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Methodological considerations on estimating medication adherence from self-report, electronic monitoring, and electronic healthcare databases using the TEOS framework

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What is already known about this subject:

- Recent recommendations on the definition, operationalization, and reporting of adherence to medications make explicit considerations of three adherence phases (initiation, implementation, discontinuation), and their different properties
- The operationalization of medication adherence is facilitated if researchers outline 1) the *timelines* of prescribing, dispensing, recommended and actual medication use events, and among them 2) the key *events* that distinguish initiation, implementation, and discontinuation, and relate them to 3) the study *objectives* and 4) the data *sources* available.

What this article adds:

- The ABC taxonomy implies several preconditions to estimating adherence, e.g. a specific medication prescribed for a given duration with a known recommended dosing involving repeated regular events, which already delineate some general quality criteria for measurement

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- The TEOS framework draws attention on the complementarity of SR, EM and EHD regarding adherence estimation, and leads to several study design recommendations that maximize precision of adherence measurement

Abstract

Aim: Measuring adherence to medication is complex due to the diversity of contexts in which medications are prescribed, dispensed, and used. The Timelines-Events-Objectives-Sources (TEOS) framework outlined a process to operationalize adherence. We aimed to develop practical recommendations for quantification of medication adherence using self-report (SR), electronic monitoring (EM), and electronic healthcare databases (EHD) consistent with the TEOS framework for adherence operationalization.

Methods: An adherence methodology working group of the International Society for Medication Adherence (ESPACOMP) analysed implications of the process of medication adherence for all data sources and discussed considerations specific to SR, ED, and EHD regarding the information available on the prescribing, dispensing, recommended and actual use timelines, the four events relevant for distinguishing the adherence phases, the study objectives commonly addressed with each type of data, and the potential sources of measurement error and quality criteria applicable.

Results: Four key implications for medication adherence measurement are common to all data sources: adherence is a comparison between two series of events (recommended and actual use); it refers to one or more specific medication(s); it applies to regular repeated events coinciding with known recommended dosing; and it requires separate measurement of the three adherence phases for a complete picture of patients' adherence. We propose recommendations deriving from these statements, and aspects to be considered in study design when measuring adherence with SR, EM and EHD using the TEOS framework.

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Conclusion: The quality of medication adherence estimates is the result of several design choices that may optimize the data available.

Introduction

Concern about the quality and reproducibility of research methods continues.[1] Adherence to medication is a behaviour central to effective healthcare. It is a complex behaviour to study due to the diversity of contexts in which medications are prescribed, dispensed, and used. Several methodological recommendations[2–4] have been proposed for strengthening the quality of evidence from research on adherence measurement and intervention. In particular, the Timelines-Events-Objectives-Sources (TEOS) framework proposed a process of identifying and reporting characteristics of the context of medication prescribing, dispensing, and use, that can guide the *operationalization* of adherence, i.e what needs to be done practically to observe this behaviour in a study sample. In brief, TEOS outlines four actions for good operationalisation: identify how prescribing, dispensing, recommended and actual use of medication occur in time; delimit the adherence phases (initiation, implementation, discontinuation) based on key events; reconsider study objectives and design in light of this temporal sequence; and select data that best fit the objectives chosen. Formulating clear operational definitions facilitates the *quantification* of medication adherence, a subsequent distinct measurement step. To generate accurate and precise estimates, *quantification* needs to consider general measurement principles as well as knowledge of the details of the specific adherence process in question. As medication adherence research is markedly interdisciplinary, these considerations are dispersed in methodological work from different disciplines. This dispersion contributes to a heterogeneity of practices in adherence quantification, which in turn hampers research progress and especially in relation to evidence synthesis.

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To identify best practices or standards in medication adherence measurement, we must take stock of the recent methodological work in these disciplines and formulate principles applicable to adherence measurement. The range of data sources used to study medication adherence is a challenge to standardization. Each type of data has its own methodological requirements, uses, strengths and limitations and may lead to different insights into whether patients take their medications as prescribed. Most adherence data come from three sources: self-report (SR), electronic monitoring (EM), and electronic healthcare databases (EHD)[5]. Although these are broad categories that include a range of measurement methods and instruments, they are often discussed as distinct domains. Each has been the focus of work from different methodologic perspectives and paradigms. The domain with perhaps the longest history of methodological developments –and questionable practices in applied research– is psychometrics, used to inform the design and validation of self-report measures (see [6,7] for recent reviews of current practices and recommendations). Technological advances have created opportunities to assess a variety of dynamic psychological processes during everyday activities, a methodology called ambulatory assessment that comes with its own challenges and questionable practices that have recently started to be considered[8]. A type of ambulatory assessment called experience-sampling, or ecological momentary assessment, uses self-report to investigate such things as desire to smoke or use alcohol. Electronic monitoring of adherence can be seen as a special case of ambulatory assessment, as it uses either real-time passive sensing (i.e. smart pharmaceutical packages with electronic sensors that detect medication removal from the package), active assessment (i.e. electronic devices for patient reporting of medication intake), or both, to collect data on individual medication intake events. The increasing diversity of sensors used for remote monitoring healthcare or physical performance has also led to rapid developments in methods of data collection and analysis in this domain which begin to be structured into best practices[9,10]. Measuring

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adherence from EHD has had a long tradition in pharmacoepidemiology, where the use of real-world data has generated important hypotheses and evidence. However, these have been marred by design flaws and lack of transparent reporting; several related initiatives have been developed recently to improve these practices[11–14].

In addition to these data-specific issues, the particularities of medication adherence as a process bring unique methodological challenges which need to be considered. Previous recommendations have focused either on specific types of data (e.g. EHD[15,16], SR[17,18], EM[19,20]) conditions (e.g. antiretroviral treatment[21]), conceptual issues (e.g. timing[22], common misconceptions[23]) or provided overviews of strengths and limitations of available methods[5,24,25]. However, when designing new studies on medication adherence, researchers also need to decide how to best *quantify* medication adherence in line with the operational definitions appropriate for their study setting and considering several choices across data types, conditions, and study designs. The aim of this article was to outline methodological considerations on estimating medication adherence using SR, EM, and EHD following the structure provided by the TEOS framework for adherence operationalization.

Methods

The present article has been informed by discussions among an adherence methodology working group comprising six members of the International Society for Medication Adherence (ESPACOMP) and authors of the TEOS framework. Continuing a broader initiative on measurement and analysis standards in medication adherence research, the group aimed to develop practical recommendations for *quantification* of medication adherence from the three main data sources introduced above (SR, EM, EHD), consistent with previous recommendations on *operationalization* outlined in the TEOS framework. This work was based on the group's experience with different data sources and study designs and methodological literature. By *quantification* we mean the translation of operational

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definitions into numbers in order to describe, aggregate into summary measures, and test hypotheses regarding the phenomena of interest[26]. The term corresponds to the concept of *estimator* in the clinical trial research methodology[27], in which an *estimand* (the description of the treatment effect investigated by a trial, i.e. *operational definition*) is estimated using a method of analysing clinical trial data (*estimator*) leading to a numerical value (*estimate*). In this manuscript, we will use the terms *quantification* and *estimation* interchangeably. SR refers to those measures which rely upon the subject's verbal or written historical or concurrent report of their behavior of interest. EM refers to the "automatic compilation of drug dosing histories [..] by incorporating microcircuitry into pharmaceutical packages of various designs; such that the manoeuvres needed to remove a dose of drug are detected, time-stamped, analysed, stored and communicated to the appropriate caregiver(s) and/or the researchers(s)."[24] EHD refers to electronic medical records, administrative or health insurance claims databases, and healthcare record linkage systems,[28] i.e. real-world data collected in a non-controlled setting as part of routine clinical practice.[29]

First, we present several considerations common to all data sources which are intrinsic to the process of medication adherence as outlined by the ABC taxonomy. Next, we discuss specific considerations related to the TEOS framework, as applied to SR, EM and EHD: (1) the types of information available on the four timelines, (2) the four events relevant for adherence measurement, (3) the study objectives commonly addressed with such data, and (4) potential sources of measurement error and quality criteria applicable to their related methodological domain. With these considerations, we intend to support decisions in study design and thus improve the precision of adherence measurement and of the evidence generated.

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Results

Methodological considerations resulting from defining medication adherence as a process

At the core of the adherence process and its relevance for healthcare is the expected pharmacological effect of exposure to a prescribed medication, at the dosing and frequency recommended, for the period recommended, on specific physiological parameters and, consequently, on patient health and quality of life outcomes. According to the consensus definitions proposed by the ABC taxonomy[2], adherence to medications is "the process by which patients take their medications as prescribed" and consists of three phases: *initiation* ("when the patient takes the first dose of a prescribed medication"), *implementation* ("the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen"), and *discontinuation* ("when the patient stops taking the prescribed medication"). The length of time between initiation and the last dose preceding discontinuation is termed *persistence*. This set of definitions have several important implications for adherence measurement (Table 1). First, adherence to medications is essentially a comparison between two series of events (recommended and actual use), and measuring it becomes possible only when data are available on both. While most studies focus explicitly on collecting data on actual use, recommended use events are often implicit in the selection of the patient sample and study period. However, assuming medication should be used with the same dosage and frequency throughout the study period may not be appropriate in all cases and for all patients. Irrespective of how data are collected on actual use, it is necessary to ensure that there are accurate data on recommended use and that any variation is accounted for in adherence estimation. Second, adherence refers to specific medications. Thus, recommended and actual use data need to refer to the same medication. This may be implicit in studies like clinical trials, but may require careful consideration in others, for example in longitudinal cohort

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studies in routine care, where patients may be prescribed different medications for different periods during the study; this variation needs to be made explicit and accounted for. Third, adherence to medications as defined by the ABC taxonomy refers to regimens that include repeated events with known recommended dosing for known periods. Dosage recommendations such as 'take as needed' (often associated with a maximum dose per time period recommended; e.g. 'not more than 8 per 24 hours'), or dose adjustment in response to changes in symptoms or other factors, result in a variable sequence of recommended use events that are not amenable for estimating adherence as conceptualized within the ABC taxonomy. In these cases, different operationalizations are required, for which 'medication use' might be a better suited term. Fourth, a global estimate of medication adherence that combines all three phases in a single value is not helpful: there is no valid implementation or persistence estimate for patients who do not initiate medication, and no valid implementation estimate for periods when patients have discontinued medication. Thus, each adherence phase needs to be estimated on relevant samples of patients and time periods. Medications with single dosing recommendations (e.g. single-dose vaccines) represent a special case for which only initiation (binary variable or time to event) can be measured. These four implications of the ABC taxonomy impact the validity of adherence estimates irrespective of whether adherence data is sourced from SR, EM, EHD or other sources. In essence, adherence estimates will be valid to the extent that 1) complete data on both recommended and actual use are obtained, 2) about specific medications, 3) concerning treatment regimens with known dosing schedule, and 4) data are used to estimate separately initiation, implementation and persistence.

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Methodological considerations following the TEOS framework

The TEOS framework (*Timelines-Events-Objectives-Sources*) builds on the ABC taxonomy and aims to make explicit four main sources of variation in designing adherence studies: the changes occurring in the temporal sequences of prescribing, dispensing, recommended and actual use events (*timelines*), differences four key *events* (first recommended and actual dose, and last recommended and actual dose) delimiting the adherence phases; the study *objectives* which may range from observational studies on prevalence, determinants or consequences of one or more adherence phases, to accounting for adherence or improving it in clinical trials, or developing, evaluating and implementing adherence support practices at different scales in healthcare systems; and the availability, quality and comprehensiveness of data from different *sources*. By using the TEOS framework, operational definitions may be formulated that specify the data collected, as well as the time period and method applied. For example, initiation could be operationalized as "*at least one refill recorded within 10 weeks after the first dispensing event and self-report of at least one actual dosing event within 10 weeks, as noted in the patient record*", and quantified as a binary variable (yes/no). 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*[30] *at week 10*", and quantified as a continuous variable (percentage, range 0 to 100) as per scoring instructions[4]. Once an operational definition is formulated, how can researchers ensure that estimates are reflecting accurately the behaviours measured?

From the perspective of the TEOS framework, SR, EM and EHD include a diversity of measurement methods and tools that could be more or less appropriate for specific research objectives and medication regimens. Moreover, some adherence measurement methods and tools combine data from different sources to improve the accuracy of estimates[31], and combining measures is recommended for maximizing accuracy[32]. Thus, instead of choosing

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between data sources based on general statements about their qualities and limitations, we propose taking into account several methodological considerations for describing the key timelines and events, their value for different study objectives, and the measurement properties applicable (Table 2). By reflecting on these questions, adherence measurement can consider and, if needed, combine multiple types of data to achieve a more precise description of the medication adherence process in each context.

Timelines – what data are available on the four types of event sequences?

Information on *actual use* is central to medication adherence estimation, irrespective of the operational definition. The necessity of collecting data on *prescribing*, *dispensing* and *recommended use* depends on whether there is variation in these timelines in the study population. In some studies, particularly clinical trials, the same medication is prescribed and dispensed according to the protocol to all study participants; in these cases, variation only occurs in *actual use* and additional information is only needed on the (invariable) dosing recommendation. In other research contexts and in clinical practice, depending on sample homogeneity, there may be substantial variability in prescribing, dispensing and recommended use: patients may receive different prescriptions and refill them at different intervals, the recommended dosage may change several times during the study, for some patients but not others. In these cases, it is important to estimate and take into account this variation, e.g. by accessing the history of prescribing and/or dispensing in EHD.

In principle, SR can access information on all four timelines to the degree that patients (or their carers, if they provide support with medication supply and use) are able to report on these events. In practice, they are usually asked to report only on *actual use*, either by remembering the number of doses taken at each recommended time (count-based recall) or by estimating how medication use matched the dosage regimen prescribed (estimation recall)[18]. Some count-based measures also collect information on the *type of medication*

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prescribed and the *recommended use* timeline[33,34]. Estimation recall is influenced by the natural tendency to recall most recent events and telescope backwards in time and by the natural tendency to summarize events based on usual patterns[35]; therefore, it is likely to be based on most recent and usual patterns of *recommended* versus *actual use* of the most recent or common medication. EM devices collect fine-grained data on *actual use* of medication. It is therefore the data source of choice when all patients follow the same regimen for the whole study duration in a controlled setting. When prescribing, dispensing and recommended use patterns vary, this information needs to be collected from other sources (e.g. patients/carers, prescriber reports, or health records) so that it can be combined with EM data on actual use to estimate adherence. In EHD, prescribing and/or dispensing data are available retrospectively, sometimes over long time periods and for large samples. There is however large variation across databases on the type of information recorded. For example, dosage instructions (from which recommended use events can be reconstructed) are available in some databases in open text format requiring validation of algorithms to transform into numeric values(ref), and lacking in others, requiring use of Defined Daily Dose values which are only appropriate for medications with little or no variation in prescribed dosage in routine practice.[36] The lack of data on *actual use* is a considerable limitation of EHD data, as actual use events are commonly inferred based on the assumption that the medication is used as prescribed until supply ends (with some exceptions[25]); drug dosing histories from EM data show that this assumption is often untenable.[37]

Thus, for optimal quantification of medication adherence behaviours, we recommend 1) prioritizing data that capture *actual use* over the period of interest (EM or SR), and ensuring that either 2a) little or no variation is present in the study sample on *recommended use* events or 2b) recommended use is also captured (e.g. via SR). If data on *actual* and *recommended use* are not accessible, 3) data on *prescribing* and *dispensing* events can estimate adherence

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(e.g. via prescriber reports or EHD) provided that dosage recommendations are available and strong assumptions on the use of dispensed medication are made.

Events – how do the data available relate to the four key events?

Operational definitions focus on initiation, implementation or persistence. To estimate these phases precisely, it is necessary to ensure that they are correctly delimited for all study participants and adherence phases are aligned between participants for comparison. Thus, we need to situate in time at least the prescription start and end, and the first and last use event. For example, for estimating implementation it is necessary to ensure that all patients have initiated and not yet discontinued treatment, while for initiation and persistence it is essential to know whether the first and last use events are calculated in relation to the correct first prescription. In drug clinical trials, these dates are created by the study protocol. In real-world studies and clinical practice, these dates need to be captured (via SR or EHD) and inform (sub)sample selection.

In some adherence studies using SR, e.g. general population surveys, it is common to measure implementation without asking participants to report on these key events. In these cases, depending on the medication regimen investigated, the estimation will be less precise or altogether invalid because it risks focusing on periods during which the patient is not implementing the medication prescribed. Thus, collecting data on whether patients are on active treatment would strengthen the study design. In EM, data collection starts from the first medication intake using the device; if the device is adopted at treatment initiation, the first event recorded corresponds to the first actual dose. The last medication intake using the device may occur earlier than the last actual use, whether planned or by non-adherence to device use. No information is available on the start and end of recommended use according to prescriptions issued, therefore it needs to be ensured by study design or be reconciled with other data sources. In EHD, the prescription start date may be available in some databases,

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the first use date is usually inferred from first dispensing date assuming immediate use, and the last use date is inferred from lack of dispensing over a (pre-)specified gap period. The prescription end date is often unavailable and assumed from insight into prescribing practices in a specific clinical setting. These assumptions need to be supported by qualitative data regarding the medication and health condition investigated.[38]

Thus, a key recommendation resulting from the delimitation of adherence phases is to ensure that 1) there is no variation in the sample during the study period (e.g. all participants are on active treatment for estimating implementation, the period is short enough for provider discontinuation of medication not to occur) or 2) variation is appropriately captured (e.g. by recording treatment changes or deprescribing) and estimation of each phase is performed on subsamples that correspond to these temporal criteria.

Objectives – for what study objectives is each data source particularly valuable?

The choice of operational definitions is informed by the study objectives. From this perspective, SR, EM and EHD have complementary strengths and uses. A key strength of SR is that it taps into patients' perceptions of their own adherence, and it is thus valuable for studying adherence from a patient-centered perspective. Moreover, it allows measuring behaviours, determinants, and outcomes of adherence at the same time, which makes data collection feasible. For this reason, SR has been the most extensively used method in adherence research and is crucial for studying adherence causes and consequences and developing adherence support interventions. However, most available SR measures focus on implementation. The potential of SR for capturing initiation and persistence has been less explored to date. EM allows the most granular record of actual use and thus can be used to quantify differences between the two time-series of recommended use and actual use events. It is therefore the method of choice for studying patterns of deviation from recommended use during implementation. As it can collect large longitudinal data at individual level, it enables

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studying within-patient and between-patient variation, and associations with potential causes if linked with longitudinal data from other sources. EM can generate contemporary data for optimizing adherence and provide a basis for adherence support interventions in routine clinical care. Linked with pharmacokinetic or pharmacodynamic information, EM data can support therapeutic drug monitoring, and facilitate greater understanding of the effects of variable implementation on drug response. EHD can offer indirect measures of initiation and persistence, and low-resolution estimates of implementation. Its main strength is estimating adherence for many patients long-term, due to retrospective access to data collected with no participation burden for patients and clinicians. This is extremely valuable for estimating adherence patterns at population level, e.g. for prioritizing research efforts or assessing impact of health system-level interventions. If socio-demographic and clinical variables are accessible in the same database or via database linkage, EHD can be valuable for identifying at-risk groups and studying long-term impact of adherence on clinical outcomes. If data is fed back to clinicians and patients at individual level, it can inform development and implementation of adherence support interventions in clinical care.[39]

Thus, precision of estimation, as operationalization, depends to large extent of the match with study objectives and therefore a key recommendation would be to select the data sources that best answer the research questions and maximize precision within the given constraints.

Sources – what are the key sources of variation in data quality and how they could be addressed?

Each data source may produce estimates of high or low quality depending on how well data collection and analysis can minimize and adjust for its specific sources of error. The accuracy of SR measures is affected by the nature of autobiographical memory[27], the willingness of the participant to accurately report their behavior, and their ability to identify the behavior, recall any directions for engaging in the behavior, and communicate their

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recall.[40] A SR measure needs to meet criteria of validity (e.g. face, construct, criterion), and reliability (e.g. internal consistency, test-retest) (COSMIN[26]). For example, construct validity may be affected by measure contamination with questions on behaviour determinants or outcomes (construct overlap). Reliability criteria differ between count-based and estimation recall, due to different sources of error in question response[17]. EM data are time-stamped device use events (e.g. bottle opening, button pressing, inhalation). While its reliability depends on the technical properties of the device, its validity (similarly to patient-reported diary data) is to a large extent influenced by the context of data collection, especially by device acceptability and adherence to the data collection protocol. Therefore, it is essential that these devices do not add burden to patients nor induce stigma. EHD data represent time-stamped prescribing or dispensing events; at minimum, adherence estimation requires these dates, the type of medication, the quantity dispensed and the dosage prescribed (or duration of dispensed supply). Depending on their provenance, they may include different information and have different sources of error. Reliability is influenced by the use given to the data in routine practice. For example, dosage recommendations in open text fields do not serve financial or audit purposes and therefore may be less reliably recorded. On the other hand, their validity is strengthened by completion as part of daily practice, which does not add supplementary burden or bias for study participation.

Thus, estimating adherence accurately is about maximizing reliability and validity during data collection and analysis by identifying sources of error and reducing or correcting for unwanted variation in the signal captured.

Discussion

This conceptual analysis outlines several considerations when measuring and estimating medication adherence. Using the TEOS framework, we discuss the complementary strengths

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of SR, EM and EHD in relation to the accessibility of data on recommended and actual medication use over a given time period, and the necessary prescribing and dispensing events over that period. To delimit the phases of initiation, implementation and persistence, each data source may have different constraints to consider: recall bias (SR), data collection setup (EM); or completeness of data (EHD). Measurement modalities are often complementary in addressing different study objectives but differ appreciably in measurement properties. While validity and reliability apply to all, these manifest in fundamentally different ways: structural validity, test-retest reliability (SR); precision of time-stamping events (EM), accurate recording of prescriptions and dispensations (EHD). Our analysis highlights the importance of considering the complementarity of these data sources when designing and interpreting studies. Transparency, reproducibility, and the need for standardized best practices apply to all.

Following the TEOS framework allowed a conceptual analysis of the potential of each type of data irrespective of the quality of individual tools and measures. However, this work does not provide a complete summary of all methodological aspects of adherence measurement and should be considered in conjunction with other recommendations, specific to adherence or applicable to research design and data analysis.

This conceptual analysis indicates that the quality of adherence estimates resides equally in the study design choices and in the choice of measurement tool and set up of data collection processes.

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Conflict of interest statement:

BV is CEO and shareholder of AARDEX Group.

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Contributors:

A.L.D., S.A., J.D.J., D.H., B.V. and I.W. participated in synchronous and asynchronous discussions to outline the methodological considerations presented in the manuscript. A.L.D. wrote the manuscript draft. S.A, J.D.J., D.H., B.V. and I.W. reviewed and edited the manuscript.

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Table 1. General considerations resulting from applying the ABC taxonomy to the measurement of medication adherence

Statement	Recommendations
1. Adherence to medications is a comparison between two series of events (recommended and actual use).	Ensure that patients included in the study are all prescribed the medication investigated for the entire study period; if not, ensure variation in prescription information is measured and accounted for in the estimation of adherence (i.e. only compute adherence for periods where medications are prescribed)
2. Adherence is about a specific medication(s).	Ensure that data collected about both recommended and actual use refer to the same medication(s); if prescribed medication changes during the study period, ensure that these changes are taken into account in the estimation.
3. Adherence requires regular repeated events coinciding with known recommended dosing.	If prescribed as needed, the recommended use sequence is unknown → adherence cannot be calculated. As needed medication should be considered as "(appropriate) medication use" If a flexible dose administration is recommended, which depends on change in symptoms, exposure to triggers, or other factors → more complex to measure If dose unknown/unclear due to suboptimal prescribing practices or lack of documentation clarity → adherence cannot be calculated or assumptions (e.g. use of defined daily doses) need to be validated and clearly described.

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4. The three adherence phases need to be measured separately for a complete picture of patients' adherence	Each adherence phase needs to be measured on relevant samples of patients and measurement periods. Single dose regimens represent a special case for which only initiation (binary variable or time to event) can be measured.

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Table 2. Mapping SR, EM and EHD on the TEOS framework

TEOS component		SR	EM	EHD
Timelines – what data are available on the four types of event sequences?	Prescribing	Possible, but uncommon.	Not applicable.	Data available retrospectively, sometimes over long time periods.
	Dispensing	Possible, but uncommon.	Not applicable.	Data available retrospectively, sometimes over long time periods.
	Recommended use	Possible, but uncommon.	Smart packages are increasingly used with an app that can capture information on prescribing.	Information available in some databases.
	Actual use	Measurement period looks back on a relatively short time and affected by memory (recall bias) as well as social desirability bias. Data are collected either on actual use, or as patient's (or carer's) estimation of actual versus recommended use.	Measurement period starts with a first medication intake using the smart package; it can correspond to the first dose of the treatment if the device is adopted at treatment initiation. Last medication intake using the device maybe earlier than the last actual use, whether planned or by non-adherence to device use. Smart package use indicates but does not prove medication administration (e.g. ingestion, inhalation).	Not applicable.
Events – how do the data available relate to the four	Prescription start	Anteriority to measurement period usually ensured by study design, i.e. sample selection.	Not applicable, anteriority ensured by study design, i.e. sample selection.	Data may be available in some databases (e.g. prescription records).

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key events?	First use	Usually not in focus in available measures, as the measurement period commonly starts after first use.	Inferred from first device use. Needs verification with other data sources or based on study design.	No data, inferred from first dispensing date (in claims databases) or first prescribing date (in prescription records).
	Last use	Usually not in focus in available measures. Ensured by study design, i.e. selection of sample and measurement period.	As above.	No data, inferred from lack of dispensing over an agreed gap period.
	Prescription end	Posteriority usually ensured by study design, i.e. study duration shorter than prescribed treatment duration, verification with other data on treatment changes during the study period.	Not applicable, posteriority ensured by study design, i.e. study duration, verification with other data (see SR).	Available in some databases, often assumed from insight into the specific clinical setting.
Objectives – for what study objectives is each data source particularly valuable?		Most available measures focus on *implementation*; *initiation* and *persistence* may also be estimated, but limited measure development to date. Taps into patients' perceptions of their own adherence behaviors (or carer's perceptions of the patient's adherence); thus, valuable for studying adherence from a patient-centered perspective.	Focuses on implementation. Allows the most fine-grained follow-up of actual use; thus, valuable for studying patterns of deviation from recommended use. Allows large longitudinal data at individual level; thus, valuable for studying within-patient and between-patient variation and associations with potential causes (if linked with data from other sources).	Indirect measure of *initiation* and *persistence*, coarse-grained estimate of *implementation*. Allows estimating adherence for many patients and long periods of time, given retrospective access to data collected with no participation burden for patients and clinicians; valuable for estimating adherence

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	Allows measuring medication adherence at the same time with collecting data on determinants and patient-reported outcomes; thus, valuable for developing and implementing adherence support interventions in clinical care.	Linked with pharmacokinetic or pharmacodynamic information, EM data can support therapeutic drug monitoring, and facilitate greater understanding of the effects of variable implementation on drug response Can generate contemporary data for optimizing adherence and provide a basis for adherence support interventions in routine clinical care.	patterns at population level, e.g. for prioritizing research efforts or assessing impact of system-level interventions. Allows links with socio-demographic and clinical variables (if accessible in the same database or via database linkage); valuable for identifying at-risk groups and studying long-term impact of adherence on clinical outcomes. If data fed back to clinicians and patients at individual level - valuable for developing and implementing adherence support interventions in clinical care.
Sources – what are the key sources of variation in data quality and how they could be addressed?	Data are either count-based, or estimation of agreement between recommended and actual use. Depending on number of repeated measures and length of questionnaire – balance between	Data are time-stamped device use events (e.g. bottle opening, button pressing, inhalation). High burden (willing to use a device) Lower sample size (patients), high sample size	Data represent time-stamped prescribing or dispensing events. Needs at minimum: date, patient ID, medication, quantity & dosage (duration of supply if used

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	burden and sample size Recall bias Social desirability Construct overlap with adherence determinants and outcomes. Autobiographical memory is not discrete event based and relies of recent performance for estimates.	(observations per patient). Duration of use depends upon battery life of the device. Depends upon patient using the device for each dose, as opposed to removing medication once a day for 'pocket dosing' of additional doses.	as prescribed computed). Coarse grain follow-up for longer time period and larger population. No participation burden for patients Sample size depends on coverage of database and selection criteria. Challenges accessing the EHD data.

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