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ORIGINAL ARTICLE

The impacts of undetected nonadherence in phase II, III and post-marketing clinical trials: An overview

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Abstract

Aims: This research aims to provide an overview of the consequences of undiagnosed nonadherence (noninitiation, suboptimal implementation, nonpersistence) in randomized clinical trials (RCTs).

Methods: This research was conducted by combining a literature review and qualitative semistructured interviews with key opinion leaders. Based on this groundwork, the consequences of undiagnosed nonadherence in RCTs were summarized and reported in a figure. This study focused on phases II, III and post-marketing in ambulatory settings across a variety of therapeutic areas and indications.

Results: Various consequences of nonadherence in RCTs were investigated. In phase II, drug efficacy may be underestimated, variability in the outcomes may be high and a distorted picture of side effects could be reported, resulting in an uncertain impression of the investigational product's profile and complicating decision-making. The sponsor may need to increase the sample size of the upcoming phase III study to improve its power, representing additional costs, or even terminate the study. In phase III, similar phenomena may be observed, making demonstration of efficacy to the regulatory bodies more difficult. Lastly, after commercialization, a distortion in pharmacometrics may occur: the drug may underperform, prescriptions may be refilled less often than expected or extra expenses may be incurred by the payers. This can result in post-marketing dose reduction, new competitors coming into the market and, eventually, product withdrawal.

Conclusions: This research highlighted the many potential adverse consequences of undiagnosed nonadherence in RCTs, including additional costs. Collecting accurate data appeared to be crucial for decision-making throughout the drug development process.

KEYWORDS

clinical trials, consequences, medication adherence, patient compliance, phase II, phase III, undiagnosed nonadherence

The principal investigator of this study is Elise Le Flohic.

1 | INTRODUCTION

Randomized clinical trials (RCTs) are generally considered the gold standard for assessing the quality, safety and efficacy of new medicines. According to Blaschke et al,[1] RCTs may be seen as systems in which an input (ie, a drug) is tested and an output (ie, estimates of safety and efficacy) is produced (see Figure 1). However, the accuracy of the output depends on the level of adherence to the protocol-specified dosing regimen during the trial. Indeed, patient adherence to the prescription determines the quality of the drug response.[2] Additionally, certain drug classes or properties, such as medications with a narrow therapeutic index or those with complex dosing schedules, may exhibit a higher likelihood of disproportionate effects when patient adherence is compromised, underscoring the importance of adherence in optimizing both efficacy and safety.[3] Nonadherence, or suboptimal adherence, can be defined as any of the following deviations from the prescribed dosing regimen: non-initiation of the treatment, suboptimal implementation of the dosing regimen and/or non-persistence of the treatment.[4]

In RCTs, deviations in medication adherence commonly occur after treatment initiation, significantly impacting the interpretation of the study's outcome variable. Medication nonadherence may be intricately linked with treatment efficacy and side effects and cannot simply be treated as a covariate, as nonadherent patients are not likely to represent a random sample of the study population. As such, medication nonadherence is classified as an intercurrent event according to the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials, necessitating appropriate statistical analysis to accurately estimate the causal effect of a treatment while accounting for time-varying confounding due to nonadherence.

This problem of nonadherence concerns all drug development phases, from earlier stages (safety trials, efficacy trials, dose-finding, etc) to the latest stages (pharmaco-vigilance, post-marketing studies, etc).[1] It is therefore crucial to monitor medication adherence during all phases of drug development, as well as in post-marketing evaluations.

Despite the evident limitations, traditional methods such as manual pill counting or patient self-reporting are still extensively employed in RCTs. However, these methods present inherent flaws, often leading to a distorted representation of the truth and fostering the misconception that all patients participating in RCTs are adherent to the prescribed treatment. With the advent of digital adherence technologies, such as smart packages, continuous electronic monitoring of dosing events provides a reliable and precise measure of medication adherence.

The implementation of digital adherence technologies has brought to light that 50% of patients involved in clinical trials do not adhere to the dosing regimen specified in the protocol.[1] Despite this gap, drug developers tend not to sufficiently consider poor adherence and regulatory bodies do not mandate or incentivize them to do so.[5] Indeed, while the rate of adherence assessment in clinical trials has improved over time, poor measurement methods, lack of consistent operational definitions and various biases still hamper sound evaluation of medication adherence in RCTs.[6]

What is already known about this subject

- Many articles describe the causes of nonadherence and how to perform more accurate monitoring of patient adherence.
- Some papers raise awareness about the risks of underestimating efficacy and side effects or miscalculating the dosing regimen.

What this study adds

- Various consequences may arise from undiagnosed nonadherence in clinical trials.
- Collecting accurate data is crucial for decision-making throughout the drug development process and for avoiding a late trial failure. Doing so, however, requires rigorous monitoring of medication adherence.

Neglecting the importance of suboptimal therapeutical adherence in trials may have serious consequences on drug development outputs and related healthcare decision-making. These include failure to show efficacy or underestimates of drug efficacy, struggles to bring innovative medicines to the market, the miscalculation of side effects incidence and overestimation of required doses.[1] Aside from deteriorated health outcomes and decreased reliability of clinical trial results, the need for additional recruitment and delay to market access can drive up costs.[7] It should also be noted that the more a medicine progresses through the phases of its development, the higher the financial loss of failure in bringing the medicine onto the market. Thus, looking at the consequences of undiagnosed suboptimal adherence is particularly significant during phase II and III trials.

To our knowledge, no complete overview of the consequences of nonadherence in clinical trials has been compiled to date. The existing literature on this topic is limited, leaving significant gaps in our understanding. Furthermore, an additional challenge arises from the fact that many trialists are aware of the issue of nonadherence in RCTs but tend to avoid confronting this reality due to the discomfort and uncertainties it brings forth. Hence, the objective of this research is to bridge the gap in the existing evidence base by combining a comprehensive literature review with qualitative semistructured interviews involving key opinion leaders. By adopting this approach, we aim to enhance our understanding of the subject matter and generate valuable insights. Such a review would be helpful in highlighting the burden of the problem and in raising awareness among pharmaceutical industries and authorities.

The extent of medication nonadherence's impact on RCTs relies heavily on the pharmacometric properties of the drug(s) being studied, as well as the specific characteristics of the trial (eg, population,

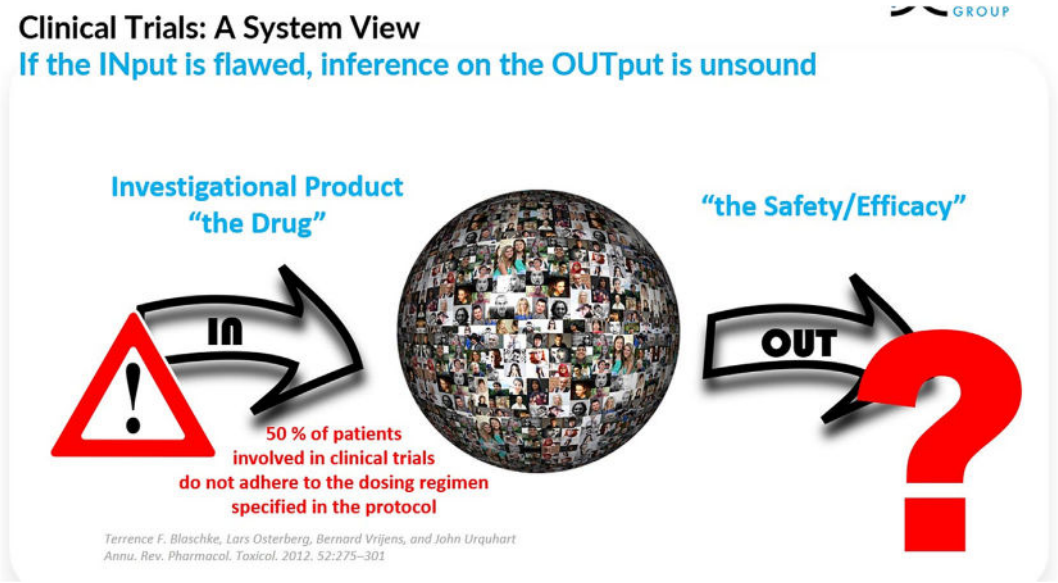

FIGURE 1 A system view of clinical trials.

duration, frequency of visits and endpoint). Since the aim of this paper was to maintain a comprehensive global perspective, we refrained from delving into individual cases or classes of medications and instead kept the discussion at a general level to fulfil the purpose of this paper.

2 | METHODS

2.1 | Research nature, type and design

This research was conducted by combining a literature review and qualitative semistructured interviews with key opinion leaders. The research used a descriptive emphasis.

First, a scoping literature review gathered the current scientific knowledge. Based on this, a figure with a comprehensive description was drawn to summarize the consequences of undiagnosed nonadherence in clinical trials. The figure focused on phases II and III, which are most likely to experience nonadherence. Indeed, phase I is typically carried out in fully controlled settings, which leave little room for nonadherence.[1] We assumed the treatment was provided in an ambulatory setting, where adherence to the prescribed treatment largely relies on the patient's behaviour and the likelihood of observing nonadherence is higher.[8] We also considered that the tested drug was safe and efficacious. For simplicity, we did not examine a specific indication and considered nonadherence to be underconsumption rather than overconsumption, as this is the most common type of noncompliance.[8]

Qualitative semistructured interviews were conducted to collect key opinion leaders' views on the topic and to gather feedback on the figure. A narrative method was adopted to gather in-depth data. Indeed, interviewees often claim this approach makes it easier to tell their story and be truthful.[9,10] Thus, post-marketing activities, which were not part of the scope of the literature review, were mentioned by the experts during the interviews and therefore added to the results of this study.

2.2 | Data collection

2.2.1 | Literature review

Scientific peer-reviewed literature was collected by searching the scientific database PubMed (Medline) in April 2022. First, an exploratory search for relevant articles was performed using the following key terms combination: ((medication adherence[MeSH Terms]) OR (patient compliance[MeSH Terms])) AND ((clinical trial, phase 2[MeSH Terms]) OR (clinical trial, phase 3[MeSH Terms])) AND ((consequences/[Title/Abstract]) OR (impact[Title/Abstract]) OR (effects[Title/Abstract]) OR (effect[Title/Abstract])). All articles found were exported to EndNote for further analysis. Second, inclusion and exclusion criteria were applied to the titles of the articles, to abstracts of the remaining articles and then to the full text of the final selection. The list of inclusion and exclusion criteria is summarized in Table 1. Lastly, a backward search was performed on the included sources, leading to the selection of a few more references. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart was drawn to describe the process of articles selection (see Figure 2).

2.2.2 | Semistructured interviews

Five semistructured interviews were conducted with key opinion leaders in the field of medication adherence and clinical trials. The

experts were professionals from academia and pharmaceutical companies with experience in clinical trials and medication adherence. All were recruited using purposive sampling and the researchers' network. Before the interviews, a topic list was developed which included a short introduction of the project to the researchers. The first question asked the experts to evaluate the importance of patient adherence in phases II, III and post-marketing activities using a Likert scale ranging from 0 to 10 (0 = monitoring patient adherence not important at all, 10 = monitoring patient adherence essential). The experts then provided feedback on the figure drawn by the authors based on the literature search (see Figure 3). They were asked whether they agreed with the content, if they would add further information and to identify the most important points in each phase. They were then free to add additional comments on the investigated topic. Among others, their insights brought out elements related to the post-marketing phase. During the interview, the researchers used Steinar Kvale's prin.[12] The interviews took place online via Microsoft Teams in May 2022.

TABLE 1 Inclusion and exclusion criteria.

Category	Inclusion criteria	Exclusion criteria
Timeframe	No time limit	
Study type	• Empirical studies • Meta-analyses • Literature reviews	
Population	All	
Content	• Phase II or III trials • Consequences of suboptimal adherence in clinical trials	• Monitoring patient adherence • Improving patient adherence
Language	English	All other languages

Note: 'Monitoring patient adherence' and 'Improving patient adherence' were excluded from the scope of the research since they constitute a large field of study that is covered in distinct papers.[11]

2.3 | Data analysis

2.3.1 | Literature review

The characteristics of all included sources were extracted into a table containing the following information: author(s), year, title, journal, type of study, disease, sample size, type of study outcome and main results. Parts related to the investigated topic were identified and added to the main results. All provided values were actualized given the inflation rate. A values index is provided in Table 2.

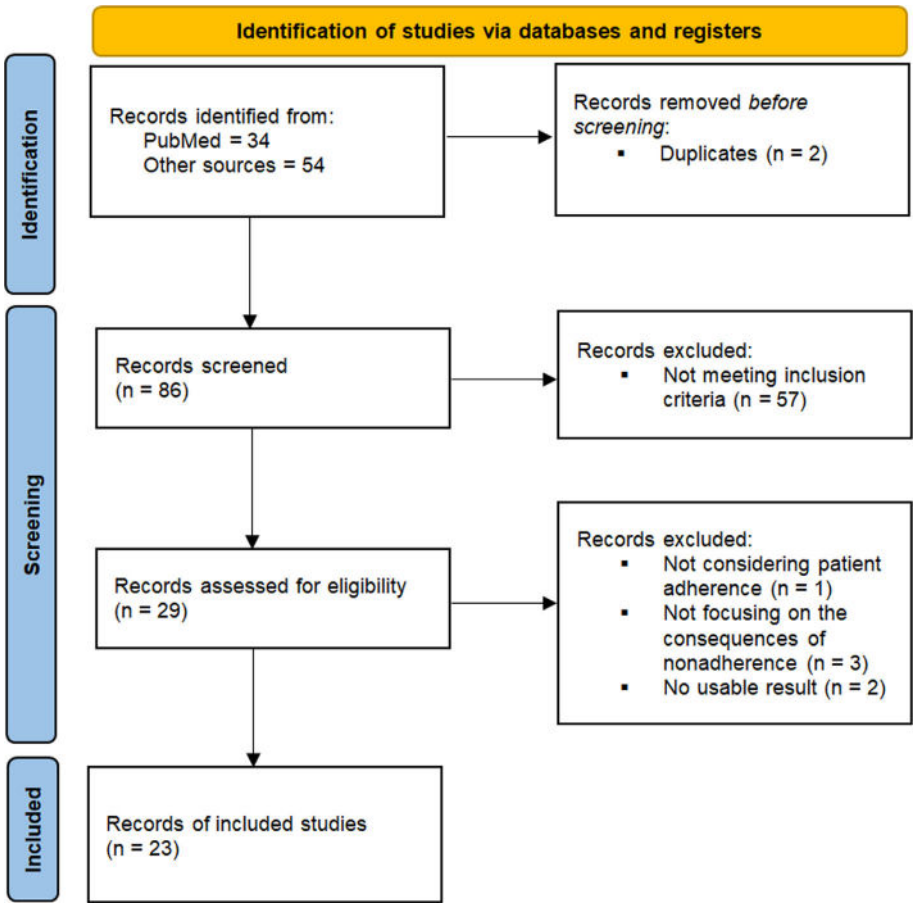

FIGURE 2 Flowchart showing the study selection process.

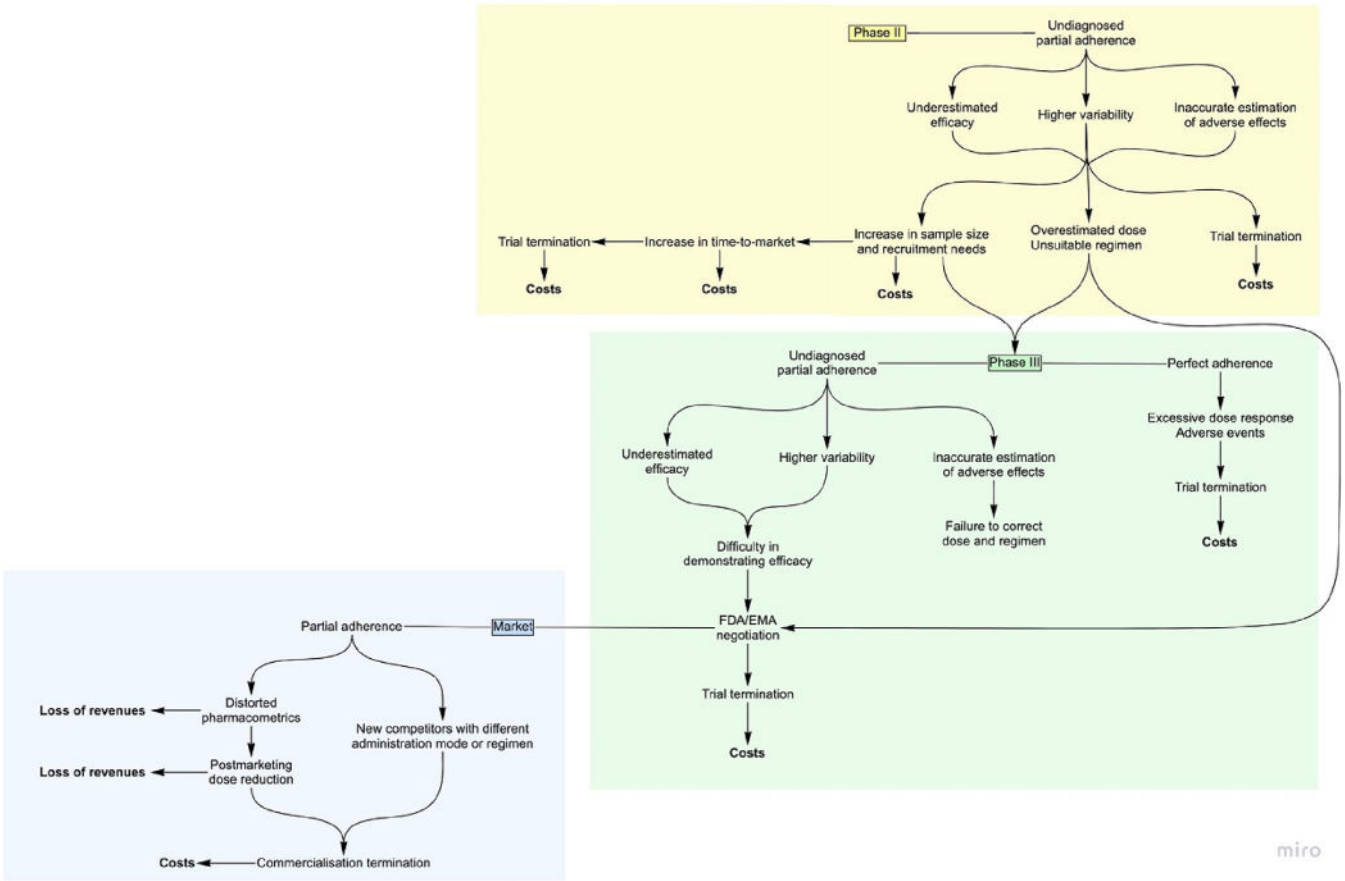

FIGURE 3 An overview of the consequences of undiagnosed nonadherence in clinical trials.

2.3.2 | Semistructured interviews

Interview data were analysed using Word, going through several steps of qualitative data analysis.[13] First, verbatim transcripts of the interview audio recording were made and used as a basis for the coding. The coding involved screening the transcripts and selecting relevant comments that were then assigned a content code. The content code categories correspond to the phases of clinical trials, from phase I to post-marketing activities. Finally, selective coding was conducted by analysing the outcomes of the previous phase and identifying the core messages from the interview. All the final topics and core messages are visualized in a synthetic table containing the following items: expert interviewed and feedback on the figure (by phase) (see Table 3).

2.4 | Ethics

Formal ethical approval form was completed by the researchers and validated by the Ethics Committee of the Faculty of Health, Medicine, and Life Sciences of Maastricht University (number FHML/HPIM/2022.100). During the study, privacy and informed consent were preserved by sending a formal consent form for approval to the interviewees prior to the day of their interview. Consent for audio recording was also requested at the start of the interview. Anonymity and confidentiality were ensured by not using the names of the interviewees during the interviews.

3 | RESULTS

The literature search conducted in April 2022 yielded 86 articles. After applying the inclusion and exclusion criteria, 23 articles were included in this research. A flow chart describing the search string is shown in Figure 2.

Based on this literature search, a figure summarizing the consequences of undiagnosed nonadherence in clinical trials was drawn (Figure 3).

3.1 | Phase II

Nonadherence has many effects on the outcomes of RCTs. In phase II, with patients taking smaller doses than prescribed, **the drug cannot demonstrate its full efficacy** and the potential benefits are underestimated.[5,14–16] Visually, this phenomenon would translate as a shift to the right of the typical dose-response curve, with the dose on the *x*-axis and the response on the *y*-axis.

TABLE 2 Detailed overview of included literature.

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
General considerations								
Smith, D.L.	2012	Patient nonadherence in clinical trials: could there be a link to post-marketing patient safety?	Drug Information Journal	Meta-analysis	N.R.	N.R.	/	Up to 30% of clinical trial participants may be discarding their study medications prior to study visits
Jayaraman, S., Rieder, M. J., & Matsui, D. M.	2005	Compliance assessment in drug trials: has there been improvement in two decades?	The Canadian Journal of Clinical Pharmacology	Systematic review	N.R.	All drug studies published in the British Medical Journal, Journal of Paediatrics and Lancet from 1997 to 1999	/	Although the rate of evaluation of compliance in drug trials has improved over the past 25 years, it continues to be examined in less than half of the clinical studies of drug effects in which compliance assessment is required
DiMasi, J.A. et al	2003	The price of innovation: new estimates of drug development costs	Journal of Health Economics	RCT	N.R.	n = 68	Average pre-tax cost of new drug development	The estimated average out-of-pocket cost per new drug is US $ 403 million (2000 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 11% yields a total pre-approval cost estimate of US$ 802 million (2000 dollars).
Sertkaya, A. et al.	2016	Key cost drivers of pharmaceutical clinical trials in the United States	Clinical Trials	Meta-analysis	All therapeutic indications	N.R.	The average cost of each phase study conducted at a US site	Phase 1: from US$1.4 million (pain and anaesthesia) to US$6.6 million (immunomodulation). Phase 2: from US$7.0 million (cardiovascular) to US$19.6 million (haematology). Phase 3: from US$11.5 million (dermatology) to US$52.9 (pain and anaesthesia). Top three cost drivers of clinical trial expenditures: clinical procedure costs (15-22% of total), administrative staff costs (11-29% of total), and site monitoring costs (9-14% of total).

(Continues)

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Lower efficacy and difficulty to demonstrate efficacy								
Czobor, P., Skolnick, P.	2011	The secrets of a successful clinical trial: compliance, compliance and compliance	Molecular Interventions	RCT	Obesity	n = 35	Weight after 8 weeks	The medication-compliant cohort had a significantly different change in weight from the placebo group and the noncompliant group (−1 kg *vs* +2 kg). Patient noncompliance had the effect of masking a potential efficacy signal.
					Chronic low back pain	n = 634	Visual analog scale (VAS) for pain after 12 weeks	Compliant patients had a significantly greater reduction in pain scale scores than placebo patients and non-compliant patients (+40 mm *vs* +25 mm).
Wood, H F. et al.	1963	Rheumatic fever in children and adolescents: a long-term epidemiologic study of subsequent prophylaxis, streptococcal infections and clinical sequelae. III. Comparative effectiveness of three prophylaxis regimens in preventing streptococcal infections and rheumatic recurrences.	Annals of Internal Medicine	RCT	Rheumatic fever	n = 431	Streptococcal infections and rheumatic recurrence over 5 years with three different prophylactic treatments (parenteral benzathine penicillin, oral penicillin and oral sulfadiazine)	94% of patients in the benzathine penicillin group were considered adherent versus only 50% of those on oral penicillin and 57% of those on sulfadiazine. 6.1% of patients in the benzathine penicillin group had a streptococcal infection over 5 years versus 20.7% of those on oral penicillin and 20% of those on sulfadiazine. 0.4% of patients in the benzathine penicillin group had a rheumatic recurrence over 5 years versus 5.5% of those on oral penicillin and 2.8% of those on sulfadiazine. The degree of adherence to prophylaxis treatments was found to be correlated to the streptococcal infection outcome and recurrence rates.
Breckenridge, A. et al.	2017	Poor medication adherence in clinical trials: consequences and solutions	New Reviews Drug Discovery	Meta-analysis	All therapeutic indications	N.R.	Consequences and solutions of poor medication adherence in clinical trials	Poor adherence may result in underestimating or failing to confirm the efficacy of a new drug, which also impairs the development of innovative drugs.

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Toms, S.A. et al.	2019	Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: a subgroup analysis of the EF-14 phase III trial	Journal of Neuro-Oncology	RCT	Glioblastoma (brain cancer)	$n = 695$	Progression-free survival and overall survival, taking compliance into account	Patients with higher compliance had better progression-free survival outcomes and 5-year survival rates
Albert, J.M., Demets, D.L.	1994	On a model-based approach to estimating efficacy in clinical trials	Statistics in Medicine	Meta-analysis	Infectious diseases	N.R.	/	A model-based approached is not recommended when adherence levels differ between the test group and the control group because it would lead to inaccurate estimates of the efficacy. In general, poor medication may severely undermine the validity of efficacy estimate.
Fewer/more side effects								
Serebruany, V.L. et al.	2005	Noncompliance in cardiovascular clinical trials	American Heart Journal	Meta-analysis	Cardiovascular diseases	N.R.	/	Reported adverse effects or morbidity/mortality rates due to side effects may be lower than actual rates because of NC
Bruckert, E., Simonetta, C., Giral, P., & CREOLE Study Team	1999	Compliance with fluvastatin treatment characterization of the noncompliant population within a population of 3845 patients with hyperlipidemia	Journal of Clinical Epidemiology	RCT	Hypercholesterolemia	n = 3845	Cholesterol levels	Results from the CREOLE study show that the 25% of the study population that were noncompliant experienced more severe and frequent adverse events than the rest of the study population

(Continues)

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Smith, D.L.	2012	Patient nonadherence in clinical trials: could there be a link to postmarketing patient safety?	Drug Information Journal	Meta-analysis	N.R.	N.R.	/	Undiagnosed nonadherence can lead to underestimating adverse events and overestimating the dose
Higher variability								
Harter, J.G., Peck, C.C.	1991	Chronobiology. Suggestions for integrating it into drug development	Annals of the New York Academy of Sciences	Meta-analysis	Asthma	N.R.	Sources of variability in drugs response and their coefficient of variation	Compliance contributes to variability via a coefficient of variation of about 50%. There is a significant interpatient variability due to chronobiological influences, which implies that markers have to be measured in each patient to adjust dose and timing.
Shiovitz, T. M., et al.	2016	Mitigating the effects of nonadherence in clinical trials	Journal of Clinical Pharmacology	Statistical analysis	N.R.	N.R.	Loss in study power	If 20% of subjects provide noninformative data, studies intended to be powered at 90% and 80% based on a true effect size would have actual power of 74% and 61%, respectively.
Mokoka, M.C., et al.	2019	Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy: results from a systematic literature review and modelling study	European Respiratory Journal	Systematic review	Asthma	n = 22 173	Study power	Power to detect clinically relevant changes in FEV1 was significantly higher in trials that reported adherence assessment (mean power achieved 59% *vs*. 49%). Modelling suggests that up to 50% of variance in FEV1 outcomes is attributable to undetected variations in adherence.

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Increase in sample size								
Alsumidaie, M.	2017	Non-adherence: a direct influence on clinical trial duration and cost	Applied Clinical Trials	Meta-analysis	All therapeutic indications	n = 368	Sample size increase	Approximately 40% of patients become nonadherent to IMP after 150 days. A phase III trial based on 368 patients would need to recruit an average 460 additional patients to offset the biases induced by a 40% nonadherence, and thus maintain an equivalent statistical power as a study that would get perfect adherence. The operational cost to recruit 460 extra patients is estimated at 12 million dollars. Average cost for recruiting one patient is $15 700 in phase I, $19 300 in phase II and $26 000 in phases III and IV. Timeline slippage results in a $600 K per day in lost revenue opportunity for niche products, and up to $8 million per day for blockbuster medical products.
Pledger G. W.	1988	Compliance in clinical trials: impact on design, analysis and interpretation	Epilepsy Research	Meta-analysis	N.R.	N.R.	/	Under certain assumptions, sample sizes have to double with 30% noncompliance and triple with 40% noncompliance to maintain equivalent statistical power.

(Continues)

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Liu, K.S. et al.	2008	Is bigger better for depression trials?	Journal of Psychiatric Research	Meta-analysis	Depression	$n = \sim 150$	Significance of the treatment	Increasing the sample size does not necessarily increase the study power because late-enrolling patients are more placebo-respondents than early-enrolling patients. The significance of the treatment effect (ie, the *P* value) starts to decrease after ~100 patients. Possible explanations: a depleted pool of depressed patients and the urge to meet the trial deadline.
Grayek, E. et al.	2022	The value of adherence information during clinical pharmaceutical trials	Clinical Trials: Journal of the Society for Clinical Trials	RCT	Hypertension	N.R.	Cost savings with an adherence monitoring method	The sample size required to achieve a 80% study power when there is no adherence monitoring is ~30 in case of high adherence and high forgiveness (ie, how sensitive the drug's effectiveness is to nonadherence), but ~210 in case of low adherence and low forgiveness. The use of a monitoring method does not substantially reduce the required sample size in case of high adherence and high forgiveness. However, in case of low adherence and low forgiveness, the need is decreased to between 100 and 125 people, depending on the targeted level of adherence. This results in up to $5 000 000 savings.

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Mokoka, M.C., et al.	2019	Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy: results from a systematic literature review and modelling study	European Respiratory Journal	Systematic review	Asthma	$n = 22\ 173$	Sample size requirements	The sample size required to detect a mean difference of 0.1 L in FEV1 with 80% power would be reduced from ~450 to 220 participants.
Increase in time-to-market								
Nuttall, A.	2012	Considerations for improving patient recruitment into clinical trials	Clinical Leader	Meta-analysis	N.R.	N.R.	/	Nearly 80% of all clinical studies fail to finish on time, and 20% of those are delayed for 6 months or more
Trial termination								
Marrazzo, J.M. et al.	2015	Tenofovir-based preexposure prophylaxis for HIV infection among African women	The New England Journal of Medicine	RCT	HIV-1	n = 5029	Incidence of HIV-1 infection	The trial of pre-exposure prophylaxis was terminated early because efficacy appeared to be too low. 90% of the patients self-reported 100% adherence and pill counts suggested that 86% of prescribed doses were taken, but 30% of the blood and cervicovaginal fluid samples showed detectable drug, indicating that partial adherence was a likely cause of the failed trial.
Distorted pharmacometrics								

(Continues)

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Urquhart, J.	1999	Pharmacoeconomic consequences of variable patient compliance with prescribed drug regimens	Pharmacoeconomics	Meta-analysis	Coronary events	N.R.	Cost to prevent one coronary event	In the United Kingdom, Canada and the United States, chronic-use medicines are usually given by a prescription that allows multiple refills that have to be collected by the patient when needed. Nonadherent patients take longer to exhaust their supply of medicine and ask for a refill, which is reducing sales. The cost to prevent one coronary event in for a fully compliant patient (100% doses taken) is estimated at $US 180 810 *vs* $US 174 150 for the average patient (45% doses taken) and $US162 755 for a very low compliant patient (25% doses taken).
Breckenridge, A. et al.	2017	Poor medication adherence in clinical trials: consequences and solutions	New Reviews Drug Discovery	Meta-analysis	All therapeutic indications	N.R.	Consequences and solutions of poor medication adherence in clinical trials	Poor adherence may result in a treatment failure
Labbé, L., Verotta, D.	2006	A non-linear mixed effect dynamic model incorporating prior exposure and adherence to treatment to describe long-term therapy outcome in HIV-patients	Journal of Pharmacokinetics and Pharmacodynamics	RCT	HIV-1	n = 470	Intersubject variability in the long-term response to treatment of HIV-1 RNA	Sub-optimal adherence is estimated to be one of the main factors associated with the failure of the treatment
Dose reduction								

TABLE 2 (Continued)

Data extraction form								
Authors	**Year**	**Title**	**Journal**	**Type of study**	**Disease**	**Sample**	**Study outcome**	**Main results**
Landman, R. et al.	2022	A 4-days-on and 3-days-off maintenance treatment strategy for adults with HIV-1 (ANRS 170 QUATUOR): a randomised, open-label, multicentre, parallel, non-inferiority trial	The Lancet	RCT	HIV-1	n = 647	Safety and efficacy	The treatment strategy of 4-consecutive-days-on and 3-days-off achieves better outcomes than the standard continuous ART triple therapy over 48 weeks (similar rate of success and rate of virological failure, less adverse events, higher daily life satisfaction).

Abbreviations: ART, antiretroviral therapy; FEV1, forced expiratory volume; RCT, randomized clinical trial.

Efficacy outcomes may also be heterogeneous. They may vary within a patient because of changing adherence behaviour. They may also differ between patients depending on their personal response to a given dose and their adherence behaviour. Overall, research has shown that nonadherence could explain up to 50% of the variability in the outcome.[2,17] Results with high variability are also unreliable. They may even be inconsistent between different phase II trials. One of the interviewed experts pointed out that some sample data may thus be considered unusable. Shiovitz et al[18] describe noninformative data as results coming from patients not taking the study medication and falsely reporting side effects or clinical improvements, thus providing no relevant information for the study. They found that with 20% of patients providing noninformative data, studies with an intended power of 90% had an actual power of 74%. A precise measurement of the adherence level could disambiguate scenarios where efficacy is unclear.

Nonadherent patients will also **report inaccurate side effects**, resulting in an incorrect characterization of the dose-adverse effect relationship. Research has shown cases of fewer side effects being reported[19,20] as well as cases of more severe and frequent adverse events.[21] In both scenarios, the potential harms will be inaccurately estimated. Ultimately, the drug developer will get a biased picture of the drug's efficacy and safety profile. Additional phase II studies may be required.

Uncertainty in study outcomes will complicate decision-making within the project team, especially around dosing and regimens, leading to time-consuming discussions. If the drug is considered effective, the chances that the dose will be overestimated are high.[20] An increase in the dose has to be integrated to offset the loss of efficacy induced by nonadherence.

To reduce uncertainty, the drug developer may have to **increase the sample size of the upcoming phase III study**.[17,22-24] This implies additional recruitment needs and costs. It has been estimated that a phase III trial with 368 patients would need to recruit an average of 460 additional participants to offset the bias induced by a 40% nonadherence and maintain equivalent statistical power to a study with perfect adherence.[7] Recruiting those extra patients would cost an estimated US$14.31 million.[7] The increase in the study size also extends the trial duration and delays the potential market entrance, leading to additional revenue loss. Each day of delay to market can cost an estimated US$715 500 for niche products and up to US $9.54 million for blockbuster products.[7] When time-to-market is prolonged, the drug developer may terminate drug development due to its limited intellectual property period, even if the product is promising.

The trial may also be terminated when nonadherence is so high that the drug fails to demonstrate any efficacy.[25] When a project is ended, the drug developer incurs the costs of the phase I and II studies, but forfeits any possible future revenues from the product. A phase I study can cost an estimated US$1.7 million to US$8 million, and a phase II can cost between US$8.53 million and US$23.87 million.[26] It means sponsors can be incentivized to increase the dose to compensate for nonadherence and prevent product termination.

TABLE 3 Main points made by each expert during their interview.

Expert	Feedback on the figure	
Expert A Clinical pharmacologist	Phase II	The term "side effects" should be replaced by "adverse events". Suboptimal adherence may also arise with issues of performance. For instance, only one-third of patients can adequately instil eyedrops.
Expert B Previously managing director of a pharmaceutical company	Phase II	Nonadherence should be precisely defined: it could be narrowly comprehended as taking less of the treatment than prescribed, but it could also be understood in broader way by including cases of patients sometimes overconsuming their treatment. It should be considered that suboptimal adherence also happens once the drug has entered the market. Somehow, not correcting the dose allows the drug developing company to sell the drug with a regimen that is suitable for the average patient, who is not fully compliant. If the dose is only calculated for perfectly adherent patients, the drug might underperform because of real-life suboptimal adherence. Extra studies might have to be done if the outcome of planned studies is not matching expectations. The impact of suboptimal adherence is not the same with drugs having an immediate effects and drugs not having an immediate effect (those used for prevention purposes for instance). The variability is also a factor in phase II and should appear on the figure. There is both variability within a given patient (who might be sometimes skipping a dose) and between patients (who are not reacting the same way to a given dose).
	Phase III	Discussions with the FDA or the EMA are all the more complicated that the efficacy is questioned, and the safety margin is low. If a trial is not sufficiently powered (ie, the sample size is too small), there will be uncertainty in upcoming decision-making (dosing, regimen, etc), which will create long discussions within the project team. The indication matters: the impacts of suboptimal adherence will be higher in the case of oncology clinical trials than the development of a pain killer.
	Post-marketing	If suboptimal adherence arises because of a constraining administration mode or regimen, new competitors might come to the market with a new drug that is more comfortable to take. Loss of revenues is the most important aspect in the figure.
Expert C Professor of medicine and pharmacology	Phase II	The term "nonadherence" should be replaced by "imperfect adherence" or another similar wording. The term "lower efficacy" should be replaced by "inaccurate estimate of efficacy" since the actual degree of adherence is not known. The efficacy information is the most important. Inaccurate estimation of side effects is less worrying.
	Phase III	The way information from phase II is used to make decisions for phase III (especially regarding the dosing) is a concern. The term "overefficacy" should be replaced. It is very unlikely that patients will get a surplus of efficacy because they adhere perfectly to the prescription. However, some patients might indeed face toxicity if the dose was overestimated. There is variability both in the dosing and in the response to a given dose.
	Post-marketing	Aside the risk of post-marketing dose reduction, there is also a chance, when patient adherence is suboptimal, that the dose has to be increased by the prescriber to get the targeted efficacy. Pharmaceutical companies do not have much interest in monitoring patient adherence in the commercialization phase because they do not want to find out that their patients are overdosed, have to recommend a reduction in the regimen and then lose revenues.
Expert D Consultant Previously managing director of a pharmaceutical company	Phase II	The term "overestimated dose" should be moved up in the figure because it is very important. Studies are often powered assuming perfect adherence, so most studies are underpowered. Monitoring nonadherence in clinical trials cannot be neglected on the grounds that it happens in real life as well because the data obtained for developing the treatment are not accurate. If variability in sample data is too high, it might be unusable, which is a loss of money for the pharmaceutical company.
	Phase III	A surplus of efficacy might not be bad for some indications, but it might turn into an adverse event for others. In addition to having to recruit more, the protocol might need to be amended.

TABLE 3 (Continued)

Expert	Feedback on the figure	
	Post-marketing	There are three types of losses when patients are not adhering to the prescription: (i) patients are not getting the expected benefits of the treatment, (ii) if patients are not refilling their prescription as much as they should be, there is a loss of revenues for the pharmaceutical company and (iii) payers are reimbursing the treatment but might still have to pay for a more expensive therapy down the line if the patient ends up with the condition that the initial treatment was designed to prevent. There is no guarantee that the competitors will have come up to the market with a better treatment.
Expert E Professor of pharmaco-economics Co-director of a health economics centre	Phase II	The goal of phase II studies is to establish a dose-response curve (having the dose as the *x* axis and the response as the *y* axis). The impact of nonadherence is to shift this curve to the left on the *x* axis. In some cases, such as the development of cancer treatments, it is not required to process a phase III study. It is considered that phase II evidence is enough to apply for a market authorization. So, there should an arrow going directly from phase II to the FDA or EMA negotiation.
	Phase III	The role of a phase III trial is to confirm results obtained in the phase II trial. There is a learning and confirming cycle in place. Suboptimal adherence in the test group is relative to adherence in the control group. If adherence degrees are similar, there is no bias in the comparison. Adherence assessment cannot focus only on the active drug. It would be useful to have real case examples for each of these consequences. "Underestimated efficacy" is the result of the phase III trial. So, "increase in sample size" must appear before this. This decision is made in the end of the phase II trial for the phase III trial, not in the end of the phase III trial. From the perspective of a pharmaceutical company, the most problematic consequence is a failure of the trial at the end of the line.
	Post-marketing	From the perspective of the payer, what matters most is what happens once on the market. If a drug turns out to be more effective than foreseen, it is a win for the patient and the payer, but not for the pharmaceutical company. What is a benefit to one is a loss for one other. There is a rising focus on biomarkers and pharmacogenomics to predict responses to a drug. Aside from nonadherence, there are indeed genetical dispositions explaining a drug reaction. We are thus evolving towards a more personalized way of approaching medicine.

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

3.2 | Phase III

In phase III, two scenarios may occur. By **monitoring patient adherence closely**, sponsors can achieve near-perfect adherence. However, if the dose was overestimated at the end of the phase II study, there may be overdosing in phase III. With high adherence levels, this may translate into excessive response and adverse events for some indications. This scenario was not considered very likely by the interviewed experts.

If the drug developer **continues to neglect the monitoring of patient adherence**, suboptimal adherence will also continue. In this case, efficacy will be underestimated and a high variability will be observed. In addition, suboptimal adherence will lead to observing fewer side effects and adverse events, which will prevent any adaptation of the dose and regimen.

Ultimately, the **demonstration of the efficacy is made more difficult** in the context of a placebo-controlled trial. The outcome of the trial is all the more biased when adherence levels differ between test groups and control groups.[27] The remaining uncertainty around the true potential of the drug will give rise to additional conversations with regulatory bodies, making market authorization more challenging, or even leading to a denial of authorization. However, terminating a drug development programme at a late stage is particularly costly, since much expenditure would have already incurred. In fact, it has been estimated that the full drug development process could cost up to US$1303 million.[28]

In the particular case of a positive controlled trial, uncertainty regarding the drug's effects may introduce **a bias towards equivalence with another drug**. This can result in a wrongful allowance of a product that may not actually be as effective as its comparator. Ultimately, long-run effects might not be observed, even though expenses were incurred by the payers.

3.3 | Post-marketing

On the market, adherence flaws may lead to a **distortion in pharmacometrics**. The real-life results might indeed differ from what was

foreseen. If patients are not fully adherent, they might not refill their prescriptions as often as they should, representing a loss of revenue for the drug developer. Urquhart[29] wrote that in the case of treatment preventing coronary events and delivered by multiple refills, sales could be estimated at $US317 231 for a fully adherent patient versus $US285 553 for a patient taking only 25% of the doses. In the case of poor adherence, the treatment might also fail.[5,30] The prescriber could thus decide on a new treatment, which is another loss of revenue. Nevertheless, we could also imagine the prescriber could increase the dose if targeted effects are not obtained, which would translate as an increase in sales, assuming patients are refilling at a pharmacy. In any case, if the drug looks to be underperforming, the price and reimbursement rate granted by regulatory bodies might be revised downwards. Lastly, the payers may also lose since they are paying for treatment, but not getting the benefit expected from it and might even have to cover extra expenses related to a worsened health condition.

When regulatory bodies consider the dose was overestimated, they may also decide on a **post-marketing dose reduction**. For instance, Landman et al[31] found that antiretroviral therapy for patients with HIV-1 achieved better outcomes when taken 4 days a week than when taken daily, supporting a dose reduction. This again constitutes a loss of revenue for the drug developer and compromises the achievement of a positive return on investment. Eventually, the treatment might even be considered as not effective enough, and its commercialisation might come to an end.

Lastly, if nonadherence is caused by a constraining mode of administration or regimen or severe side effects, **new competitors might come to the market** with a drug that is more comfortable to take (ie, pills instead of injections and less frequent dose taking). As an example, evolocumab by Amgen was authorized in 2015 to reduce cholesterol in the blood and had to be taken either once every 2 weeks or double the dose once a month.[32] In 2020, Novartis entered the market with inclisiran for the same indication, which only had to be taken once every 6 months.[33] Thanks to the added convenience, the sales of inclisiran could exceed those of evolocumab by 2027 ($2.5 billion *vs* $2.2 billion), according to the forecast of Global Data's Pharma Intelligence Center.[34]

3.4 | Expert views

The five experts evaluated the importance of patient adherence in the investigated phases of clinical trials using a Likert scale ranging from 0 to 10. Their answers are summarized in Table 4. The average score for phases II and III was 8.8, versus 7.2 for the commercialization phase.

Throughout the interviews, it appeared that the term "the importance of adherence" was ambiguous. On the one hand, one expert understood it as the importance of patients adhering to the prescription to derive the benefits of treatment. From this perspective, post-marketing is considered to be the stage in which adherence is most important. After all, the goal of clinical trials is to develop a drug product that will have an effect on patients once on the market, and suboptimal adherence may threaten this aim. The expert also pointed out that phases II and III are usually smaller, more tightly controlled and patients are aware that they are taking part in a clinical trial, therefore these phases would be less affected by problems of nonadherence.

"The importance of adherence" may also be interpreted as the importance of measuring adherence to comprehend the data related to the drug being developed more accurately. This was the intended interpretation and was adopted by the four other experts. From this perspective, adherence is considered most important in phases II and III, with a particular emphasis on phase II. Experts indicated that these phases are crucial to understanding the efficacy and safety of a treatment. They also provide information about forgiveness, ie, the duration of effective action after taking a dose, minus the recommended dosing interval.[35] The experts stated that accurate estimates of these parameters are necessary for future decision-making. Indeed, a biased picture of the drug's efficacy and safety profile may result in incorrect

TABLE 4 The importance of patient adherence on a Likert scale.

	Phase II	Phase III	Post-marketing
Expert A Clinical pharmacologist	8	6	2
Expert B Consultant Previously managing director of a pharmaceutical company	6	8	9
Expert C Professor of medicine and pharmacology	10	10	7.5
Expert D Consultant Previously managing director of a pharmaceutical company	10	10	10
Expert E Professor of pharmaco-economics Co-director of a health economics centre	10	10	7.5
Average	**8.8**	**8.8**	**7.2**

decisions, such as dose overestimations or the design of unsuitable regimens. In some cases, the development of an efficacious product may be terminated. The importance of measuring adherence phases II and III relies on avoiding these consequences.

4 | DISCUSSION

Trials occasionally report failures attributed to nonadherence, but a formal analysis is lacking, primarily because adherence is not adequately assessed, leading post-mortem analyses to overlook medication nonadherence as a potential factor. An intriguing quantitative insight into the potential impact of nonadherence on dose response comes from the observation of drugs undergoing post-marketing dose reduction. A recent study by Ogata et al[36] further supports the conclusions of two earlier papers, indicating that one in five drugs on the market is prescribed at a dosage at least 50% higher than required.

Combining a scoping literature review and qualitative interviews, this research aimed to present a structured overview of the potential impacts of undetected nonadherence in clinical trials, from phase II to post-marketing. It appeared that meeting the regulators' expectations to estimate the efficacy of a drug without an accurate picture of patient adherence is challenging for developers. Indeed, estimated outcomes should always be interpreted given the degree of adherence, but this is impossible when medicine-taking behaviour is not monitored.

This study also investigated which consequences of nonadherence are the most problematic. In phase II, the experts reported the main concern was the accurate estimation of the efficacy because this would determine the dosing regimen. In phase III, the increase in sample size was seen as important because of the costs and the loss of time it involves. Overall, it appeared crucial to avoid a trial termination at a late stage because this is the most expensive scenario. For drugs on the market, three main nonadherence-related losses were identified (i) patients are not deriving the expected benefits of the treatment, (ii) if patients are not refilling their prescription as often as they should, the drug developer will lose revenue, and (iii) payers are reimbursing a treatment but might still have to pay for a more expensive therapy down the line if the patient develops the condition that the initial treatment was designed to prevent. It must be noted that a benefit for one might also be a loss for another. For instance, if a drug turns out to be more effective than foreseen and goes through a dose reduction, it is a win for the patient and the payer, but a loss for the drug developer.

Lastly, different views were expressed on the way to deal with nonadherence. Because suboptimal adherence happens both during clinical trials and on the market, one of the experts mentioned that not correcting the dose depending on the degree of adherence somehow allows the drug developing company to sell their treatment with a regimen that is suitable for the average patient, who is not fully compliant. Indeed, if the dose is only calculated for perfectly adherent patients, the drug might underperform because of real-life suboptimal adherence. On the contrary, another expert argued that monitoring nonadherence in clinical trials cannot be neglected on the grounds that it also happens in real life. According to this expert, the data obtained for developing the treatment would be inaccurate and might lead to poor decision-making.

In the age of evidence-based medicine, it is imperative to maintain transparency in clinical trials by recognizing nonadherence as a critical factor; strategies like utilizing adherence data proactively for risk assessment and prevention, in line with Food and Drug Administration (FDA) Enrichment guidelines, are recommended to ensure adherence to research protocols. Additionally, during analysis, nonadherence should be treated as an intercurrent event per ICH E9 (R1) addendum, necessitating an adherence-informed analysis for accurate study results. With the increasing use of digital adherence tracking technology, the problem of medication nonadherence in drug development is becoming more apparent than historically documented using pill count. Without a robust methodology in place, study results will be distorted and put patient safety at risk. Adherence-informed analysis should be mandatory to provide a more patient-centric approach to estimating treatment effects "as taken".

Finally, this discussion reminds us of the importance of developing personalized medicine. The dosing regimen can indeed be adapted to the adherence degree of the patient. Other parameters such as sex, age or weight could also be considered. Last but not least, the use of biomarkers and pharmacogenomics makes it possible to include genetic dispositions for drug response in the calculation.

The main strength of this research was to combine two methods of investigation: a scoping literature review and semistructured interviews with field experts. A triangulation approach was used to compare the findings from these two approaches. Our contribution is a synthetic overview of the consequences of undiagnosed adherence in phases II, III and IV clinical trials. With this work, we intend to raise awareness among drug developers and regulatory bodies of the importance of monitoring patient adherence.

This research contains several limitations. First, for simplification purposes, we did not look at a specific therapy area or drug indication. We are aware that our conclusions should be adapted to drug type. For instance, treatments with immediate effects (such as pain killers) and those with a long-run effect (such as prevention treatments) do not represent the same challenges. Severity disease will also play a role. Second, there are only a few published scientific articles dealing specifically with the consequences of nonadherence in clinical trials because patient adherence is not often precisely measured.[37] The lack of resources identified in the scoping review did not allow us to strongly support each element in the figure with scientific evidence and probabilities of occurrence. Third, the inclusion of more search terms, like post-marketing, pharmacovigilance, health outcomes or pharmacoeconomics, would help to draw a more comprehensive picture of all the consequences of nonadherence. Lastly, limited interviews were conducted, but the interviewees involved key opinion leaders who mostly agreed with our results. Their comments were considered to adjust the study results. Finally, the cost estimates for the consequences of undiagnosed nonadherence are still vague. Further research could provide more detailed insight on this topic.

5 | CONCLUSION

This research highlighted that undiagnosed nonadherence in clinical trials has a number of consequences, including additional costs for pharmaceutical companies and payers. Collecting accurate data appeared to be crucial for decision-making throughout the drug development process and for avoiding a late trial failure. However, monitoring patient adherence is still often neglected in practice, potentially exposing drug developers to severe consequences.

AUTHOR CONTRIBUTIONS

Conceived and designed the analysis: Elise Le Flohic and Bernard Vrijens. *Collected the data*: Elise Le Flohic. *Contributed data or analysis tools*: Elise Le Flohic and Mickaël Hiligsmann. *Performed the analysis*: Elise Le Flohic and Bernard Vrijens. *Wrote the paper*: Elise Le Flohic.

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CONFLICT OF INTEREST STATEMENT

AARDEX Group is conceiving and commercializing solutions to measure and monitor medication adherence.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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