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CURRENT OPINION

The Importance of Assessing Drug Exposure and Medication Adherence in Evaluating Investigational Medications: Ensuring Validity and Reliability of Clinical Trial Results

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Abstract
The objective of this current opinion paper is to draw global attention to medication adherence, emphasizing its crucial role in drug trials. Frequently, trialists lean on traditional approaches to assess medication adherence, which, while comfortable, may only reveal what trialists desire rather than offering the essential insights needed for informed decision making in drug development. Understanding drug exposure and medication adherence is paramount when evaluating the effectiveness and safety of investigational medications. Without a comprehensive understanding of how patients adhere to their prescribed treatment regimens, the integrity and dependability of clinical trial results can be compromised. This paper emphasizes the need for measures that accurately and reliably assess medication intake behaviors, enabling the differentiation between minor dosing errors and significant deviations that may impact the drug's efficacy and safety. Accurate knowledge of drug exposure empowers researchers to make informed decisions, identify potential confounding factors, and appropriately interpret study outcomes, ultimately ensuring the validity and reliability of the research findings. By prioritizing drug exposure assessment and medication adherence measurement, clinical trials can enhance their scientific rigor, contribute to more accurate evaluations of investigational medications, and ultimately speed up the development process.

Key Points

Accurate measurement of medication adherence and drug exposure in drug trials is crucial for reliable research outcomes, but it is often overlooked compared to other aspects of the study.

Pre-electronic methods to measure adherence in trials (i.e. pill count, self-report, bioanalytical assays) are imprecise and biased.

Electronic monitoring is a precise and reliable method to capture variability in adherence behaviors, such as timing deviations, missed or extra doses, drug holidays, and discontinuation.

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1 Introduction

Drug trials can be conceptualized as a dynamic system, where the investigational product (i.e., "the drug") serves as the input, and the resulting estimates of drug efficacy and safety represent the output (see Fig. 1). Within this system, the individuals selected to participate in the study are carefully chosen to represent specific characteristics of the target population.

Curiously, despite substantial efforts and investments directed towards ensuring the selection of the population and sound output assessment, relatively little attention is devoted to guaranteeing the quality and precision of the input data. Similar to other logical processes, the adage "garbage in, garbage out" holds true, emphasizing the importance of reliable input data about the drug to ensure meaningful output. In drug development, typically, the study protocol outlines a dosing regimen that is assumed to be followed religiously by the patients involved.

However, it is crucial to acknowledge that in ambulatory care settings, adherence to the dosing regimen specified in the study protocol often deviates from expectations.

In 2012, Blaschke et al. [1] conducted an analysis of a database containing electronically compiled dosing history data from 95 clinical studies. Their findings revealed that half of the 16,907 study participants exhibited substantial deviations from the dosing regimen outlined in the study protocol.

For instance, when it comes to once-daily medications, only a small fraction of study participants adhere strictly to a 24-h dosing schedule. Instead, most patients exhibit variability in the timing of their medication intake, typically within a few hours interval. This common variability in medication adherence is depicted in Fig. 2 for 4 patients with typical patterns of dosing schedules while having taken 100% of their prescribed doses.

Furthermore, besides variability in the time of drug intake, occasional occurrences of missed doses or extra doses are not uncommon. For instance, in a study analyzing drug trials for once-daily prescribed anti-hypertensive medications, Vrijens et al. [2] emphasized that approximately half of the patients experienced a monthly rate of missing a single day's dose. Figure 3 depicts patterns of single missed doses and errors in medication intake that are common in ambulatory care.

Interestingly, this suboptimal adherence behavior is often considered acceptable and even desired in drug trials, as it reflects how the medication is likely to be taken in real-life situations. Acknowledging the inherent variability in patients' adherence patterns ensures that the findings derived from the trial are more representative of actual clinical practice. It accounts for the diverse factors that can influence adherence, such as individual routines, lifestyle demands, and occasional forgetfulness or mistakes [3].

By allowing for this accepted variability in medication exposure, clinical trials aim to generate findings that can be extrapolated to real-world scenarios. This approach increases the generalizability and applicability of the study results once the drug is available on the market. It acknowledges that patients' adherence behaviors in routine clinical practice may not follow a strictly predefined dosing regimen.

Extensive research on medication adherence in drug trials reveals a concerning prevalence of more significant adherence errors. In addition to the previously mentioned variations in timing and occasional missed or extra doses, more severe issues such as interruptions in dosing, or even complete discontinuation of medication are frequently observed within these trials [1]. The occurrence of drug holidays, characterized by two or more consecutive days without medication dosing, poses a particular concern. In such instances, participants intentionally or unintentionally cease taking the medication for a brief period or longer (see 4 examples in Fig. 4). Conversely, overdosing is also prevalent in most trials, characterized by the intake of additional doses or the consumption of doses too closely together. This issue is a cause for concern as it increases the likelihood of encountering side effects. These findings shed light on the complex nature of medication adherence within drug trials, indicating that it extends beyond minor deviations in dosing timing. The identification of more significant adherence errors emphasizes the importance of understanding the full spectrum of adherence behavior and its potential impact on treatment outcomes.

A motivating example highlighting the issue discussed in this paper can be seen in the disappointing outcomes of the MOUNTAIN Phase III study, which investigated zuranolone in major depressive disorder (MDD) [4]. As it is typical for the interpretation of Phase III studies according to the intention-to-treat (ITT) principle, the authors report incredibly high medication adherence rates, claiming 'overall adherence to study drug was 98.3%'. However, this figure is highly improbable in a population known to struggle with adherence issues [1]. Noncompliance with antidepressant therapy remains a significant concern for MDD patients. Strikingly, despite this purportedly exceptional adherence rate, an exploratory post hoc analysis revealed that 9% of the samples showed no detectable plasma zuranolone concentration. When these patients with no measurable plasma zuranolone concentration were excluded, a notable difference in clinical outcomes between intervention and control

Fig. 1 Visual representation of the systemic perspective on drug trials

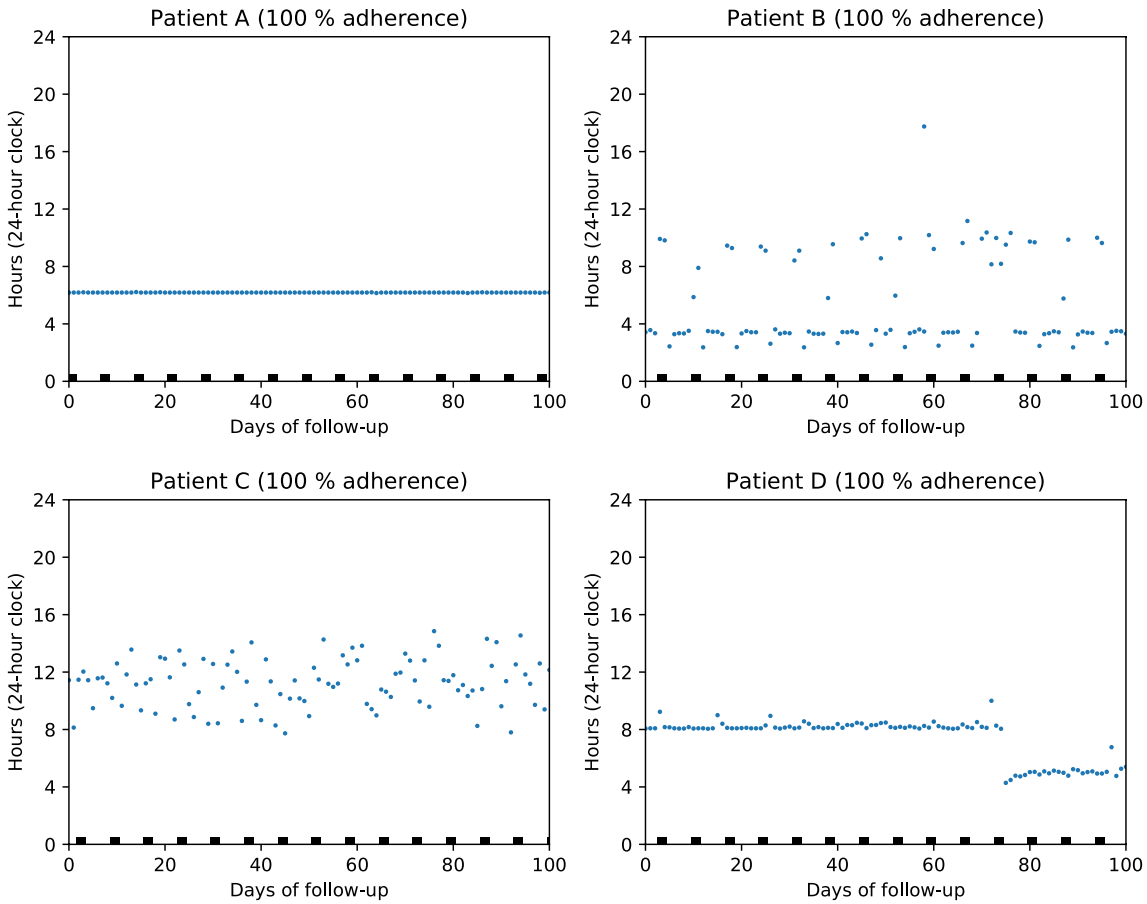

Fig. 2 Dosing chronology plots of four patients. Index date of follow-up in the study is shown on the horizontal axis, and 24-h clock time is shown on the vertical axis. Blue dots indicate the electronically recorded time and date of dosing. All four patients adhered 100% to the prescribed one dose per day, but there were variations in the timing of intake

groups was observed, which was not the case in the ITT analysis.

To avoid these types of discrepancies, it is essential to employ precise and reliable measurement methods of medication adherence that can differentiate between minor and more significant deviations.

1.1 Methods of Measuring Medication Adherence in Drug Trials

Medication adherence plays a vital role in determining the efficacy and safety of medicines. Therefore, it is crucial to assess adherence with precision and accuracy during drug trials. A review by Mantila et al. [5] has reported the frequency of methods used to measure medication adherence in registration trials, which resulted in the approval of new medicines in Europe. In the following sections, we will explore the theoretical framework of these measurement methods and examine their actual performance, shedding light on the challenges encountered during trial execution. The following items will provide a description of the authors' experience in utilizing those measures to evaluate medication adherence. We will present them in the order corresponding to their reported usage.

1.2 Pill/Dose Count: Used in 90.2% of Trials

In theory, the method consists in counting manually the number of pills or tablets remaining in a medication container at specific time points, typically at study visits. The assumption behind pill count is that the number of pills dispensed minus the number of pills remaining reflects the number of doses that have been taken by the study participant. By comparing the expected number of pills to be taken with the actual count, researchers can estimate the average level of adherence to the prescribed medication regimen. While manual pill count is simple, and well-accepted, it is a sparse method providing only an average measure of drug consumption and it is well known to have several potential

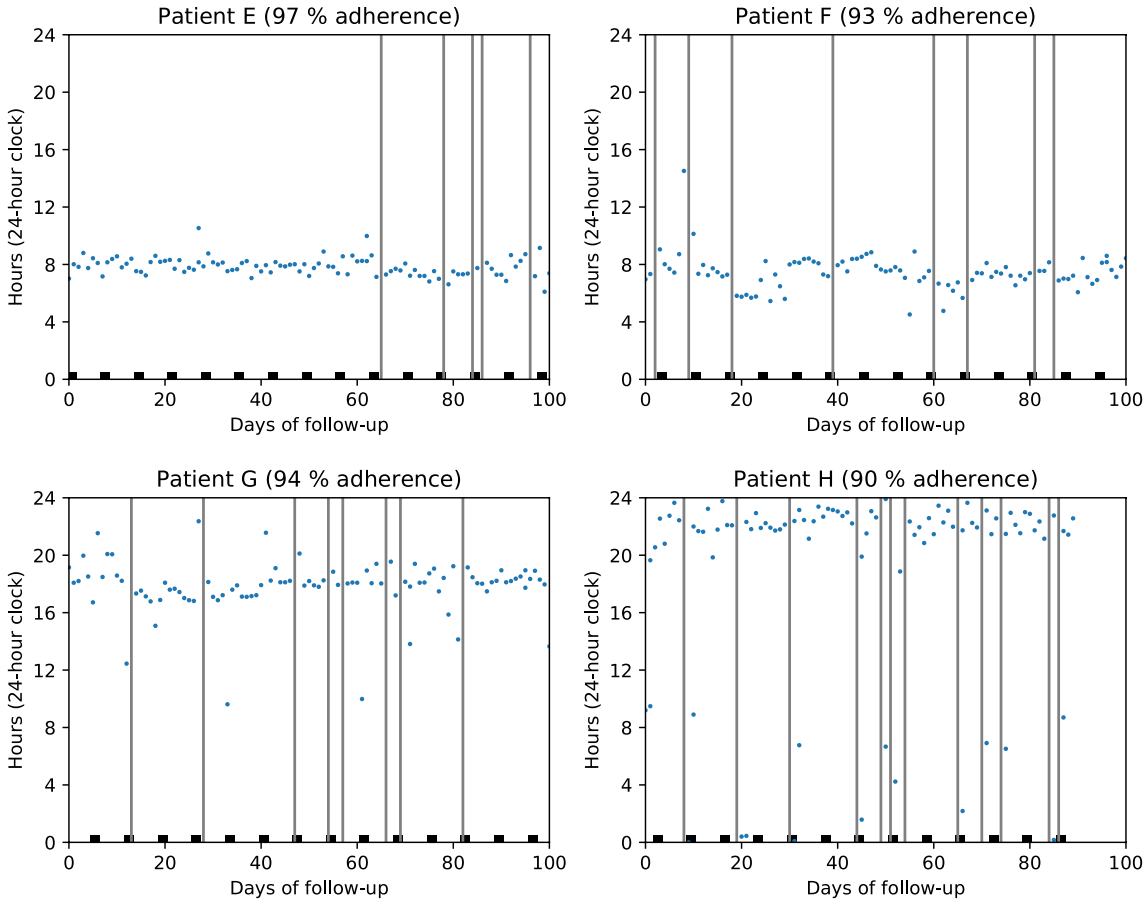

Fig. 3 Dosing chronology plots of four patients. Index date of follow-up in the study is shown on the horizontal axis, and 24-h clock time is shown on the vertical axis. Blue dots indicate the electronically recorded time and date of dosing. The vertical tan lines depict missed doses

sources of measurement error, including human error in counting pills, patients not consuming the pills removed from the packaging, and instances where patients drop pills prior to their visit.

In drug trials for registration, the situation may be worse as both sponsors and investigators have strong incentives to adhere to the study protocol, which leads to a high emphasis on recruiting adherent patients. However, pill counting suffers from a significant drawback: it is susceptible to the creation of fraudulent reports that indicate good adherence [6]. Patients are encouraged to bring back empty study drug packages to avoid retraining by investigators on study requirements and eventually being excluded from the trial. This results in a recognized desirability bias towards favorable outcomes in pill count measurements, which is further amplified when adherence data from excluded non-adherent patients are censored for further evaluation and thus not reported.

To inflate adherence estimates, an arbitrary threshold, often around 80%, is frequently set to dichotomize between an adherent and non-adherent patient, allowing for some tolerance in adherence levels. However, this low threshold is seldom justified using pharmacometrics analysis and may permit gaps in dosing that compromise the effectiveness of the medication, for instance, it allows a treatment interruption of 2 full weeks out of 10.

Furthermore, it is important to note that while returned tablet counts are typically recorded in the randomization system (IRT/RTSM) for drug accountability, they often do not make their way to the study data repository (EDC). As a result, pill count data are often unavailable to study statisticians and are not utilized for risk-based quality management (RBQM). For instance, when Rudd et al. reported in 1988 [7] that a significant number of patients (35%) participating in drug trials had pill counts well above 100%, it should have served as a warning sign. However, regrettably, even to this day, such cautionary measures are often overlooked.

In summary, manual pill counting is a convenient system that masks the uncomfortable truth of medication nonadherence in clinical trials. It is often employed by investigators as a checkbox method to document presumed good adherence, regardless of the actual level of drug exposure.

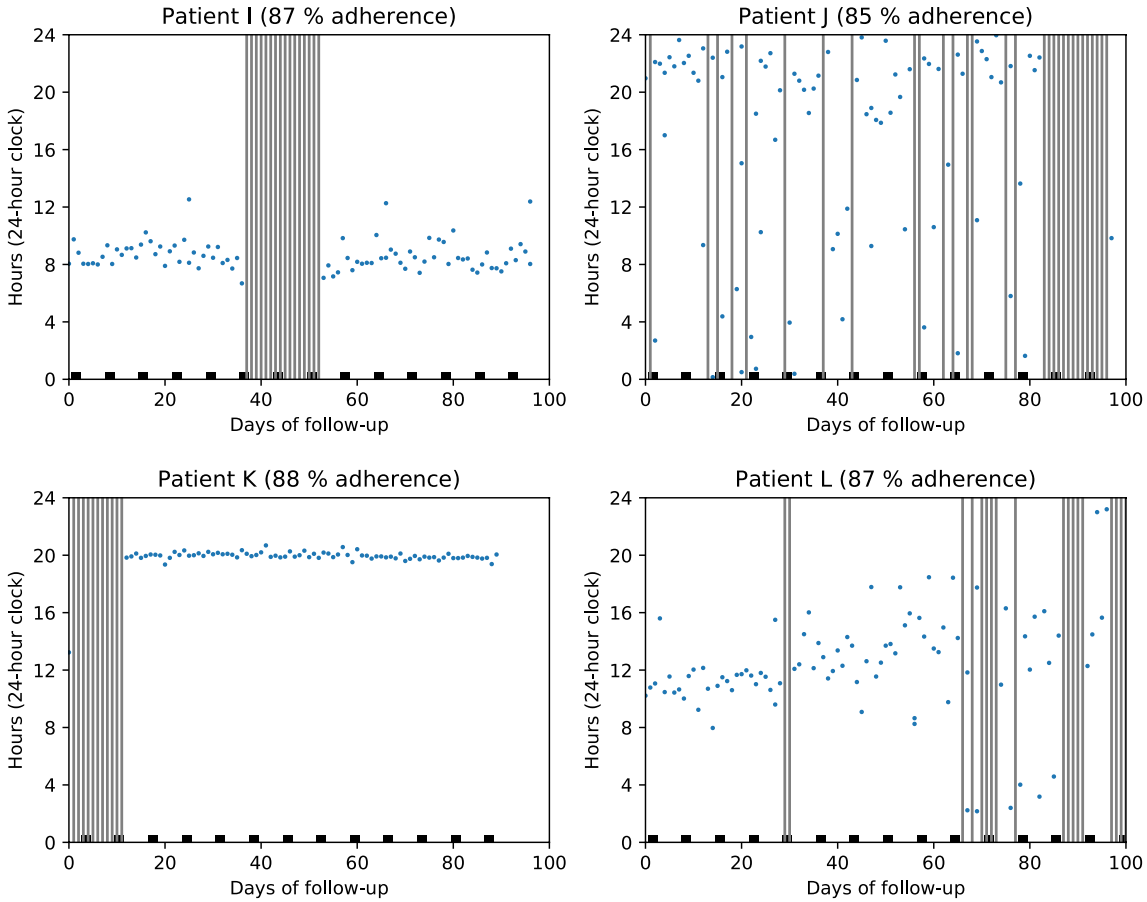

Fig. 4 Dosing chronology plots of four patients. Index date of follow-up in the study is shown on the horizontal axis, and 24-h clock time is shown on the vertical axis. Blue dots indicate the electronically recorded time and date of dosing. The vertical tan lines depict missed doses. Extended periods without dosing (drug holidays) are shown by vertical tan bars, the width of which reflects the number of days without dosing

This information is typically utilized to assert a high level of adherence to the prescribed dosing regimen outlined in the protocol, which is essential for interpreting data analysis based on the well-established ITT principle.

1.3 Patient Self-Report: Used in 27.0% of Trials

In theory, patient self-reporting of medication adherence encompasses a wide range of methods, including retrospective questionnaires, prospective diaries, or electronic diaries (e-diaries). It is often used in complement to pill count.

In practice, similar to manual pill counting, retrospective questionnaires are susceptible to desirability bias, making it easy to generate a favorable adherence record by simply answering positively to the questions. The wide choice of questionnaire (e.g., 121 as reported by Kwan et al. [8]), method of administration (e.g., at the study site vs at home, in person vs by phone), the person administering the questionnaire (e.g., independent nurse or study investigator) and their attitude (empathic vs authoritative) can significantly influence the results, leading to considerable variability and lack of reliability. The retrospective time period covered by the questionnaire (e.g., 1 day, few days, 1 month, or unspecified) is also a major factor contributing to the variability. A recall period longer than 4 days backwards about medication adherence is nearly impossible for anyone, in particular if the medication-taking process is habitual, which is desirable [9].

Prospective diaries, when recorded on paper (i.e. paper diaries), encounter similar challenges [10]. Non-adherent patients often fill in the diaries hastily in the parking lot or waiting room before study visits. It is common to observe seemingly perfect adherence reported in paper diaries, almost as if individuals were robots. If scrutinized appropriately, such perfect data would be flagged as fraudulent in an RBQM. However, paper diaries are typically used to document adherence checkboxes at the site but are not electronically entered into the study database.

Electronic diaries aim to overcome these issues by timestamping the records. In the case of electronic diaries, an

upward bias is typically introduced through reminder functions in the system. Patients are reminded at specific times to take their medication, and later the system prompts them to indicate whether or not they have taken it. If they state that they did not, they are asked to provide a reason. This creates an effective nudging system to generate a perfect adherence record, even though the action of recording the event is often disconnected from the actual medication intake, leading to exaggerated levels of adherence. To overcome this problem, it is possible to require the patient to capture a video of each intake to prove ingestion. This approach has, however, shown low accuracy and poor acceptability by patients because of the additional burden [11].

In summary, patient self-reporting of medication adherence is prone to biases and variability due to factors such as desirability bias, questionnaire choice and administration method, recall period covered, hurriedly filled diaries, and the introduction of reminder functions in electronic diaries that can easily conceal the uncomfortable truth about medication non-adherence.

1.4 Bioanalytical Methods: Used in 4.1% of Trials

In theory, using drug concentration in body fluids (such as blood, plasma, or urine) as a direct measure of adherence seems promising. This method relies on the assumption that the presence of the drug indicates its ingestion and, therefore, adherence to the prescribed medication regimen. In this sense, it is considered a reliable approach to assess adherence.

The results are not influenced by patient recall or reporting biases, as they directly reflect the presence or absence of the drug in the body.

Although drug concentration in body fluids is considered a reliable measure of adherence, its precision is compromised by inherent limitations as it does not account for various factors such as individual variations in drug metabolism, absorption, distribution, elimination, and interactions with other medications or substances that can influence drug concentrations. To facilitate the interpretation of concentration and reduce its variability, sampling is typically carried out at trough, i.e. just before the next scheduled dose.

Due to the limited frequency of drug concentration measurements, the validity of this measure is hindered by a phenomenon known as "white-coat adherence." This refers to a temporary increase in adherence observed a few days before a scheduled visit [12]. In drug studies, this effect is further reinforced by a common practice of making a phone call prior to the visit, reminding patients to strictly adhere to the medication schedule.

More advanced biosensing technologies [13] that allow for continuous drug monitoring offer a transformative approach to drug exposure assessment, enabling real-time tracking of therapeutic drug concentrations. Wearable and in vivo sensors hold promise for automated, non-invasive monitoring, revolutionizing treatment optimization. However, challenges in sensor integration, clinical validation, and data privacy remain critical considerations for widespread adoption.

When comparing groups in randomized controlled trials, bioanalytical methods have however a limitation tied to typical different pharmacometric characteristics of the drugs, potentially introducing a systematic bias in adherence assessment as a behavior. This issue becomes more critical when a placebo group is involved, as no drug exposure is available to assess adherence behavior in this context. This limitation precludes appropriate causal inference analysis that require an unbiased measure of adherence behavior in all randomized groups [14].

To summarize, bioanalytical methods, although direct and reliable are currently sparse, limiting the reliability of this adherence measure to a few days preceding the sampling. Furthermore, they are subject to large variability, affected by white-coat adherence, and thus limited in their ability to differentiate between minor and more significant deviations in medication adherence.

1.5 Electronic Monitoring: Used in 2.7% of Trials

The concept, pioneered by the MEMS® Cap, involves integrating a microchip into pharmaceutical packages commonly used in clinical trials (such as pill bottles or blisters) and has been expanded to include injectables, inhalers, cream tubes, and eye drop containers. The chip automatically timestamps each action required to access or administer the medication, providing real-time tracking of dosing histories. It should be noted that removing the drug from its package does not necessarily indicate ingestion. Studies have demonstrated that electronically recorded dosing histories align with bioanalytical measures in 97% of cases, while providing rich and continuous assessment of drug exposure in-between visits [15].

For solid oral forms, some companies have moved the sensor from the package to the pill itself ("smart pill") with the intention of proving ingestion. A microcircuit integrated into an ingestible drug is activated by gastric acid to generate a weak radio signal that contains information on the drug's identity and the timing of ingestion. This signal is detected, amplified, and retransmitted to a more distant source via a signal-detection skin patch or necklace worn by the patient. While this technique of proving ingestion has strong value in some settings (e.g., Phase I studies), it is tough to deploy at scale due to drug stability, patient intrusiveness, and logistics [16].

Incorporating electronic monitoring into pharmaceutical packages for drug trials involves several important considerations that require sound preparation. First and most important the logistic preparation for electronic monitoring entails selecting and deploying the appropriate devices for data collection. The utilization of electronic monitoring packages, such as smart pill bottles or blisters, generates substantial and intricate data related to medication adherence. This involves not only data storage to handle the extensive volume of data generated but also an appropriate processing to ensure its relevance and usefulness for various stakeholders involved in the trials. Electronically compiled adherence data can then be used to support several objectives:

- For patients, the processed data can be utilized to provide feedback on their adherence behavior, fostering engagement and motivation in the study.
- Investigators and study monitors can leverage the processed data to monitor patient adherence patterns, identify potential issues, and make informed decisions regarding patient care.
- Sponsors, who bear the responsibility for ensuring the success of the trial, can utilize the processed data to evaluate the impact of adherence on study outcomes and adjust strategies if needed.

In summary, the incorporation of electronic monitoring in pharmaceutical packages is a passive method that compiles the adherence data automatically without burdening patients. Subsequent processing and storage of the data are vital steps to enhance the accuracy, reliability, and relevance of data, contributing to the success and integrity of the drug trials.

2 What Next if We Start to Measure Medication Adherence Accurately in Drug Trials?

In an era of evidence-based medicine, one can no longer accept not knowing about drug exposure in clinical trials (the system input). The "omerta", or keeping silent about non-adherent patients, needs to be broken and trialists will have to live with the truth and thus with non-adherent subjects. Implementation of the following strategies will then be recommended to address non-adherence in trials.

1. By acknowledging the issue of non-adherence, study staff can openly discuss the difficulties associated with patient adherence and identify approaches to minimize its effects. It is crucial to understand that the presence of non-adherent patients does not indicate failure or incompetence but rather represents a necessary step in promoting transparency and maintaining the integrity of clinical trials. The FDA (Food and Drug Administration) guidance on enrichment strategies for clinical trials recommends utilizing adherence data to manage medication adherence throughout the study, providing targeted feedback, risk stratification, and preventive measures.
2. The rise in electronic monitoring has shed more light on the issue of medication non-adherence in drug development, revealing a greater extent of the problem. Without a reliable methodology in place, study findings may be distorted, jeopardizing patient safety after the drug reaches the market. In randomized clinical trials, deviations in medication adherence occur typically after treatment initiation and impact the interpretation of the study's outcome variable. Consequently, medication non-adherence is considered to be an intercurrent event, as defined in the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials. To embrace a patient-centric approach and accurately estimate treatment effects based on actual medication intake, it is imperative to incorporate adherence-informed analysis, making it mandatory.

3 A Note on the Drug's Forgiveness to Differentiate Between Minor and Significant Deviations in Adherence

The concept of forgiveness [17] pertains to a drug's ability to accommodate deviations in adherence without significantly compromising its effectiveness. Essentially, it acknowledges the drug's capacity to continue its beneficial action even if patients deviate from their prescribed dosing schedule.

Forgiveness is determined by the therapeutic window of the drug and may vary not only between different drugs but also among individuals and over time. The extent of forgiveness often relies on the chosen dose and dosing regimen. Therefore, during the drug development process, it is important to strike a balance between the drug's therapeutic window and the most common variations in adherence to determine the optimal level of forgiveness for a drug.

Knowing a drug's forgiveness allows establishing the adherence threshold separating acceptable deviations in adherence from significant deviations. For instance, take cardio-aspirin (acetylsalicylic acid), commonly administered once daily. Despite its plasma half-life being a mere 20 min, its effect persists for the duration of the platelets' lifespan, which spans several days. This forgiving characteristics allows for acceptable occasional lapses of one or two consecutive doses. In stark contrast, direct oral anticoagulants (DOACs), some of which are also administered once daily,

exhibit an unforgiving nature, where even a single missed dose has the potential to disrupt the continuous anticoagulant effect [18].

4 Consequences of Inadequately Measuring Medication Adherence in Drug Trials

Inadequately measuring medication adherence in drug trials is like driving blind on a highway and can have repercussions that significantly impact the validity and interpretation of study findings.

Given that approximately 50% of patients do not adhere to the prescribed dosing regimen outlined in study protocols [1], the consequences of neglecting adherence measurement in drug trials are substantial, as illustrated in Fig. 5. One of the primary outcomes is the inability to accurately determine the appropriate dosage, often leading to overestimated dosing requirements as nicely suggested by Ogata et al. [19] with post-marketing dose reductions. Medication adherence plays a pivotal role in establishing the effectiveness and safety of a drug. If adherence is not adequately assessed, it introduces bias and confounds the results of the study. Without adherence data, the uncertainty surrounding estimates of efficacy and safety, coupled with the lack of knowledge about actual drug exposure, hampers the ability to make informed decisions regarding the optimal dosing regimen. This optimal regimen should aim to optimize treatment forgiveness while maximizing the chances of successful drug approval and commercial viability. Consequently, in the absence of sound information on adherence, doses are frequently set too high, resulting in an elevated risk of side effects and treatment discontinuation.

To mitigate these consequences, it is crucial to incorporate reliable and validated approaches for evaluating medication adherence in pharmaceutical trials. Thorough sound measurement and reporting of medication adherence contribute to the credibility, consistency, and applicability of research outcomes, resulting in well-informed clinical judgments and enhanced patient care. Assuming responsibility for adherence management reduces the likelihood of clinical trial setbacks, lowers expenses, and expedites the time-to-market for drugs.

5 Discussion

In our era of evidence-based medicine, it is no longer acceptable to remain ignorant about drug exposure in clinical trials, which refers to the accurate knowledge of whether patients are taking their medications as prescribed (the system input). The concept of omerta must be challenged and broken. It is crucial for study personnel to confront and acknowledge the truth, which is the existence of non-adherent patients within clinical trials.

Embracing the truth with regard to non-adherent patients also highlights the need for comprehensive measures to assess adherence accurately. Completely neglecting to quantify adherence, as observed in 13% of drug trials according to Mantila et al. [5], or relying solely on conventional approaches like pill counting or self-reporting, is no longer considered acceptable. The state of adherence to oral oncological drugs is particularly concerning, as a staggering 33.9% of articles fail to mention or address the issue altogether [20]. Instead, a multidimensional approach incorporating objective measures (e.g., electronic monitoring devices, biomarker

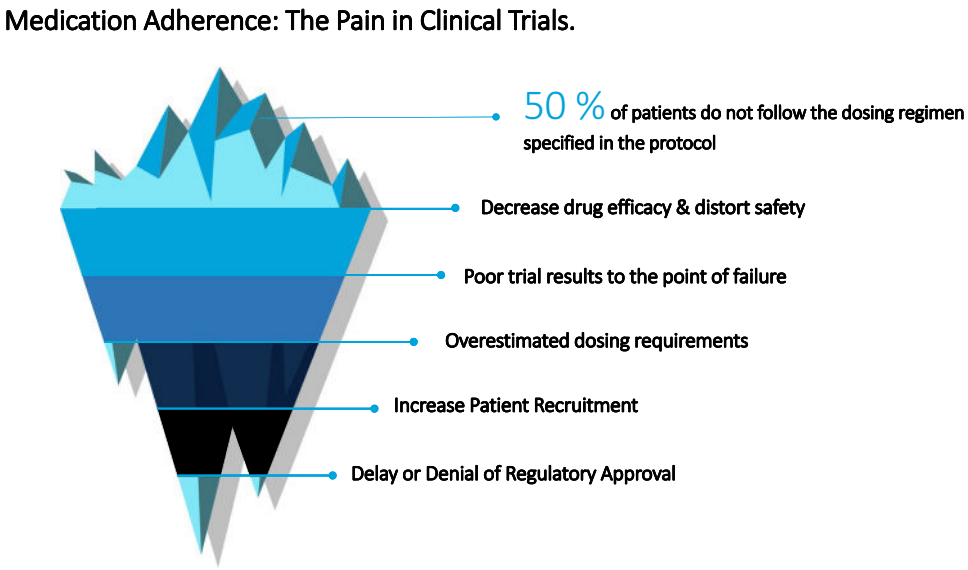

Fig. 5 High level summary of consequences of not addressing nonadherence in drug trials

analysis) and subjective measures (e.g., patient-reported outcomes, qualitative interviews) should be considered [21]. For example, a focused discussion with a patient based on reliable dosing history data allows for a more comprehensive understanding of adherence patterns and facilitate targeted interventions [22]. Depending on the context, different combinations of measurement methods can prove valuable. For instance, electronic monitoring paired with bioanalytical methods can be beneficial in dose-finding studies, while electronic monitoring combined with pharmacy refill data can be valuable in post-marketing surveillance studies. Ultimately, breaking the silence and openly addressing non-adherence in clinical trials aligns with the principles of evidence-based medicine. It promotes scientific rigor, transparency, and a patient-centered approach to research. By embracing the truth and actively addressing non-adherence, study personnel can contribute to the advancement of knowledge, the development of effective interventions, and ultimately improve patient care and outcomes.

By recognizing the prevalence of drug holidays and discontinuation, researchers can better assess the real-world adherence challenges that patients may face. This knowledge contributes to a more comprehensive understanding of medication adherence patterns and assists in the development of strategies to improve adherence and ultimately optimize treatment effectiveness.

Addressing these more serious adherence errors within drug trials can lead to valuable insights and interventions that promote better medication adherence in clinical practice. By proactively addressing these challenges, researchers can enhance the reliability and validity of trial outcomes and ensure that the results translate into meaningful clinical benefits for patients.

6 Conclusion

Comprehending drug exposure is essential for evaluating the effectiveness and safety of investigational medications. Without a clear understanding of how patients adhere to their prescribed treatment regimens, the integrity and dependability of clinical trial results can be compromised.

Measures employed to evaluate medication adherence must possess the capability to assess medication intake behaviors accurately and reliably, while also differentiating between minor dosing errors and more significant deviations that may impact the drug's efficacy and safety.

Having accurate knowledge of drug exposure enables researchers to make informed decisions, identify potential confounding factors, and appropriately interpret the study outcomes. Such understanding is crucial in ensuring the validity and reliability of the research findings.

Declarations

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Conflict of interest All authors are employees of AARDEX Group. BV is a shareholder of AARDEX Group.

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Ethics approval Not applicable.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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