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**TEOS: A framework for constructing operational definitions of medication adherence based on Timelines – Events – Objectives – Sources**

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**What is already known about this subject:**

- The recent ABC and EMERGE guidelines provide recommendations on defining and reporting on adherence to medications but implementing these in research practice offers numerous challenges.

**What this study adds:**

- We propose TEOS, a framework for constructing operational definitions of medication adherence.
- It outlines four components: Timelines, key Events, research Objectives and design, and available data Sources.
- TEOS guides researchers to consider a broad range of questions regarding each component and record decisions and operational definitions explicitly.

**Abstract**

**Aim:** Managing adherence to medications is a priority for health systems worldwide. Adherence research is accumulating, yet the quality of the evidence is reduced by various methodological limitations. In particular, the heterogeneity and low accuracy of adherence measures have been highlighted in many literature reviews. Recent consensus-based guidelines advise on best practices in defining adherence (ABC) and reporting of empirical studies (EMERGE). While these guidelines highlight the importance of operational definitions in adherence measurement; such definitions are rarely included in study reports. To support researchers in their measurement decisions, we developed a structured approach to formulate operational definitions of adherence.

**Methods:** A group of adherence and research methodology experts used theoretical, methodological and practical considerations to examine the process of applying adherence definitions to various research settings, questions and data sources. Consensus was reached through iterative reviewing of discussion summaries and framework versions.

**Results:** We introduce TEOS, a four-component framework to guide the operationalization of adherence concepts: 1) describe treatment as four simultaneous interdependent *timelines* (recommended and actual use, conditional on prescribing and dispensing); 2) locate four key *events* along these timelines to delimit the three ABC phases (first and last recommended use, first and last actual use); 3) revisit study *objectives and design* to finetune research questions and assess measurement validity and reliability needs, and 4) select data *sources* (e.g., electronic monitoring, self-report, electronic healthcare databases) that best address measurement needs.

**Conclusion:** Using the TEOS framework when designing research and reporting explicitly on these components can improve measurement quality.

## Introduction

Research on medication adherence has developed substantially in recent years.[1] It has produced to date important knowledge on adherence behaviours and their determinants [2,3], their relationship to health and economic outcomes[4–7], and possible solutions to enhance adherence[8]. These findings show that suboptimal adherence is common and multidetermined, and that enhancing adherence is important for reducing the individual and societal burden of disease. However, evidence synthesis is constrained by considerable heterogeneity in study results; systematic reviews continue to highlight the low quality of measurement and high heterogeneity in adherence measures as one of the barriers for synthesizing results across studies.[3,4,8–10] So far, various measures have been used in research and clinical practice, many with limited theoretical grounding and little or no validation.[11] Important differences in estimates of adherence and its relationships with determinants and outcomes have been reported depending on the methods used for calculating adherence to the same medication, on identical or comparable populations and time periods.[12–16] Improvement of adherence measurement is therefore a priority for the field.

Several guidelines and recommendations have been proposed to improve the precision and standardization in adherence definitions and measurement. The consensus-based theoretical framework developed within the ABC (Ascertaining Barriers to Compliance) project[17] provided conceptual definitions for adherence and terminology that have been widely adopted in adherence research. ABC distinguished between three phases: initiation (starting treatment), implementation (following the treatment as prescribed), and discontinuation (stopping treatment). It also highlighted the need to measure each independently and investigate specific causes and consequences for effective adherence management. Several literature reviews have proposed recommendations on adherence measurement and its three phases either by comparing different data sources[11,18–20] or by reviewing alternative methods using the same type of data

source.[16,21] They converge towards the view that there is no single, 'gold standard' measure for the overarching concept of medication adherence. Instead, optimal measurement needs to consider numerous theoretical, methodological and practical aspects and find a balance between generalizability and adaptation to the specific needs of individual studies.

Guidelines for reporting adherence research have been proposed recently. For clinical trials, an outcome specification format has been suggested which requires information on four levels: domain, specific measurement, specific metric, and aggregation method.[22] The EMERGE guidelines[23] adapted this general format for adherence research and recommended four reporting criteria largely following the same process of specification from abstract to concrete: adherence phase(s), operational definitions, measurement methods including metric and statistical details, and summary results. However, while conceptual definitions and measures are commonly reported in empirical studies, *operational definitions* are rarely detailed. In this paper we propose practical recommendations we believe will facilitate the development and description of operational definitions.

## Methods

Following the development of the EMERGE guidelines, an adherence methodology working group was convened, comprising of six experts in adherence measurement (each a member of ESPACOMP, four also members of the EMERGE steering committee). The working group collaborated between November 2016 and November 2019 to develop practical recommendations for operational definitions of medication adherence, consistent with components of good research practice, as part of a broader initiative to improve measurement and analysis standards in adherence research. Key theoretical and methodological bases were the ABC adherence taxonomy, the EMERGE guidelines and the three-step measurement process well-established in psychometric literature.[24] The first step of this measurement process

– *definition* – identifies the attribute(s) to be measured and is represented in adherence research by the ABC taxonomy. The second step – *operationalization* – ascertains what needs to be done practically to know how the attribute(s) manifest(s) in a particular case; it thus translates the definition into a set of operations by which the previously defined attribute(s) will be observed in the study sample, and thus arrives at a more precise *operational definition*. The third step – *quantification* – translates operational definitions into numbers and thus allows data analysis and aggregation into summary measures.

The group aimed to articulate general *operationalization* recommendations that would be consistent with the ABC and EMERGE principles and applicable to various types of medications, health conditions, healthcare systems, research designs, and data sources. By following this approach, researchers should be able to identify whether/how the ABC phases apply to their own study, and which measures are most appropriate for their needs. Group members used their experience in adherence research to assess critically the applicability of the principles proposed to various examples of adherence research.

The study was funded by ESPACOMP, and group members co-authored this article. We present below the resulting recommendations with examples of research applications and discuss their implications and further developments necessary.

## Results

The working group identified four main sources of variation that impact decisions concerning the measurement of adherence in clinical trials and routine clinical care. We present them in order of importance relative to defining adherence as a temporal sequence. First, treatment *timelines* may vary substantially for the same medication regimen, depending on prescribing, dispensing, dosing and usage practices. While these timelines may be more tightly controlled in clinical trials, treatment regimens become less standardized in clinical practice as they are

adapted to patients' individual needs and preferences. Second, key *events* occurring on these timelines, such as starting and stopping medication, may vary between participants in clinical trials despite strict protocols, and even more so in routine care, where changing or reinitiating treatment may occur, either in agreement with the treating physician or independently. Third, studies may have various *objectives*, such as studying adherence predictors or consequences, accounting for the influence of non-adherence on drug exposure and efficacy, improving individuals' adherence, or driving organization- or system-wide change. Depending on these objectives, the study design beyond adherence measurement may need adjustments depending on how related variables are placed in the temporal sequence described by adherence timelines and events. Fourth, various data *sources* may be available, with different limitations and possibilities, which may restrict how research questions are formulated and the type of evidence that can be generated about this temporal sequence.

Due to these sources of variation, no single measure of adherence is appropriate in all situations. Instead, careful consideration of these domains would lead to selecting the most appropriate measure for each study. We therefore introduce TEOS (Timelines – Events – Objectives – Sources, Figure 1), a four-component iterative process that researchers can follow to include these considerations in adherence measurement and record decisions transparently.

*[insert Fig 1 here]*

### *The TEOS framework*

*Timelines – what are the temporal characteristics of the medication regimen(s) under study?*

Adherence to medications is defined broadly as the process by which patients take their medications as prescribed. This implies comparing two timelines: recommended and actual dosing events. Moreover, as patients can only use medications if these are available to them, we also need to consider prescribing events and whether they are followed by dispensing events. Therefore, a first step is to understand conceptually how prescribed and actual use occurs in real

life for each medication in the study context and represent this information explicitly on four parallel timelines:

1. Prescribing events: start dates and durations of prescriptions,
2. Recommended dosing events (dosing regimen): quantity (e.g. two tablets) and frequency (e.g. twice daily) of the recommended sequence of dosing events during prescription intervals,
3. Dispensing events: dates and durations of dispensations related to the specific prescriptions, which make medications available to patients, and
4. Actual dosing events: date and time of administration of available medications.

Figure 2 provides a representation of these timelines for one prescribed medication. They occur simultaneously during an observation window (OW; a period of interest for adherence estimation, e.g. a year, or a month), before or after a specific event (index date) in a follow-up window (FUW; a broader time period around the OW on which data relevant for adherence estimation may be available). The index date may be a clinical event, a consultation, or a first prescription of a specific medication after a period of no treatment. Mapping these timelines on each patient's medication history is the first step towards accurate adherence measurement.

*[insert Fig 2 here]*

*Key events – what are the boundaries delimiting adherence phases?*

The ABC taxonomy delimits the three adherence phases by four key events: (1) first recommended dosing event, (2) first actual dosing event ("initiation"), (3) last actual dosing event ("discontinuation"), and (4) last recommended dosing event. These four events are boundaries for all other prescribed and actual dosing events. Between a first and a last actual dosing event, the time-series of actual dosing events may correspond to a variable extent to the time-series of recommended dosing events; this variability is captured by the concept of "implementation". In long-term care, patients may interrupt treatments multiple times for

extensive time periods covered by the same prescription; depending on the length of the FUW and OW, these periods of interruption may count towards low implementation or non-persistence. At the same time, prescriptions may be stopped by a provider (event 4) and then restarted (event 1) at a later date. Identifying these events represents the second step in measuring adherence, as it allows the investigator to distinguish between the three adherence phases and subsequently identify suitable adherence metrics for each phase. Depending on the follow-up window length, the timelines may include one or more of the four key events, e.g. the probability of discontinuation increases with the duration the follow-up window. Understanding how the timing of these events varies is essential for deciding the timing of observation windows for adherence calculations within the same study, as well as for explaining inconsistencies in results between studies.

Additional events may occur within an implementation phase, such as changes in recommended dosage and generic or therapeutic substitution which need particular consideration when assessing adherence outside controlled environments.[25] These situations may be followed by a recommendation to finish the previous supply with the same or the new dosage regimen, or to discard any remaining medication and start the new prescription. Dose changes may also occur between prescription events, for example when prescribed regimens include recommendations to step up or down dosage depending on clinical need. These events may impact measurement, and therefore need to be recorded and considered in sample selection or adherence calculations.

*Research objectives and design – what adherence-related evidence we want?*

Operationalization is strongly related to research design, and the choice of adherence measures can impact relationships between predictors and outcomes.[26] Understanding in depth the temporal characteristics of treatments and how we can delimit adherence phases will generate deeper insights into the adherence-related evidence we need and can generate, with new and

perhaps unanticipated implications for research objectives and study design. We therefore recommend that researchers reflect on how the other variables they aim to measure in their study in relation to adherence (predictors, outcomes, mediators, moderators, potential confounders) are situated on the timelines described above. Without aiming to be comprehensive, we highlight here four examples of such considerations, which we explain below: 1) are these variables measured separately from adherence behaviors?; 2) do they change over time?; when do they occur or change and in what order relative to adherence timelines?; and 3) at what levels of analysis do they vary? For most studies, answering these questions would improve substantially the quality of the study design and the interpretation of results.

Operational definitions of adherence require clear boundaries between the actual behavior, as per the ABC taxonomy, and other proximal variables. Irrespective of the adherence measure selected, valid causal inference between two measures requires that they are separate entities with little or no measurement overlap. For example, when examining relationships between adherence determinants and behaviors, researchers should avoid self-reported adherence scales that conflate questions on behaviors and determinants into single scores. Such scales are common in the literature.[27]

Once conceptual boundaries are established, an analysis of the temporal properties of these variables would inform the timing of adherence measurement in relation to the study hypotheses. These variables may be time-invariant or time-varying properties, or single events. Their duration and how much they change in time should be considered when choosing the timing, frequency and duration of measurement for adherence, and the relevant adherence phases. Identifying the temporal sequence between adherence phase(s) and adherence-related variables is necessary for causal claims. For example, adherence would need to be measured after predictors and before outcomes, and the time lag between measurements should reflect causal effects that are biologically plausible.

In thinking about adherence predictors and outcomes, it is important to note that healthcare systems are naturally hierarchical and causal influences can occur at multiple "levels." Patients' beliefs about health and healthcare, income, and access to health are examples of adherence predictors at the patient level which may remain stable during a study and thus amenable to investigation at between-person level. Other adherence predictors, such as symptom severity or emotional states, may vary and thus within-person causal effects can be studied. Healthcare professionals who prescribe and supply medicines may support or undermine medication adherence in a variety of ways, such as their interest and skill in collaborating with patients on medication taking, or the organizational infrastructure they establish for prescription refills or patient support. Similarly, some predictors are stable and be amenable to study at between-person level, while others may vary and thus allow the study of causal effects within-person, i.e. healthcare professional. Finally, there may be city, county, regional, or national-level factors affecting care. Both study questions and methods should reflect this multilevel nature of healthcare delivery[28] and aim to detect and explain relevant variation at within- or between-patient level, healthcare professional, organization, or policy levels.[29] The choice of analysis level(s) will depend on the practical applications envisaged, e.g. adherence indicators at practice level are less useful for intervention at patient level, but could be a target of healthcare professional behavior change.[30] It will result in different temporal dynamics to be captured, as some phenomena may have higher temporal variation within-patient and more stability at policy level. For example, if we aim to produce evidence for managing adherence in provider-patient consultations, we might focus on individual-level implementation patterns or persistence measures and a short- to medium timeframe. Alternatively, if we are interested in organization-level or system-wide diagnosis and change, we might examine population-level initiation and persistence distributions. The limited awareness of the importance of levels of analysis in adherence research so far is detrimental to

the field, as evidence produced at one level is often interpreted at another.[31] We therefore encourage researchers to perform this mapping exercise explicitly and refine research objectives in light of these considerations.

*Data sources – what is accessible?*

In order to match what we want to know with what we can know in specific settings, operational definitions need to consider the possibilities and limitations of available data sources in relation to the evidence required, which in essence is the temporal sequence of actual versus prescribed dosing and its place within the broader causal process involving the treatment regimen. The most common data sources in adherence research are electronic healthcare databases (e.g. electronic health records, claims, record linkage systems),[32] electronic monitoring devices, and self-reports. Advantages of different data sources and measures have been discussed elsewhere in relation to adherence stages.[11,18,19]

To maximize data quality, it is essential to evaluate several data sources potentially available for research with respect to quality dimensions specific to each source (e.g. reliability, validity, responsiveness, and interpretability for self-report).[33] This evaluation needs to be performed in relation to the adherence phase(s) and research objectives targeted. A single data source may contain information about one or multiple timelines and therefore makes it possible to compute markers for one or more adherence phase(s). Examples include: a dated note in an electronic health record indicating that a prescription was written; a medication plan detailing the prescribed regimen; a date in an administrative dataset showing that a prescription was filled; a smart (electronic) package opening event with date and time; a self-reported statement of no missing dose in the previous week; and a dated note in a health record that a medication was re-prescribed after a 6-month gap. Alternatively, combining multiple data sources may reduce bias and measurement error by aggregating complementary information on different

timelines and events to generate a comprehensive data set and check consistency, e.g. in composite measures[34] or by linking prescribing and dispensing data.[35]

These four types of information – **timelines**, **events**, **objectives**, and **sources** – are necessary to describe the events required to measure adherence according to the ABC taxonomy, and the temporal dynamics of the relationships of interest. Sometimes all the desired information is directly available, but more often we can only approximate the theoretical time series of prescribed and actual dosing events. For example, we infer from a first dispensing event that someone started a treatment (initiation), from a smart package opening event that someone took a dose (implementation), or from a certain gap between refill events that medication taking has been discontinued (persistence).

***Using the framework***

We therefore propose to consider, when constructing operational definitions of adherence, a series of questions addressing the four TEOS components (Table 1). The question order in Table 1 highlights the importance of adherence timelines as described above, but the process we propose is by no means linear. As TEOS components interact, the order in which the questions are tackled in a specific study may vary and decisions in one component may require adjustments in another. For example, decisions related to data sources following quality evaluation may induce changes to study design features, such as inclusion criteria and measurement of other variables. Answering these questions might prove straightforward in some contexts, for example if the study population is homogeneous and information is easily available, while in others more research might be necessary to support operationalization choices, such as method validation or sensitivity analyses. Nevertheless, we believe that these questions would help researchers make informed choices on operational definitions of adherence.

*[insert Table 1 here]*

After this exercise, operational definitions can be formulated for all relevant adherence measures consistent with the ABC taxonomy. We provide an example for reporting the TEOS exercise in tabular form (Table 2) and as graphical representation (Figure 2) for an intervention study to support medication adherence for patients starting any new chronic treatment. The operational definitions for each adherence phase are provided in Box 1, together with possible *quantification* and summary measures. Two additional examples are presented in Appendix 1.

*[insert Table 2 here]*

*[insert Figure 3 here]*

**Discussion**

A solid evidence base for adherence to medications requires shared standards and definitions, for which the ABC taxonomy and EMERGE guidelines have set the foundation. Applying them in practice requires shared procedures for understanding and measuring adherence processes in various clinical settings.[36] We propose TEOS, a four-component framework that researchers may use to perform a conceptual analysis of adherence *timelines* and key *events* in relation to research *objectives* and data *sources*. By using TEOS, we hope to encourage researchers to explore more options for study design and identify more accurate ways to measure adherence, formulate hypotheses and analyze data. Although full replication and cross-study comparability will always be difficult to achieve as rarely two studies will share the same specifics, we believe that reporting operational definitions using TEOS will improve transparency and reproducibility of adherence studies and thus facilitate comparisons.

TEOS highlights the fact that many important research questions regarding medication adherence are not being asked with sufficient rigor. Prior reviews have noted that initiation and persistence are less studied than implementation,[9] and adherence has been studied more at

patient level than at the provider or health care site levels.[29] Moreover, TEOS points to several key limitations in previous studies regarding the temporal properties of adherence and its multilevel variation.[28] Not separating adherence phases is common, and a source of measurement error and confusion in interpreting results.[37] Current interventions targeting changes in adherence within-person rely mostly on evidence at the between-person level, which may be subject to different influences; distinguishing between- and within-person variation in adherence holds promise for improving adherence interventions.[31] We hope that the explicit use of TEOS will stimulate new research in these less explored areas, and result in the formulation of more precise hypotheses which can generate more actionable evidence for adherence management.

The TEOS framework focuses on operationalization of medication adherence and design of research involving this construct and is intended to stimulate debate and promote consensus among the research community. The format of the examples we give of operational definitions represents an initial proposal for discussion. We intentionally did not review or endorse specific adherence measures or approaches to quantification or aggregation, as their appropriateness depends on the interactions between the four components we illustrated here and the relevance of the different choices to specific settings. Several options for summarizing adherence across values (e.g. median implementation percentage) or across patients (e.g. percentage of patients implementing as prescribed over a specific threshold value) have been proposed and raise various analysis challenges[38] which are beyond the scope of this article. Guidance on how to operationalize clinical outcomes in relation to adherence is also beyond its scope; TEOS needs to be used in combination with other guidelines relevant for the type of study conducted.

TEOS is described here for a single medication, yet long-term treatments typically involve multiple medications (polypharmacy), often aiming for non-additive effects.[39,40]

Adherence timelines may differ substantially between medications, resulting in potential overlapping intervals of initiation, persistence/implementation, and non-persistence for different medications. In certain cases, it might be useful to consider adherence to a treatment consisting of multiple medications instead of single medications.[41,42] Treatment effects of some medications are importantly affected by the concomitant/sequential use of other medications, or other substances, such as food, etc., which may need to be taken into account in how adherence to polypharmacy is operationalised; these other events may represent additional layers of information to consider in adherence studies. Operational definitions of polypharmacy could build on the TEOS framework and add questions specific to multiple medication regimens.

The ESPACOMP adherence methodology working group aims to provide the research community with practical tools for developing a high-quality evidence base for adherence management decisions from individual to policy level. TEOS is part of this objective, as well as of the broader movement towards transparency and reproducibility in research. Its application to different medication regimens and clinical settings would advance our understanding of adherence to medications and the role of adherence management in improving population health.

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## References


1. Kronish IM, Moise N. In Search of a “Magic Pill” for Medication Nonadherence. *JAMA Intern Med*. 2017;177(5):631. doi:10.1001/jamainternmed.2016.9658

2. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. *Pharm Med Outcomes Res*. 2013;4:91. doi:10.3389/fphar.2013.00091

3. Holmes EAF, Hughes DA, Morrison VL. Predicting Adherence to Medications Using Health Psychology Theories: A Systematic Review of 20 Years of Empirical Research. *Value Health*. 2014;17(8):863-876. doi:10.1016/j.jval.2014.08.2671

4. 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. doi:10.1136/bmjopen-2017-016982

5. McGrady ME, Hommel KA. Medication Adherence and Health Care Utilization in Pediatric Chronic Illness: A Systematic Review. *Pediatrics*. 2013;132(4):730-740. doi:10.1542/peds.2013-1451

6. Bitton A, Choudhry NK, Matlin OS, Swanton K, Shrank WH. The Impact of Medication Adherence on Coronary Artery Disease Costs and Outcomes: A Systematic Review. *Am J Med*. 2013;126(4):357.e7-357.e27. doi:10.1016/j.amjmed.2012.09.004

7. Asche C, LaFleur J, Conner C. A Review of Diabetes Treatment Adherence and the Association with Clinical and Economic Outcomes. *Clin Ther*. 2011;33(1):74-109. doi:10.1016/j.clinthera.2011.01.019

8. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2014. Accessed January 11, 2015. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000011.pub4/abstract

9. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M, the ASTRO-LAB group. Asthma inhaler adherence determinants in adults: systematic review of observational data. *Eur Respir J*. 2015;45(4):994-1018. doi:10.1183/09031936.00172114

10. Demonceau J, Ruppar T, Kristanto P, et al. Identification and Assessment of Adherence-Enhancing Interventions in Studies Assessing Medication Adherence Through Electronically Compiled Drug Dosing Histories: A Systematic Literature Review and Meta-Analysis. *Drugs*. 2013;73(6):545-562. doi:10.1007/s40265-013-0041-3

11. Whalley Buono E, Vrijens B, Bosworth HB, Liu LZ, Zullig LL, Granger BB. Coming full circle in the measurement of medication adherence: opportunities and implications for health care. *Patient Prefer Adherence*. 2017;11:1009-1017. doi:10.2147/PPA.S127131

12. Jönsson AK, Schiöler L, Lesén E, Sundell KA, Mårdby A-C. Influence of refill adherence method when comparing level of adherence for different dosing regimens. *Eur J Clin Pharmacol*. 2014;70(5):589-597. doi:10.1007/s00228-014-1649-2

13. Orrell C, Cohen K, Leisegang R, Bangsberg DR, Wood R, Maartens G. Comparison of six methods to estimate adherence in an ART-naive cohort in a resource-poor setting: which best predicts virological and resistance outcomes? *AIDS Res Ther*. 2017;14(1):20. doi:10.1186/s12981-017-0138-y

14. Souverein PC, Koster ES, Colice G, et al. Inhaled Corticosteroid Adherence Patterns in a Longitudinal Asthma Cohort. *J Allergy Clin Immunol Pract*. 2017;5(2):448-456.e2. doi:10.1016/j.jaip.2016.09.022

15. El Alili M, Vrijens B, Demonceau J, Evers SM, Hiligsmann M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *Br J Clin Pharmacol*. 2016;82(1):268-279. doi:10.1111/bcp.12942

16. Garber M, Nau D, Erickson S, Aikens J, Lawrence J. The Concordance of Self-Report With Other Measures of Medication Adherence: A Summary of the Literature. [References]. *Med Care*. 2004;42(7):649-652. doi:http://dx.doi.org/10.1097/01.mlr.0000129496.05898.02

17. 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. doi:10.1111/j.1365-2125.2012.04167.x

18. Elseviers M, Vrijens B. Assessment of medication adherence in field research. In: Elseviers M, Wettermark B, Almarsdóttir AB, et al., eds. *Drug Utilization Research*. John Wiley & Sons, Ltd; 2016:361-368. doi:10.1002/9781118949740.ch35

19. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. *Int J Clin Pharm*. 2013;36(1):55-69. doi:10.1007/s11096-013-9865-x

20. Williams AB, Amico KR, Bova C, Womack JA. A Proposal for Quality Standards for Measuring Medication Adherence in Research. *AIDS Behav*. 2012;17(1):284-297. doi:10.1007/s10461-012-0172-7

21. Vollmer WM, Xu M, Feldstein A, Smith D, Waterbury A, Rand C. Comparison of pharmacy-based measures of medication adherence. *BMC Health Serv Res*. 2012;12(1):155. doi:10.1186/1472-6963-12-155

22. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov Results Database — Update and Key Issues. *N Engl J Med*. 2011;364(9):852-860. doi:10.1056/NEJMsa1012065

23. De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). *Ann Intern Med*. 2018;169(1):30-35. doi:10.7326/M18-0543

24. Thorndike RM, Thorndike-Christ TM. *Measurement and Evaluation in Psychology and Education*. 8 edition. Pearson; 2009.

25. Arnet I, Kooij MJ, Messerli M, Hersberger KE, Heerdink ER, Bouvy M. Proposal of Standardization to Assess Adherence With Medication Records: Methodology Matters. *Ann Pharmacother*. 2016;50(5):360-368. doi:10.1177/1060028016634106

26. Dunbar-Jacob J, Rohay JM. Predictors of medication adherence: fact or artifact. *J Behav Med*. 2016;39(6):957-968. doi:10.1007/s10865-016-9752-8

27. Nguyen T-M-U, Caze AL, Cottrell N. What are validated self-report adherence scales really measuring?: a systematic review. *Br J Clin Pharmacol*. 2014;77(3):427–445. doi:10.1111/bcp.12194

28. Meyers DJ, Cole MB, Rahman M, et al. The association of provider and practice factors with HIV antiretroviral therapy adherence. *AIDS*. 2019;33(13):2081–2089. doi:10.1097/QAD.0000000000002316

29. Berben L, Dobbels F, Engberg S, Hill MN, De Geest S. An Ecological Perspective on Medication Adherence. *West J Nurs Res*. 2012;34(5):635-653. doi:10.1177/0193945911434518

30. Genberg BL, Rogers WH, Lee Y, et al. Prescriber and pharmacy variation in patient adherence to five medication classes measured using implementation during persistent episodes. *Pharmacoepidemiol Drug Saf*. 2016;25(7):790-797. doi:10.1002/pds.4025

31. Dima AL, Ganse E van, Stadler G, Bruin M de, Group the A-L. Does adherence to inhaled corticosteroids predict asthma-related outcomes over time? A cohort study. *Eur Respir J*. Published online January 1, 2019:1900901. doi:10.1183/13993003.00901-2019

32. Pacurariu A, Plueschke K, McGettigan P, et al. Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation. *BMJ Open*. 2018;8(9):e023090. doi:10.1136/bmjopen-2018-023090

33. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*. 2010;19(4):539-549. doi:10.1007/s11136-010-9606-8

34. Rotzinger A, Cavassini M, Bugnon O, Schneider MP. Development of an algorithm for analysing the electronic measurement of medication adherence in routine HIV care. *Int J Clin Pharm*. 2016;38(5):1210-1218. doi:10.1007/s11096-016-0354-x

35. García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs. *Curr Med Res Opin*. 2019;0(0):1-10. doi:10.1080/03007995.2019.1601944

36. Khan MU, Kohn M, Aslani P. The need for a paradigm shift in adherence research: The case of ADHD. *Res Soc Adm Pharm*. 2019;15(3):318-320. doi:10.1016/j.sapharm.2018.04.033

37. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ*. 2008;336(7653):1114-1117. doi:10.1136/bmj.39553.670231.25

38. Dunbar-Jacob J, Houze MP, Kramer C, Luyster F, McCall M. Adherence to Medical Advice: Processes and Measurement. In: Steptoe A, ed. *Handbook of Behavioral Medicine: Methods and Applications*. Springer; 2010:83-95. doi:10.1007/978-0-387-09488-5_7

39. Choudhry NK, Shrank WH, Levin RL, et al. Measuring Concurrent Adherence to Multiple Related Medications. *Am J Manag Care*. 2009;15(7):457-464.

40. Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting Measures of Adherence with Simple Drug Use, Medication Switching, and Therapeutic Duplication. *Ann Pharmacother*. 2009;43(1):36-44. doi:10.1345/aph.1K671

41. Youn B, Shireman TI, Lee Y, Galárraga O, Wilson IB. Trends in medication adherence in HIV patients in the US, 2001 to 2012: an observational cohort study. *J Int AIDS Soc*. 2019;22(8):e25382. doi:10.1002/jia2.25382

42. Youn B, Shireman TI, Lee Y, et al. Ten-year trends in antiretroviral therapy persistence among US Medicaid beneficiaries. *AIDS*. 2017;31(12):1697–1707. doi:10.1097/QAD.0000000000001541

43. Elliott RA, Boyd MJ, Salema N-E, et al. Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the New Medicine Service. *BMJ Qual Saf*. 2016;25(10):747-758. doi:10.1136/bmjqs-2015-004400

44. Wilson IB, Lee Y, Michaud J, Fowler FJ, Rogers WH. Validation of a New Three-Item Self-Report Measure for Medication Adherence. *AIDS Behav*. 2016;20(11):2700-2708. doi:10.1007/s10461-016-1406-x

*Table 1: Examples of questions to consider for each TEOS dimension.*

| **TEOS Dimension** | **Examples of questions to consider for each prescribed/recommended medicine in the research setting** |
|---|---|
| Timelines | **Prescribing events:**<br>1. When are the prescriptions issued? |

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| | 2. How long are they valid for?<br>3. When are they renewed?<br>. **Recommended dosing events:**<br>1. When is dosing expected to begin after prescription?<br>2. Are doses and dosing intervals (frequency of administration) fixed or do they vary within patients, between patients or at other levels? If they vary, what is the range of values?<br>3. Do medication effects depend on additional recommendations? (e.g. inhaler technique, administer with food, etc.)<br>. **Dispensing events:**<br>1. For how many days are medications supplied?<br>2. What is the expected refill frequency?<br>3. Does automatic dispensing occur?<br>. **Actual dosing events:**<br>1. What are the administration routes?<br>2. How can patients modify medications (e.g. tablet splitting)?<br>3. If additional recommendations apply (e.g. with food), are these followed when administering? |
| Events | General questions in relation to all events:<br>1. When does the follow-up window (time for which data are available) start and end?<br>2. When does the observation window (time for which adherence is measured) start and end?<br>Specific questions about particular events |

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| | 1. **First recommended dosing event:** What minimum duration without prescribed use should precede a first recommended dosing event so that this event can be considered the start of a new treatment?<br>2. **Last recommended dosing event:**<br>    1. How is the date of treatment end identified?<br>    2. How is treatment end differentiated from treatment switching (e.g. brand versus generic, single versus combination drugs)?<br>3. **First actual dosing event:** What is the maximum duration between first recommended dosing event and first actual dosing event before non-initiation is assumed?<br>4. **Last actual dosing event:**<br>    1. What is the minimum duration with no actual dosing events to differentiate between poor implementation and non-persistence?<br>    2. How is discontinuation differentiated from treatment switching? |
| Objectives | **Intervention**: What intervention(s) will be provided with a potential impact on medication adherence?<br>**Predictors**: What potential predictors of adherence will be measured and/or targeted by the intervention(s)?<br>**Outcomes**: What outcomes will be measured? How are they affected by medication adherence?<br>**Moderators/mediators**: What variables will be measured? How do they intervene in the causal process? |

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| | General questions in relation to all variables:<br>1. Are they measured separately from adherence behaviors?<br>2. Do they change in time (i.e., time-varying)?<br>3. What is the temporal sequencing in relation to adherence?<br>4. At what levels of analysis do they vary? (within- or between-patients, healthcare professionals, etc.) |
| Sources | 1. What data sources are available to derive the four 4 key events?<br>2. What additional data are available to measure adherence?<br>3. For what time period(s) are data available?<br>4. How complete are the available datasets?<br>5. What is the validity/reliability of the available data?<br>6. What are the options for additional data collection?<br>7. What are potential sources of measurement error? |

*Table 2: TEOS for an intervention study to support medication adherence for patients starting any new chronic treatment. The intervention will be provided in cluster-randomized pharmacies within 6 weeks after the first dispensing event and consist of 2 interviews, the first until up to 3 weeks, and the last at 4-6 weeks after the start of the treatment. We want to measure the impact of the intervention on short-term adherence (example adapted from published study).*[43]

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| Timelines: | **Prescription events:** one first prescription issued, typically for 30 days (duration $D_1$), that can be filled 1 time and is followed by subsequent prescriptions for long-term use (6+ months, $D_2$)<br>**Recommended dosing events:** treatments will be prescribed to start immediately, for regular use (e.g. daily to weekly, dosing varies; 'as needed' use is excluded),<br>**Dispensing events:** the first dispensing event can happen within 30 days after the first prescription and covers up to 30 days ($D_3$). Subsequent dispensing events may cover up to 90 days ($D_4$). Automatic dispensing does not occur.<br>**Actual dosing events:** patients are expected to self-administer their medication, the mode of administration varies, any type of modification is possible (e.g. reducing/increasing doses, skipping/delaying administration; seasonal variability may play a role for some medications and needs to be considered when selecting medications for the study). |

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| Events: | **First recommended dosing event:** date of first prescription (time $T_0$) after a 1-year baseline period with no prescriptions for the same substance – it represents the start of the observation window (OW, $T_0$)<br>**Last recommended dosing event:** date of prescription discontinuation (if within the OW), or after the end of the OW ($T_2$)<br>**First actual dosing event:** occurs after first dispensation ($T_1$), date may vary but most participants are likely to initiate before the first interview which takes place up to 3 weeks after first dispensation.<br>**Last actual dosing event:** possibly occurring anytime during the OW if initiated, or after the end of the OW ($T_3$) |
| Objectives: | The **intervention** will be initiated at the first dispensing event in the pharmacy. We are interested in the short-term effects of this intervention on patients' adherence, compared to a control group receiving usual care. We want to measure the impact of the intervention on initiation, implementation and persistence in the first 10 weeks after the first dispensing event.<br>We also aim to investigate the correlation between **occurrence of side effects** and adherence at 10 weeks.<br>Cluster randomization will occur at **pharmacy** level. Several **patient-level** time-invariant (non-modifiable) characteristics will be controlled for. **Health system** level variables are likely to remain constant. |
| Sources: | We can collect participants' **self-reports** of behavior and side effect occurrence (standardized battery of items during the intervention). We also have access to **pharmacy refill** dates and quantities (electronic records of actual dispensing events) and **prescription** dates (manually entered by pharmacy staff), but only for medications dispensed in the pharmacy |

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| | providing the first dispensation. Recommended dosages are not easily accessible in routine data but could be obtained from patients or healthcare professionals. **Electronic monitoring** is not feasible due to logistics, mainly because of variations in mode of administration (oral, injection, spray, etc.). |

Box 1: Operational definitions for measuring adherence in the example study

**Initiation**:

Patients with at least one refill recorded within 10 weeks after the first dispensing event and who self-reported at least one actual dosing event within 10 weeks (data extracted from patient record).

Quantification: Binary variable (yes/no).

Summary measure: percentage initiating patients

**Persistence**:

Patients who initiated treatment, have no documented end of recommended use and self-reported at least one actual dosing event in week 10 (data extracted from patient record).

Quantification: Binary variable (yes/no).

Summary measure: percentage persistent patients

**Implementation**: Self-reported quality of implementation by patients who were persistent at week 10, as measured by the Three-Item Self-Report Measure for Medication Adherence at week 10.[44]

Quantification: Continuous variable as per scoring instructions (percentage, range 0 – 100).

Summary measure: median implementation score (inter-quartile range)

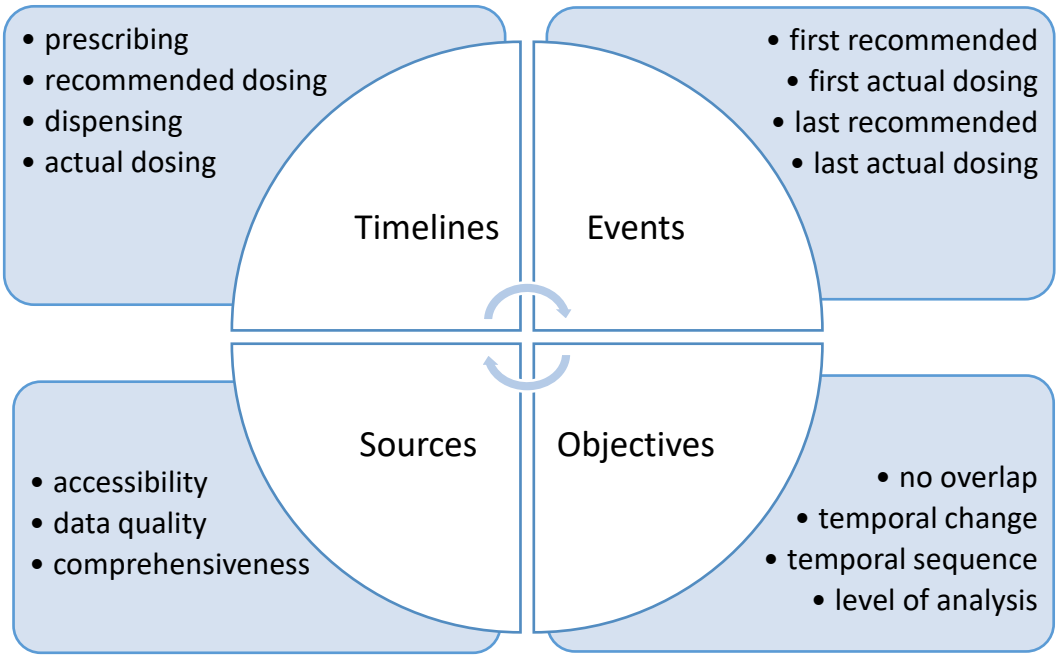


*Figure 1: The TEOS framework*

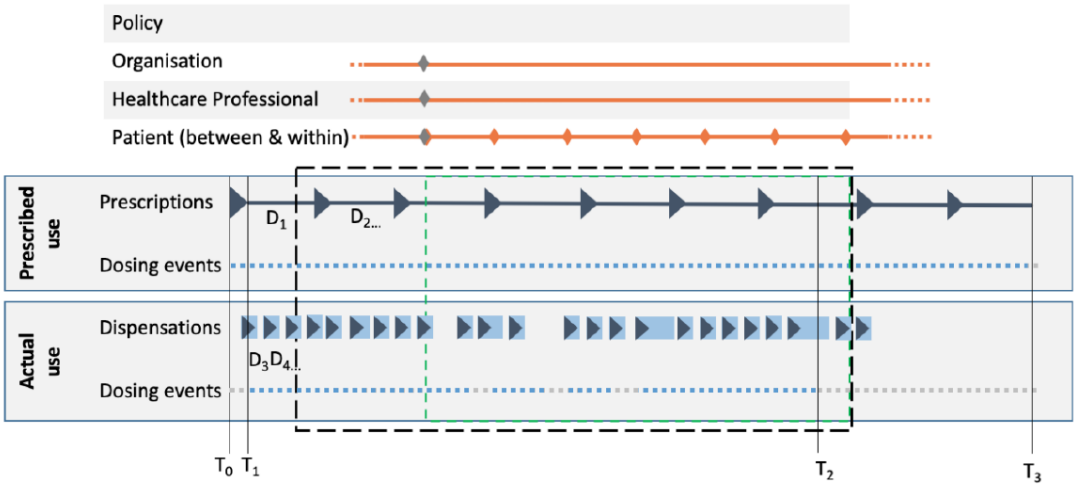


*Figure 2: Four timelines of medication adherence: Prescribed use with prescriptions and recommended dosing events and Actual use with dispensations and actual dosing events. Dashed rectangles: Follow-up window (black) and observation window (green).*

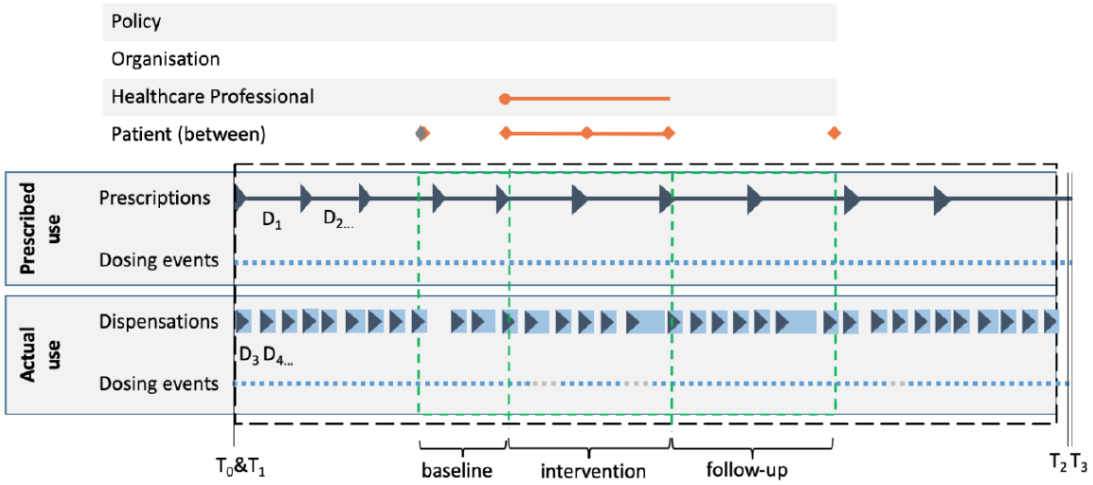


*Figure 3: Example for a graphical representation of the TEOS exercise. $D_1$-$D_4$ and $T_0$-$T_3$ refer to the timelines and events, respectively, mentioned in Table 2 above. Dashed rectangles: Follow-up window (black) and observation window (green). The intervention (orange line) is provided by healthcare professionals to patients and consists of two interviews which occur at up until 3 weeks and 4-6 weeks after intervention start; self-reported adherence data are collected at these times (orange diamonds). Additional predictors and outcomes are measured at the patient level (grey lozenge).*