the analysis (ie, payer, provider, or societal perspective) and the type of the MAEI being investigated. For example, in case of an economic analysis performed from the provider perspective, the implementation costs of adherence services should also be considered. From the societal perspective, all costs borne by the patients, their families, and informal caregivers (eg, transportation costs, productivity loss of the patient or informal caregiver) should also be included in the analysis. Health economics guidelines are highly necessary on the standard principles of good economic analysis specific for MAEIs and a better understanding of the accurate economic outcomes of adherence interventions. Enhancing the quality of studies, as assessed by international guidelines (eg, Consolidated Health Economic Evaluation Reporting Standards, Agency for Healthcare Research and Quality), could significantly enhance decision makers' confidence in the comparative effectiveness results of MAEIs.

Integrating the patient's perspective is crucial in the evaluation of adherence interventions given that patients are the ultimate decision makers in adhering to their treatment plan. Their subjective feedback can provide valuable insights into the acceptability and effectiveness of MAEIs, which can contribute to improving adherence interventions in the future. However, it is concerning that health-related QOL was measured in <20% of studies and patient satisfaction in only 10% of studies, highlighting the need to prioritize the patient voice in future adherence intervention evaluations. It is also important to note that the relationship between medication nonadherence and health-related QOL can be influenced by various factors.^{44,45} Non-adherence can lead to a decrease in a patient's health-related QOL

because of increased morbidity or side effects (eg, resulting from overdosing). However, in some cases, nonadherence may actually improve a patient's health-related QOL, if the therapy has unpleasant side effects, interferes with their daily routine, or causes social stigma, such as using inhalers or injections in public. This nonlinear relationship between medication nonadherence and health-related QOL is an important phenomenon that future clinical studies and cost-effectiveness analyses must take into consideration. Furthermore, a significant shift toward patient centricity is underway, urging us to broaden our perspectives to encompass the full range of impacts associated with MAELs. This movement emphasizes the development of "patient-centered core impact sets" that comprehensively capture not only the health outcomes reported by healthcare providers but also the additional concerns that patients deem significant in relation to their disease or treatment.⁴⁶ By incorporating patient perspectives and aligning with evolving regulatory standards, we can facilitate the development of interventions that address the outcomes that hold true value for patients and enhance the evaluation of adherence interventions, making it more comprehensive and patient centered.

In our systematic review, we identified 43 additional outcomes that extended beyond the main outcome categories. These encompassed diverse aspects, including disease knowledge, self-efficacy, medication beliefs, and coping, highlighting the multidimensional nature of medication adherence-related outcomes. Future studies should prioritize investigating the significance of these additional outcomes in evaluating MAELs and exploring their interrelationships and potential mediating or moderating effects.

Considering the wide range of diverse outcomes used in the evaluation of MAELs, it is important to establish guidance on the most crucial criteria. As a follow-up, based on the results of this literature review, the ISPOR Medication Adherence and Persistence Special Interest Group plans to undertake focus groups and a Delphi panel study involving various stakeholders (ie, patients, payers, industry, healthcare providers, and industry) to develop consensus-based value criteria for evaluating MAELs. The development of such criteria would enable a standardized and consistent approach to evaluating MAELs, leading to improved accuracy and relevance of assessments.

Our results should be considered in the light of the following limitations. First, our systematic review only included articles published in English, potentially excluding relevant studies published in other languages. However, evidence suggests that the exclusion of non-English languages does not introduce bias in systematic review-based meta-analyses.⁴⁷ Second, despite conducting searches across multiple databases and performing reference mining, there remains a possibility of overlooking relevant studies given that our search was limited to published literature only. We did not conduct a search specifically targeting gray literature (eg, conference proceedings, government reports, dissertations), which may have resulted in the omission of valuable information. Third, we did not perform a risk of bias or quality assessment of the included studies. Our objective was to gather information on the outcomes used for assessing adherence interventions, without evaluating the results of these studies. It is important to note that most quality assessment tools are largely result centric, focusing marginally on the outcomes being assessed. Therefore, using these tools might not have provided a meaningful or relevant assessment in our context. Moreover, our review spans a diverse set of study designs, such as clinical trials, prospective observational studies, economic evaluations, and value frameworks. To the best of our knowledge, no existing quality assessment tool can uniformly and comprehensively gauge the quality of these varied study

formats. Using multiple quality assessment tools for different study categories could have potentially introduced a degree of inconsistency in our review process. We assumed that the study quality does not affect the outcomes used in the study. However, it is important to note that further studies would be needed to thoroughly investigate this assumption and provide a more comprehensive understanding of it. Fourth, it is also important to acknowledge that our data extraction and analysis were limited to studies published from January 2018 to September 2020. This time frame restriction could potentially limit the generalizability of our findings; however, it is worth noting that data saturation was achieved during the study.

Conclusions

This systematic literature review focused on outcomes of studies examining MAELs. Most interventions found in the review were behavioral, with the most common methods being reminders and monitoring technologies. Our findings highlight a lack of agreement on appropriate outcome measures for evaluating MAELs and provide evidence that only a small number of studies explored economic and patient-reported outcomes. To address these limitations, developing consensus-based value criteria for assessing MAELs can be suggested. Such criteria could aid in standardizing evaluation methods and ultimately improve the effectiveness of MAELs.

Author Disclosures

Links to the individual disclosure forms provided by the authors are available [here](#).

Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2023.10.016>.

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REFERENCES

- Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*. 2018;8(1):e016982.
- Inotai A, Ágh T, Maris R, et al. Systematic review of real-world studies evaluating the impact of medication non-adherence to endocrine therapies on hard clinical endpoints in patients with non-metastatic breast cancer. *Cancer Treat Rev*. 2021;100:102264.
- Mongkhon P, Ashcroft DM, Scholfield CN, Kongkaew C. Hospital admissions associated with medication non-adherence: a systematic review of prospective observational studies. *BMJ Qual Saf*. 2018;27(11):902–914.
- Cross AJ, Elliott RA, Petrie K, Kuruvilla L, George J. Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. *Cochrane Database Syst Rev*. 2020;5(5):CD012419.
- Gohil S, Majd Z, Sheneman JC, Abughosh SM. Interventions to improve medication adherence in inflammatory bowel disease: a systematic review. *Patient Educ Couns*. 2021;105(7):1731–1742.
- Whiteley LB, Olsen EM, Haubrick KK, Odoom E, Tarantino N, Brown LK. A Review of interventions to enhance HIV medication adherence. *Curr HIV AIDS Rep*. 2021;18(5):443–457.
- Ágh T, Hadziabdić MO, Garuoliene K, et al. Reimbursed medication adherence enhancing interventions in European countries: results of the EURECa Study. *Front Pharmacol*. 2022;13:892240.
- Kostalova B, Ribaut J, Dobbels F, et al. Medication adherence interventions in transplantation lack information on how to implement findings from randomized controlled trials in real-world settings: a systematic review. *Transpl Rev Or*. 2022;36(1):100671.
- Systematic review: closing the quality gap series: medication adherence interventions: comparative effectiveness. Effective Health Care Program, Agency for Healthcare Research and Quality. <https://effectivehealthcare.ahrq.gov/products/medication-adherence-interventions/research>. Accessed March 15, 2021.
- Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014;11:CD000011.
- Simon-Tuval T, Neumann PJ, Greenberg D. Cost-effectiveness of adherence-enhancing interventions: a systematic review. *Expert Rev Pharmacoecon Outcomes Res*. 2016;16(1):67–84.
- Al-Aqeel S, Alsugair J, Alghamdi R. Economic evaluation of interventions to improve medication adherence among patients with chronic diseases: an overview of systematic reviews. *Expert Rev Pharmacoecon Outcomes Res*. 2023;23(2):153–179.
- Angelis A, Kanavos P. Multiple criteria decision analysis (MCDA) for evaluating new medicines in health technology assessment and beyond: the advance value framework. *Soc Sci Med*. 2017;188:137–156.
- Annemans L, Ayme S, Le Cam Y, et al. Recommendations from the European working group for value assessment and funding processes in rare diseases (ORPH-VAL). *Orphanet J Rare Dis*. 2017;12(1):50.
- Brixner D, Maniadakis N, Kaló Z, Hu S, Shen J, Wijaya K. Applying multi-criteria decision analysis (MCDA) simple scoring as an evidence-based HTA methodology for evaluating off-patent pharmaceuticals (OPPs) in emerging markets. *Value Health Reg Issues*. 2017;13:1–6.
- Santos FA, Margotti AE, Garcia R. Multi-criteria decision aid (MCDA) as a tool to support health technology incorporation process. Paper presented at: World Congress on Medical Physics and Biomedical Engineering; May 26–31, 2012, Beijing, China.
- Brereton L, Wahlster P, Lysdahl KB, et al. Integrated assessment of home based palliative care with and without reinforced caregiver support: a demonstration of INTEGRATE-HTA methodological guidances. University of Lincoln. <https://eprints.lincoln.ac.uk/id/eprint/26368/>. Accessed March 15, 2021.
- Neumann PJ, Willke R, Garrison LP. A health economics approach to US value assessment frameworks - introduction: an ISPOR Special Task Force Report [1]. *Value Health*. 2018;21(2):119–123.
- Henshall C, Schuller T, HTAI Policy Forum. Health technology assessment, value-based decision making, and innovation. *Int J Technol Assess Health Care*. 2013;29(4):353–359.
- Garrison LP, Pauly MV, Willke RJ, Neumann PJ. An overview of value, perspective, and decision context—a health economics approach: an ISPOR Special Task Force Report [2]. *Value Health*. 2018;21(2):124–130.
- Porter ME. What is value in health care? *N Engl J Med*. 2010;363(26):2477–2481.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
- Amir-Behghadami M, Janati A. Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. *Emerg Med J*. 2020;37(6):387.
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.
- ICD-10: international statistical classification of diseases and related health problems : tenth revision, 2nd ed. World Health Organization. <https://apps.who.int/iris/handle/10665/42980>. Accessed March 15, 2021.
- Tellier M, Claudine A, Bier N, Demers L. Use of an electronic pillbox by older adults with mild Alzheimer's disease: impact on medication administration and adherence. *Gerontechnology*. 2020;19(1):66–76.
- Johnson K, Kirby J, Kayse A, Brookhart A, Frede S, Hincapie A. Impact of an adherence intervention program on patient adherence and star ratings measures in a large community pharmacy chain. *J Am Pharm Assoc (2003)*. 2020;60(4):e70–e78.
- Geneen LJ, Dorée C, Estcourt LJ. Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia. *Cochrane Database Syst Rev*. 2023;3(3):CD012349.
- Davies A, Mullin S, Chapman S, et al. Interventions to enhance medication adherence in pregnancy- a systematic review. *BMC Pregnancy Childbirth*. 2023;23(1):135.
- Shrivastava TP, Goswami S, Gupta R, Goyal RK. Mobile app interventions to improve medication adherence among type 2 diabetes mellitus patients: a systematic review of clinical trials. *J Diabetes Sci Technol*. 2023;17(2):458–466.
- Al-Arkee S, Al-Ani O. Community pharmacist-led interventions to improve medication adherence in patients with cardiovascular diseases: a systematic review of randomised controlled trials. *Int J Pharm Pract*. 2023;31(3):269–275.
- Chilala CI, Kassavou A, Sutton S. Evaluating the effectiveness of remote behavioral interventions facilitated by health care providers at improving medication adherence in cardiometabolic conditions: a systematic review and meta-analysis. *Ann Behav Med*. 2023;57(2):99–110.
- Lin G, Zheng J, Tang PK, Zheng Y, Hu H, Ung COL. Effectiveness of hospital pharmacist interventions for COPD patients: a systematic literature review and logic model. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2757–2788.
- Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health Syst Pharm*. 2003;60(7):657–665.
- Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care*. 1998;36(8):1138–1161.
- Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med*. 2015;5(4):470–482.
- Wilson IB, Carter AE, Berg KM. Improving the self-report of HIV antiretroviral medication adherence: is the glass half full or half empty? *Curr HIV/AIDS Rep*. 2009;6(4):177–186.
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–497.
- Raebel MA, Schmittiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care*. 2013;51(8 suppl 3):S11–S21.
- De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP medication adherence reporting guideline (EMERGE). *Ann Intern Med*. 2018;169(1):30–35.
- Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691–705.
- Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51(9):789–796.

43. Kardas P, Bago M, Barnestein-Fonseca P, et al. Reimbursed medication adherence enhancing interventions in 12 European countries: current state of the art and future challenges. *Front Pharmacol*. 2022;13:944829.
44. Ágh T, Dömötör P, Bártfai Z, Inotai A, Fujsz E, Mészáros Á. Relationship between medication adherence and health-related quality of life in subjects with COPD: a systematic review. *Respir Care*. 2015;60(2):297–303.
45. National Collaborating Centre for Primary Care (UK). *Medicines Adherence: Involving Patients in Decisions About Prescribed Medicines and Supporting Adherence*. London, United Kingdom: Royal College of General Practitioners UK; 2009.
46. Perfetto EM, Oehrlein EM, Love TR, Schoch S, Kennedy A, Bright J. Patient-centered core impact sets: what they are and why we need them. *Patient*. 2022;15(6):619–627.
47. Morrison A, Polisen J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care*. 2012;28(2):138–144.