Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2024, Volume 4, Issue 2, Page No: 161-175

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

From Pill Counts to Digital Phenotypes: A Meta-Narrative Review of How Medication-Adherence Technologies Define, Infer, and Misclassify Medicine-Taking, 2017–2025

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Received: 07 October 2024; **Revised:** 12 December 2024; **Accepted:** 16 December 2024

ABSTRACT

Medication-adherence technologies are often compared as though they measure the same behavior with different degrees of precision. In practice, pill counts, pharmacy dispensing records, electronic monitors, ingestible sensors, mobile applications, and passive digital traces observe different events and require different inferential steps before those observations can be interpreted as medicine taking. This review examined how distinct research traditions have defined adherence through technology and where their assumptions can produce false classifications of adherence or nonadherence. A RAMESES-informed meta-narrative approach was used to identify research traditions concerned with medication-adherence definition, measurement, digital monitoring, implementation, and behavioral inference between 2017 and 2025. Searches identified 84 records; 19 duplicate or version records were removed, leaving 65 records for screening. Twelve were excluded at title or abstract screening and 53 full records were assessed; 11 were excluded at full-record assessment, leaving 42 substantively eligible sources. Five were used only for lineage or saturation checking and 37 carried distinct evidence or methodological functions in the final synthesis. Traditions were compared according to the event directly observed, adherence construct inferred, major sources of missingness or error, and validation required for the intended interpretation. Seven traditions were identified: operational-definition and reporting research; dispensing and possession measurement; electronic event monitoring; programmatic digital adherence technologies; ingestible and digital-pill systems; adherence applications and digital patient-reported tools; and passive sensing/digital phenotyping. Discordance was not simply a progression from inaccurate older methods to accurate newer technologies. Refill records can misclassify possession as use, electronic devices can misclassify interaction as ingestion, ingestible systems remain vulnerable to technical and observation-window failures, and passive phenotypes introduce additional inference between behavior and medication taking. Conversely, indirect measures can be adequate when matched to an appropriate question and validated target. Medication adherence should be interpreted as a set of related but non-equivalent constructs. Measurement validity depends on whether the observed event is appropriate for the intended inference, not on technological granularity alone.

Keywords: Medication adherence, Electronic adherence monitoring, Digital phenotyping, Refill adherence, Ingestible sensors, Digital health

How to Cite This Article: Kowalska A, Johansson E, Mendes S. From Pill Counts to Digital Phenotypes: A Meta-Narrative Review of How Medication-Adherence Technologies Define, Infer, and Misclassify Medicine-Taking, 2017–2025. Ann Pharm Pract Pharmacother. 2024;4(2):161-75. https://doi.org/10.51847/dEbw6VAry7

Introduction

Medication adherence is routinely expressed as though it were a single measurable property, yet adherence research distinguishes initiation, implementation of the prescribed regimen, persistence, discontinuation, and the outcomes that follow medication use. Reporting guidance consequently requires investigators to specify what

aspect of adherence is being measured and how it was operationalized [1]. The Timelines–Events–Objectives–Sources approach makes the underlying problem explicit: an adherence estimate is interpretable only when the time interval, observable event, analytical objective, and data source correspond to one another [2]. A pharmacy claim, bottle opening, sensor-detected ingestion, questionnaire response, and smartphone-derived behavioral signal can therefore all be relevant to adherence while representing different empirical objects.

This distinction becomes consequential when observations are used as substitutes for more distal behavior. Self-report, electronic monitoring, and electronic healthcare databases differ in temporal resolution, missingness, measurement reactivity, and the events from which medicine taking is inferred [3]. Medication-adherence research consequently contains multiple opportunities for selection, measurement, and analytical bias, some generated specifically by the measure or metric chosen [4]. The problem is not that indirect measures are inherently invalid. Rather, validity depends on whether the observation answers the question assigned to it. A refill record may be well suited to studying medication availability over months while remaining incapable of demonstrating that a dose entered the body.

Patient-reported measures illustrate the opposite danger: assuming that technological proximity to ingestion makes contextual information dispensable. The 15-STARS questionnaire was developed to identify patient-reported adherence problems in a pharmacy setting [5], while consensus work on adherence-intervention outcomes has retained medication-taking behavior alongside persistence, clinical outcomes, and patient-relevant consequences [6]. Such evidence indicates that adherence evaluation frequently includes constructs that no sensor can directly observe. Reasons for missed doses, intentional adaptation, treatment burden, or whether medicine use is clinically appropriate are analytically different from confirmation that a device registered an event.

Digital phenotyping extends this measurement problem further. Continuous personal-device data can characterize behavior at temporal resolutions unavailable to conventional encounters [7], but clinical digital phenotyping requires explicit attention to purpose, data quality, safety, and the validity of the interpretation applied to the signal [8]. Digital measurement frameworks similarly distinguish technical verification from analytical and clinical validation for a defined context of use [9]. These principles are especially relevant when medication-adherence research moves from direct medication-related events toward smartphone, wearable, mobility, communication, sleep, or interaction patterns that may correlate with medicine taking without observing it.

A meta-narrative approach is suited to this heterogeneity because it asks how research traditions developed their own questions, preferred evidence, and standards of explanation. Meta-narrative synthesis has been used to distinguish historically different traditions that coexist within a single contemporary field rather than combining them under one vocabulary [10]. The present review therefore asks how medication-adherence technologies have defined and inferred medicine taking from 2017–2025, where their assumptions generate systematic misclassification, and which distinctions must remain visible when older adherence metrics are compared with increasingly data-rich digital systems.

Materials and Methods

Meta-narrative orientation and review unit

The review followed a RAMESES-informed meta-narrative logic. The unit of inclusion was a peer-reviewed report that contributed directly to the definition, observation, validation, implementation, or interpretation of medication adherence or medicine-taking behavior. When several reports represented the same underlying trial or participant cohort, they were treated as a study family during interpretation to avoid counting repeated populations as independent confirmation. Separate reports remained analytically useful when they addressed materially different questions, such as measurement performance in one report and implementation context in another.

The RAMESES-informed orientation was operationalized by identifying traditions from recurring problem framings and standards of evidence rather than from hardware labels alone; allowing methodological, empirical, implementation, and policy reports to contribute according to their analytical role; appraising rigour and relevance in relation to study design; and synthesizing convergence and disagreement across traditions rather than statistically pooling heterogeneous outcomes. This tradition-focused logic was consistent with the meta-narrative precedent used to distinguish coexisting research traditions [10].

Research traditions were defined by recurring combinations of foundational question, directly observable event, typical data source, and inferential assumption. A tradition therefore did not correspond automatically to a device category. For example, smartphone technology could function as a reminder intervention, a self-report interface,

a source of passive behavioral data, or part of an ingestible-sensor system. Those functions were separated when they implied different meanings for an adherence observation.

Search, eligibility, screening, and report clustering

Searches combined medication-adherence concepts with terms covering pill counts, pharmacy dispensing and refill measures, electronic adherence monitoring, medication event monitoring systems, digital adherence technologies, ingestible sensors, digital pills, mobile applications, smartphones, wearables, remote monitoring, and digital phenotyping. Search development used PubMed-indexed literature, publisher and bibliographic metadata records, citation chaining, and targeted methodological searching. Records published from 2017 through 2025 were considered when they directly informed the review question.

Eligibility required a substantive contribution to at least one of four functions: defining the adherence construct; measuring or validating a medication-related observation; testing implementation or clinical use of a technology that generated adherence information; or examining the inferential assumptions connecting digital behavior to medicine taking. Technologies used only for general remote monitoring without an identifiable medicine-taking relationship were excluded. Journal quartile was not used to determine substantive review eligibility.

Screening proceeded at two levels. Title or abstract screening removed records that clearly failed the publication-period or substantive-scope criteria. Full-record assessment then applied the four eligibility functions and the report-family rule. Duplicate or version records were removed before screening, and a secondary report was retained only when it supplied a materially distinct measurement, implementation, or interpretive contribution.

The search identified 84 records. After removal of 19 duplicate or version records, 65 unique records underwent screening. Twelve were excluded at title or abstract assessment, leaving 53 full records for assessment. Eleven were excluded at that stage: two fell outside the specified publication period; four did not directly address medication adherence, medicine-taking measurement, or its inference; two concerned digital monitoring without a medication-taking relationship; two offered conceptual discussion without a usable adherence-measure contribution; and one was a redundant secondary report without a distinct measurement contribution. Forty-two sources met substantive eligibility. Five were retained for lineage or saturation checking but added no distinct interpretive contribution beyond stronger sources, leaving 37 sources with a direct role in the synthesis.

The resulting selection pattern and the transition from retrieval to tradition identification are summarized in **Figure 1**.

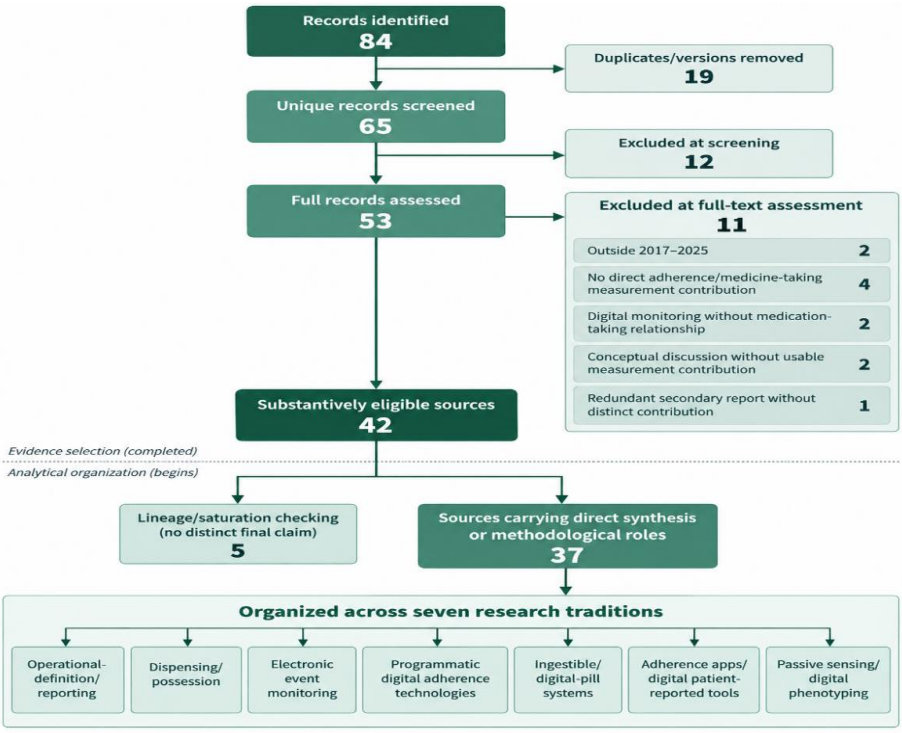

Figure 1. Evidence selection and formation of the medication-adherence research traditions. The selection sequence was 84 records identified, 19 duplicate or version records removed, 65 unique records screened, 12

excluded at title or abstract screening, 53 full records assessed, 11 excluded at full-record assessment, and 42 substantively eligible sources. Five eligible sources were used for lineage or saturation checking and 37 carried direct synthesis or methodological roles across seven research traditions.

Identifying research traditions and appraising rigour and relevance

Traditions were identified iteratively from how investigators framed the adherence problem and what they treated as sufficient evidence of medicine taking. Methodological and reporting literature informed distinctions between adherence phases, observed events, sources, bias, and context-of-use validation. Empirical studies then supplied tests of concordance, measurement performance, implementation failure, or clinical consequence.

Because the evidence included methodological articles, measurement studies, randomized trials, systematic and scoping reviews, implementation research, and policy analyses, a common numerical quality score was not imposed across designs. Rigour was assessed in relation to design: construct clarity, provenance of the adherence observation, adequacy of the comparator or reference standard, treatment of missing data and technology failure, temporal correspondence between observation and target construct, and analytical fit. Relevance reflected how directly a source informed the review question. Source-level appraisal outcomes for the 37 sources carrying direct synthesis or methodological roles are reported; judgments were role-specific and were not converted to a common numerical score.

Comparative synthesis of observed event, inferred construct, and misclassification

For each tradition, synthesis distinguished the event directly recorded from the medication behavior inferred. Potential misclassification was examined at the transition between those levels. A dispensing event could support inference about availability; an electronic opening could support inference about access to a scheduled dose; an ingestible sensor could support inference about a sensor-associated ingestion event; and a passive behavioral feature could support a still more indirect inference. These observations were then compared with persistence, pharmacological exposure, and clinically meaningful use when the evidence allowed.

Misclassification was defined as an interpretation in which the observed event supported a different adherence state from the target construct. This definition allowed both false adherence and false nonadherence and included failures arising from technology, workflow, missingness, observation-window definitions, or inappropriate clinical interpretation.

Results and Discussion

Study selection

Of 84 identified records, 19 duplicate or version records were removed, leaving 65 unique records for title or abstract screening. Twelve records were excluded at that stage and 53 full records were assessed. Eleven full records were excluded: two were outside 2017–2025, four had no direct adherence or medicine-taking measurement contribution, two concerned digital monitoring without a medication-taking relationship, two were conceptual discussions without a usable measurement contribution, and one was a redundant secondary report without a distinct contribution. Forty-two sources were substantively eligible; five were used only for lineage or saturation checking and 37 carried direct synthesis or methodological roles **(Figure 1)**.

Seven research traditions and their observational objects

Seven traditions were distinguishable in the retained literature. The first arose from adherence reporting and operational-definition research and asked how adherence should be defined before it is estimated. Its empirical object was not a technology but the specification linking event, timeline, source, and objective.

The dispensing tradition treated pharmacy supply as a longitudinal record of medication availability. Electronic event-monitoring research shifted the observable object toward device interaction, usually a bottle or package opening. Programmatic digital adherence technologies broadened the object again: pillboxes, telephone confirmation, video-supported approaches, and related systems generated signals intended both to classify adherence and support care. Ingestible systems moved the recorded event closer to swallowing by detecting a sensor-associated ingestion signal. App-based research mixed measurement with reminders, education, self-report, and behavior-change functions. Passive sensing and digital phenotyping inferred adherence-related states from behavioral traces outside the medication event itself.

Direct comparisons demonstrate why these traditions should not be ordered as a simple technological ladder. In once-weekly tuberculosis preventive treatment, treatment-completion classifications derived from electronic monitoring, self-report, and pill count differed overall, while the size of disagreement varied substantially across sites [11]. The same measurement pair can therefore be concordant in one setting and discordant in another. **Table 1** compares the foundational question and observational object that distinguish these traditions**.**

Table 1. Research traditions differ in what they accept as evidence of medicine taking

Research tradition and question		**Observed evidence and construct**			**Inferential vulnerability**
Research tradition	**Foundational question**	**Directly observed object**	**Typical data source**	**Primary adherence construct supported**	**Inferential assumption that requires scrutiny**
Operational-definition/reporting	What exactly is being called adherence?	Defined event and time rule	Protocol, questionnaire specification, data dictionary	Initiation, implementation, persistence, discontinuation	The operational event adequately represents the stated adherence phase
Dispensing/possession	Was medication available to the patient over time?	Dispensing/refill transaction	Pharmacy or claims database	Possession/availability; persistence proxies	Supplied medication was available for and used during the covered interval
Electronic event monitoring	Did the medication container/device register an expected interaction?	Opening or device event	Electronic bottle, blister, inhaler, container	Dose implementation pattern	Device interaction corresponds to dose administration
Programmatic digital adherence technology	Did a program-facing digital signal indicate expected treatment activity?	Device, phone, video, or other program signal	Digital platform linked to care workflow	Implementation and missed-dose detection	Signal presence/absence reflects patient medication behavior rather than system performance
Ingestible/digital-pill systems	Was a sensor-associated ingestion event detected?	Ingestion-linked transmitted event	Ingestible sensor/patch/receiver	Dose ingestion	Detected sensor event corresponds to successful medicine ingestion; absent event represents missed ingestion
Apps/digital patient-reported tools	Did the patient report, record, or interact with adherence support?	App entry, survey, reminder response, interface interaction	Smartphone application	Self-reported implementation, adherence support	Digital interaction corresponds to medication-taking behavior
Passive sensing/digital phenotyping	Does behavior outside the medication event predict a medicine-taking state?	Mobility, communication, sleep, device-use or other behavioral features	Smartphone/wearable/remote monitoring stream	Inferred adherence propensity or context	Behavioral signal remains calibrated to medication taking across persons, settings and platforms

Dispensing and possession: refill metrics as longitudinal proxies

Pharmacy dispensing offers scale and longitudinal continuity but observes supply rather than administration. In a direct comparison of direct oral anticoagulant dispensing and electronic monitoring, pharmacy records were

informative yet only moderately concordant with electronically observed taking behavior [12]. Database research also varies in how initiation, implementation, gaps, grace periods, switching, stockpiling, and persistence are operationalized. A systematic review of COPD database studies identified extensive heterogeneity in the methods used to derive adherence [13, 14].

This does not make refill measures intrinsically weak. They can answer questions for which medication availability is the relevant exposure. Problems arise when possession metrics are interpreted as confirmed ingestion without considering stock carried forward, hospitalization, dose changes, discontinuation, or unrecorded supply. Workflow interventions reinforce this distinction. In community pharmacies using an appointment-based refill model, refill organization changed while medication possession was already very high [15]. A supply metric can therefore encode characteristics of dispensing systems as well as patient behavior.

Electronic event monitoring: Device interaction as a dose surrogate

Electronic monitoring narrows the distance between scheduled medication use and observation by time-stamping device interaction. That temporal resolution makes it valuable for identifying irregular implementation that monthly refill metrics cannot resolve. Yet the event usually remains an opening, actuation, or device interaction rather than direct confirmation that the intended dose was swallowed or administered.

Electronic monitoring can also change the behavior it is intended to observe. Across chronic conditions, electronically monitored interventions were heterogeneous, with larger adherence effects often occurring when monitoring was combined with reminders or feedback; clinical outcomes and acceptability were less uniform [16]. Accordingly, an electronic adherence record can represent both a measurement stream and part of an intervention. Studies that compare monitored with unmonitored groups must distinguish measurement reactivity from the underlying behavior being measured.

Programmatic digital adherence technologies: Signals embedded in care workflows

The tuberculosis literature made digital adherence technology a programmatic category that included several distinct mechanisms rather than a single measurement instrument [17]. This tradition is analytically important because a digital signal frequently initiates follow-up, counseling, escalation, or differentiated care. Measurement performance and intervention performance can therefore diverge.

In a cluster-randomized trial in China, digital medication monitoring linked to adherence review did not reduce unfavorable treatment outcomes [18]. Systematic accuracy evidence likewise shows that performance varies substantially across digital platforms and the reference standards against which they are compared [19]. An absent signal may reflect a missed dose, but it may also reflect connectivity problems, non-use of the device, failure to carry required hardware, workflow interruptions, or incomplete transmission.

Implementation reviews reinforce this interpretation. Reach, engagement, adoption, fidelity, literacy, language, connectivity, stigma, staff workload, and technical complexity can alter whether a digital adherence signal is generated or acted on [20, 21]. Missing data therefore have at least two possible behavioral origins: medication non-use and technology non-use. Four pragmatic cluster trials subsequently found that digital adherence technologies did not uniformly reduce poor tuberculosis outcomes across settings [22]. In HIV, pooled evidence for real-time medication monitoring also did not establish statistically definitive improvement in adherence or viral suppression [23]. These null and context-dependent findings separate the validity of an adherence observation from the effectiveness of a service built around that observation.

Ingestible systems: Confirming a sensor event without collapsing ingestion into exposure

Ingestible sensors reduce one major inferential gap by linking an electronic signal to an ingestion-associated event. In a randomized tuberculosis study, wirelessly observed therapy achieved high confirmation of dosing events, but comparisons with directly observed therapy changed materially after days on which observation was unavailable or treatment was held were handled explicitly [24]. The denominator defining an expected observation is therefore part of the measurement model.

A review of ingestible electronic sensors similarly found high event-detection performance in selected studies alongside lower or more variable real-world performance when technical nonadherence occurred [25]. The technology can fail because the patient does not wear or synchronize required components, the receiver or patch does not function, transmission fails, or observation is otherwise interrupted. In those circumstances, absence of a sensor event is not logically identical to absence of ingestion.

Implementation adds further layers. Clinicians evaluating ingestible biosensors for tuberculosis identified substantial interest while also identifying patient willingness, cost, and infrastructure as practical constraints [26]. Broader assessment of digital-pill evidence has likewise emphasized that the clinical evidence base remains uneven across indications [27]. Multimodal studies combining digital-pill events with smartphone-derived behavioral features show how a direct medication-related event can become an anchor for more indirect behavioral inference [28], while stakeholder analyses highlight privacy, autonomy, and governance consequences of continuous medication monitoring [29].

Patient selection can also determine whose digital phenotype is available. Among men who have sex with men using PrEP in the context of substance use, willingness to share digital-phenotyping data varied [30]. In the same therapeutic area, linking ingestion events to prevention-effective adherence showed that the clinical meaning of an ingestion count depends on when protection is required, not solely on the presence of a sensor event [31]. Thus ingestion is a more proximal observation than dispensing or bottle opening, but it remains analytically distinct from pharmacological exposure, persistence across time, and clinically meaningful use.

The distinctions across technologies are summarized in **Table 2**.

Table 2. What adherence technologies record directly—and what must still be inferred

Measurement approach	Event directly available to analysis	Medicine-taking state most directly supported	Additional inference often made	Dominant failure modes	Interpretation that the event alone cannot establish
Indirect records and reported quantities					
Pharmacy dispensing/refill	Prescription supply transaction	Medication availability/possession	Regular dose implementation	Stockpiling, external supply, hospitalization, regimen change, administrative gaps	Dose ingestion
Pill count	Remaining dosage units at inspection	Discrepancy between expected and remaining quantity	Doses consumed as scheduled	Pill dumping, sharing, loss, inaccurate starting quantity	Timing or ingestion of individual doses
Self-report	Patient-reported behavior or reason	Reported medicine taking, barriers and intentionality	Actual implementation pattern	Recall, social desirability, question interpretation	Independently verified ingestion
Device-mediated medication events					
Electronic container/device	Opening, actuation or device interaction	Opportunity for scheduled administration	Dose taken after device event	Curiosity openings, multiple doses per opening, pocket dosing, non-use of monitor	Swallowing or pharmacological exposure
Programmatic digital adherence technology	Platform-specific phone/device/video signal	Technology-mediated evidence of treatment activity	Missed or completed dose	Connectivity, non-engagement, device failure, workflow failure, proxy use	Patient nonadherence when the system is silent
Ingestible/digital pill	Sensor-associated ingestion event	Ingestion-associated dose event	Drug exposure and clinically effective use	Patch/receiver failure, non-wear, synchronization problems, observation-window errors	Therapeutic exposure, persistence, benefit
Software engagement and behavioral inference					
Adherence app/digital patient report	App interaction, entry, reminder response or self-report	Engagement or reported behavior	Dose implementation	App abandonment, notification fatigue, selective reporting	Medication ingestion

Passive digital phenotype	Behavioral feature or derived pattern	Context or propensity correlated with adherence	Individual medicine-taking state	Platform drift, missingness, behavioral confounding, selection, model miscalibration	Medication taking without external validation

Apps and digital patient-reported tools: Intervention, reporting and measurement intertwined

Medication-adherence apps frequently combine reminders, education, self-monitoring, communication, and self-report. Their efficacy therefore depends on an adherence outcome that may be measured using a method independent of the app itself [32]. This distinction is lost when application engagement is treated as evidence that medication was taken.

The literature in schizophrenia illustrates heterogeneity in both digital intervention and adherence ascertainment [33, 34]. Meta-analytic estimates of app effects can change with the measurement instrument used, making the outcome definition part of the interpretation rather than a neutral endpoint. App-specific constructs add another layer. The Mobile Adherence Satisfaction Scale measures satisfaction with medication-adherence apps [35], while a pilot randomized community-pharmacy study showed that a digital tool eliciting adherence and medication beliefs could alter patient participation in pharmacist interactions [36]. Satisfaction, disclosure, communication, and interface engagement may all matter clinically, yet none is equivalent to an independently observed dose.

Passive sensing and digital phenotypes: Behavior inferred beyond the medication event

Digital phenotyping shifts the observational object away from medication handling toward patterns of everyday behavior. Mobility, sleep, communication, phone interaction, and other passive signals can potentially identify contexts in which nonadherence becomes more likely. Their value lies precisely in providing information that direct medication monitors cannot: behavioral change before a missed dose, environmental instability, routine disruption, or broader functional states.

This gain creates an additional inferential burden. Remote patient monitoring reviews encompass diverse devices and outcomes, with adherence representing only one component of a wider monitoring ecosystem [37]. A passive signal becomes an adherence measure only when its relationship to the relevant medicine-taking state has been specified and validated. Combining smartphone features with digital-pill events provides a possible route to such validation because the medication-linked event can serve as an anchor [28]. Yet small observational datasets and population selection restrict external interpretation, and willingness to contribute passive data may itself be socially patterned [30].

These traditions are connected historically and analytically, but newer approaches often inherit assumptions from older adherence measures rather than replacing them. **Figure 2** represents those relationships without implying a single linear progression.

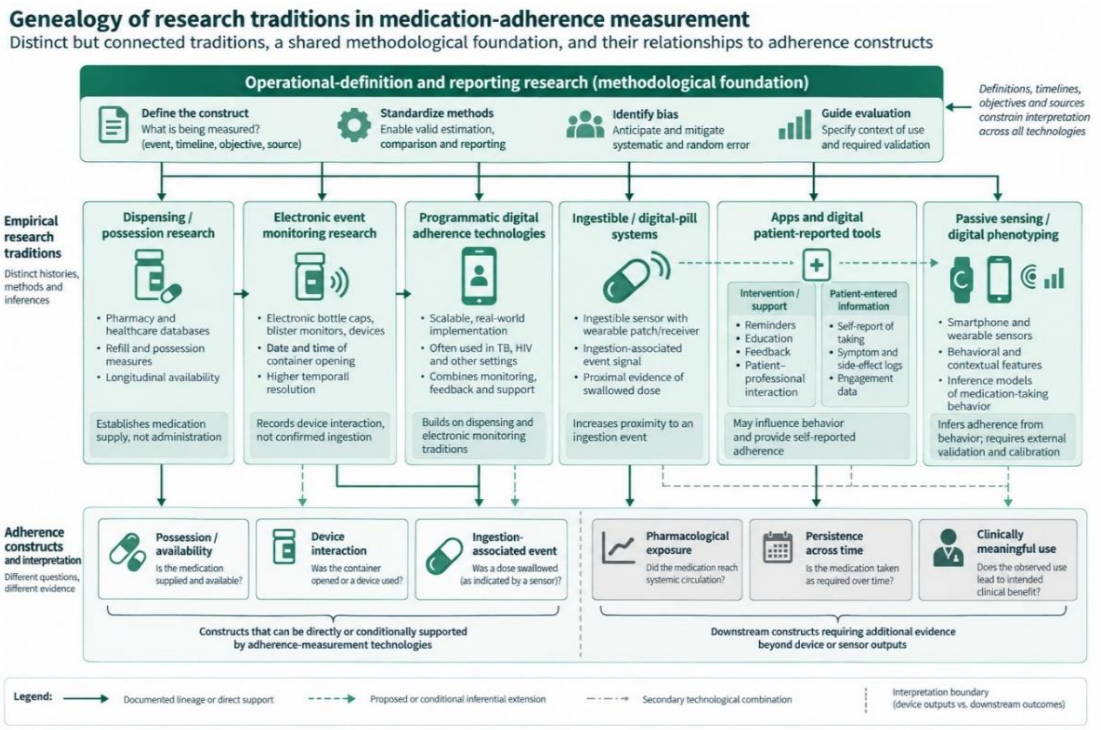

Figure 2. Genealogies of medication-adherence observation and inference across technology traditions

Cross-tradition misclassification: Where observation changes meaning

Across traditions, misclassification arose when an observation was interpreted as evidence for a medication-use state that lay beyond what the data directly supported. A filled prescription can produce false adherence when medication is collected but not used; the same refill record can produce false nonadherence when legitimate stock, hospitalization, dose reduction, or supply outside the captured database makes an apparent gap. Electronic openings can overstate taking when containers are opened without administration and understate it when doses are removed in advance.

Digital systems add technology-mediated pathways. Connectivity failure, non-wear, platform non-engagement, synchronization problems, or workflow breakdown can create apparent nonadherence even when medicine is taken. Ingestible systems remove some ambiguity around swallowing but introduce observation-window and component-use requirements. App interaction may be mistaken for medication-taking behavior, while app abandonment may be interpreted as treatment abandonment. Passive phenotypes carry the greatest distance between observed event and medicine-taking conclusion: behavioral change may correlate with adherence while also being produced by illness, employment, travel, caregiving, device changes, or unrelated routine disruption.

The reverse problem also matters. A technically correct ingestion record does not establish appropriate pharmacological exposure or clinically meaningful use. Dose timing can be incompatible with treatment requirements, persistence can fail later, or therapeutic effect can depend on physiology, interaction, disease state, and regimen-specific exposure. The PrEP literature illustrates this distinction because the meaning of an ingestion history depends on when protection is required [31].

Table 3 locates common false-adherence and false-nonadherence mechanisms at the observation where they arise.

Table 3. Technology-specific routes to false adherence and false nonadherence

Observed signal and error mechanism			Contextual discrimination	
Observable pattern	**Likely misclassification direction**	**Mechanism**	**Settings in which interpretation is especially vulnerable**	**Discriminating information before clinical attribution**
Regular refill with little evidence of actual use	False adherence	Possession interpreted as ingestion	Long refill intervals, stock accumulation, regimen changes	Dose history, patient account, complementary measurement

Apparent refill gap despite medication availability	False nonadherence	Unobserved stock or supply source	Hospitalization, early fills, external pharmacy, dose reduction	Stock history, care transitions, updated regimen
Expected electronic openings without dose administration	False adherence	Device interaction interpreted as taking	Curiosity openings, multiple openings, shared/device handling	Administration context or corroborating evidence
Few electronic openings despite regular taking	False nonadherence	Monitor bypassed during actual use	Pocket dosing, pill organizers, travel	Patient workflow and alternative storage
Missing programmatic DAT signals	False nonadherence	Technology or implementation silence interpreted as missed dose	Poor connectivity, low digital access, staff/process failure	Device function, transmission logs, workflow review
Ingestible signal absent	False nonadherence	Patch/receiver/non-wear or synchronization failure	Multicomponent digital-pill systems	Component-use status and observation eligibility
Ingestible signal present	False adherence to clinically meaningful treatment	Ingestion interpreted as adequate exposure or effective use	Regimens with timing-, persistence-, interaction- or exposure-dependent benefit	Regimen timing, persistence, exposure-relevant clinical context
App opened or reminder acknowledged	False adherence	Digital engagement interpreted as dose completion	Reminder/self-management apps	Independent medication-use measure
App abandoned	False nonadherence	Platform disengagement interpreted as treatment disengagement	Notification fatigue, app burden, device change	Patient-reported medication behavior
Passive behavioral phenotype changes	Either direction	Behavioral correlate treated as medication-specific signal	Illness change, travel, work, social disruption, platform drift	External validation against a medication-linked target

The comparative result is therefore conditional. Greater proximity to ingestion eliminates some inferential steps, but it does not produce a monotonic hierarchy of adherence validity. Every technology remains dependent on what event it actually records, how missing data arise, which medication-use construct is the target, and whether the link between observation and target has been validated in the population and context in which the measure is used.

What converges across traditions—and what remains incommensurable

The seven research traditions converge on a basic methodological requirement: an adherence estimate has meaning only in relation to a specified medication-use event, observation period, and intended interpretation. Operational-definition research makes this requirement explicit [1], and TEOS formalizes the relationship among timelines, events, objectives, and sources [2]. The empirical traditions show why that specification matters. Dispensing data document medication supply; electronic monitors record device interactions; ingestible systems capture ingestion-associated signals; apps record reports or engagement; passive sensing measures behavior from which adherence may subsequently be inferred. These observations occupy different positions in the medicine-use process and cannot be treated as interchangeable measurements of one latent quantity.

The evidence does not support a simple hierarchy in which newer technology progressively eliminates measurement error. Refill measures can be informative for longitudinal availability despite their distance from ingestion. Electronic monitoring increases temporal resolution but may remain a surrogate for administration and can itself alter behavior [16]. Digital adherence technologies add real-time visibility but also introduce connectivity, engagement, and workflow failure. Ingestible systems reduce uncertainty about some ingestion events while retaining dependence on patches, receivers, synchronization, and observation eligibility [25]. Passive

sensing can contribute contextual information unavailable to direct monitors, but the adherence inference becomes more dependent on external validation.

Some disagreement among methods is therefore expected rather than automatically evidence that one method is defective. Database definitions themselves vary [13], while direct comparisons between dispensing and electronically monitored behavior demonstrate that concordance depends on how the target is specified [12]. A measure should be judged against the construct it is intended to estimate. Agreement between two technologies is difficult to interpret when each observes a different event.

An additional distinction concerns clinically meaningful use. Confirming medicine availability, container opening, or ingestion does not establish adequate systemic exposure, persistence over the required treatment horizon, or therapeutic benefit. Medication adherence is consequently best regarded as a family of related constructs whose measurement relationships must remain visible. Collapsing those relationships into one percentage can make apparently precise estimates conceptually ambiguous.

Validation should match the inferential step, not novelty of the device

Digital measurement should be validated according to the claim made from the signal. The V3 approach distinguishes verification of technical performance, analytical validation of the derived measure, and clinical validation for a specified context of use [9]. Medication-adherence technologies require an analogous separation because different errors arise before and after the recorded event.

For a refill measure, validation may ask whether dispensing records accurately capture medication availability and whether the chosen possession algorithm handles hospitalization, stockpiling, dose changes, and discontinuation. For an electronic container, technical accuracy of event capture is distinct from evidence that an opening corresponds to administration. For an ingestible system, detection of a correctly functioning sensor-associated event is distinct from interpreting an absent signal as a missed dose. Digital-pill studies illustrate that non-wear or component failure can reduce observable event capture even when the underlying medication behavior is unchanged [25].

Passive digital phenotypes impose an additional mapping problem. A behavioral feature can be measured with excellent technical reliability while remaining a poor indicator of medication use. Its validation must therefore include the association between the phenotype and a medication-specific reference, calibration across populations and contexts, robustness to missingness, and resilience to changes in devices or platforms. Combining smartphone features with ingestion-linked digital-pill events offers one way of testing this mapping [28], but small or selected samples cannot establish general transportability.

The resulting cross-tradition validation requirements are summarized in **Table 4**.

Table 4. Where adherence-measurement traditions converge, disagree, and require different validation

Validation question	**Evidence tension**		**Validation resolution**	
Cross-tradition question	**Convergence in the evidence**	**Unresolved disagreement**	**Validation implication**	**Observation that would strengthen interpretation**
What constitutes the adherence event?	Every measure depends on an identifiable event and time rule	Traditions privilege supply, interaction, ingestion, report, or behavior differently	State the event before reporting an adherence metric	Demonstrated correspondence between recorded event and intended adherence phase
Can possession represent implementation?	Dispensing data can characterize longitudinal availability	Degree to which possession predicts actual dose taking varies by regimen and context	Validate algorithms against an appropriate medication-use target where implementation is claimed	Stable agreement with dose-level or clinically relevant reference information
Does device interaction represent administration?	Electronic events improve temporal visibility	Opening or actuation may occur without medication administration, and administration can occur without a recorded event	Separate device-event accuracy from administration validity	Concordance maintained when alternative storage, pocket dosing, or multiple openings are considered

Does an ingestion-associated signal establish adherence?	Ingestible systems can provide proximal evidence of an ingestion event	Missing signals may arise from technology non-use or failure; ingestion may still be insufficient for exposure or effective use	Validate component availability, observation eligibility, ingestion detection, and downstream interpretation separately	Reliable event capture during routine use plus correspondence with the clinically relevant dosing target
Is technology silence evidence of nonadherence?	Missing data are common across digital approaches	Patient non-use and system failure can generate the same apparent absence	Determine why the observation is missing before assigning adherence state	Device, transmission, and workflow information capable of separating technical absence from medication absence
Does app engagement indicate medicine taking?	Apps can affect reminders, reporting, knowledge, and patient–professional interaction	Engagement and adherence are often measured with different instruments	Treat engagement as a separate endpoint unless validated against medication behavior	Independent adherence measure demonstrating that app events predict the target behavior
Can passive behavior identify adherence?	Behavioral sensing may capture context associated with medicine taking	Correlation can reflect illness, routine, social context, or platform characteristics instead of medication behavior	Require medication-specific external validation, calibration, and transportability testing	Replicated prediction against a medication-linked reference across populations, devices, and context changes
Does more granular monitoring improve clinical outcomes?	Greater temporal resolution can identify potentially actionable deviations	Detection alone does not ensure effective clinical response or better outcomes	Evaluate the entire signal-to-response pathway as well as measurement accuracy	Evidence that detected deviations trigger appropriate action and improve patient-relevant outcomes

Clinical and implementation implications

The first implication is that adherence information should be labeled according to what was actually observed. A clinical dashboard should distinguish "medication supplied," "device event recorded," "ingestion-associated event detected," and "behavioral model indicates increased risk" instead of rendering all four as equivalent adherence states. This preserves the clinician's ability to decide whether further confirmation is required.

Second, missing digital information should prompt evaluation of the measurement system before attribution to the patient. Implementation studies of digital adherence technologies identify connectivity, literacy, device usability, stigma, workload, training, and technical performance as determinants of whether usable information is generated [20]. Treating system silence as patient nonadherence can therefore direct unnecessary counseling, escalation, or surveillance toward a patient whose medication behavior was never actually observed.

Third, measurement design should be linked to the decision that follows. Real-time monitoring offers little clinical advantage when an identified deviation does not produce appropriate response. The China tuberculosis trial demonstrated that introducing digital monitoring did not by itself improve treatment outcomes [18], while larger pragmatic trials similarly showed no uniform benefit from digital adherence technologies [22]. These findings do not show that the underlying observations were valueless; they show that measurement, implementation, and treatment outcome are separate parts of the clinical pathway.

Fourth, technological intensity should be proportionate to the information needed. A refill measure may be sufficient for population-level persistence surveillance. Dose-timing research may require electronic monitoring. An ingestion-associated measure may be justified when the question specifically concerns swallowed doses. Passive phenotyping may be appropriate when the target is emerging behavioral context rather than confirmation of an individual dose. Selecting the most technologically proximal measure regardless of purpose can increase burden, cost, missingness, and privacy intrusion without resolving the relevant clinical uncertainty.

Digital-pill and passive-sensing research also makes autonomy and acceptability inseparable from measurement quality. Continuous observation can create privacy and governance concerns [29], while willingness to participate in digital phenotyping may shape whose behavior enters the dataset [30]. Selection into monitoring can therefore influence both implementation and model validity.

Limitations and falsifiable tests

This review has limitations inherent to meta-narrative synthesis. Traditions overlap, and individual technologies can operate within several traditions simultaneously. Smartphones may provide reminders, collect self-report, transmit directly observed medication events, and generate passive behavioral features. Classification was therefore based on the inferential role of a technology rather than hardware alone.

The literature also remains uneven across diseases, populations, and adherence measures. Tuberculosis contributes unusually rich evidence on programmatic digital adherence technologies, whereas ingestible systems and passive phenotyping include smaller and more selected studies. Heterogeneous comparators also limit cross-study statements about accuracy because self-report, dispensing, electronic monitoring, directly observed therapy, and sensor events do not constitute equivalent reference standards. Publication through 2025 additionally captures a field in which devices, platforms, and algorithms continue to change.

The synthesis makes claims that can be tested. Its central interpretation would be weakened if dispensing, electronic interaction, and ingestion-based measures demonstrated stable, externally calibrated agreement with the same target construct across heterogeneous diseases, regimens, and settings and showed no meaningful differences in prediction of downstream exposure or outcomes. The argument that passive digital phenotyping adds an additional inferential layer would likewise be weakened if passive features reproducibly predicted missed ingestion beyond direct medication-event data, remained calibrated after device and platform changes, and retained performance under substantial missingness and contextual change. Such findings would justify collapsing distinctions that the current evidence indicates should remain explicit.

Conclusion

Medication-adherence technologies do not observe a single behavior at progressively greater resolution. They generate evidence about different events: medication supply, device interaction, ingestion-associated signals, patient reports, engagement, and broader behavioral patterns. Misclassification occurs when those observations are assigned a more distal meaning than their validation supports.

The most defensible measurement strategy therefore begins with the intended medication-use construct and selects an observation capable of supporting it. More direct observation can reduce particular uncertainties without eliminating technical failure, missingness, implementation constraints, or the distinction between ingestion and clinically meaningful treatment. Conversely, indirect measures can be appropriate when availability, persistence, context, or population-level behavior is the actual target.

Future adherence research should report the observed event, the inferred construct, the assumptions connecting them, and the evidence supporting those assumptions. This preserves the value of both established and emerging technologies while preventing increasing digital detail from being mistaken for increasing certainty about medicine taking.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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