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Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC)

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Non-adherence has been well recognized for years to be a common issue that significantly impacts clinical outcomes and health care costs. Medication adherence is remarkably low even in the controlled environment of clinical trials where it has potentially complex major implications. Collection of non-adherence data diverge markedly among cardiovascular randomized trials and, even where collected, is rarely incorporated in the statistical analysis to test the consistency of the primary endpoint(s). The imprecision introduced by the inconsistent assessment of non-adherence in clinical trials might confound the estimate of the calculated efficacy of the study drug. Hence, clinical trials may not accurately answer the scientific question posed by regulators, who seek an accurate estimate of the true efficacy and safety of treatment, or the question posed by payers, who want a reliable estimate of the effectiveness of treatment in the marketplace after approval. The Non-adherence Academic Research Consortium is a collaboration among leading academic research organizations, representatives from the U.S. Food and Drug Administration and physician-scientists from the USA and Europe. One in-person meeting

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was held in Madrid, Spain, culminating in a document describing consensus recommendations for reporting, collecting, and analysing adherence endpoints across clinical trials. The adoption of these recommendations will afford robustness and consistency in the comparative safety and effectiveness evaluation of investigational drugs from early development to post-marketing approval studies. These principles may be useful for regulatory assessment, as well as for monitoring local and regional outcomes to guide quality improvement initiatives.

Introduction

Although the mortality from cardiovascular disease (CVD) in developed economies has fallen in recent decades, CVD remains a major worldwide cause of mortality and morbidity.[1] While the reasons for this decline are multifactorial, the advent of evidence-based pharmacological therapy for primary and secondary prevention has played a significant role. However, the documented benefit of effective pharmacological therapies is attenuated significantly by non-adherence to prescribed therapy.[2–8] The extent of the problem and the complex nature of the phenomenon have only become apparent in recent years.[9,10]

Non-adherence has been well recognized for years to be a common issue that significantly impacts clinical outcomes and health care costs.[9,10] In daily practice, medication adherence is disappointingly low, especially in patients with chronic conditions, and drops dramatically after the first 6 months of therapy.[11–14] The social consequences of non-adherence are striking: non-adherence is associated with 125 000 deaths per year in the USA[9,15] and 194 500 in Europe[16,17]; the cumulative avoidable cost associated with medication non-adherence is estimated at 310 billion dollars in the USA[16] and 125 billion euros in Europe.[17] Non-adherence accounts for 33% to 69% of all medication-related hospital admissions in the USA.[16,18]

Medication adherence is remarkably low even in the controlled environment of clinical trials[11,19–21] and has complex and potentially major effects both on trials' results and interpretation. These effects reflect the interplay between the efficacy of the study medication and the trial design (superiority vs. non-inferiority) and may be discordant for safety and efficacy (e.g. suboptimal adherence may theoretically blunt the efficacy but at the same time improve the safety profile of any given antithrombotic medication). The approaches to collecting and incorporating non-adherence data in major randomized trials diverge markedly, and even when adherence data are collected, this information is rarely incorporated in the statistical analysis of major randomized controlled trials in Cardiology to test the consistency of the primary endpoint(s) (see Supplementary material online, *Section S1*).

Based on guidance from regulators, specifically the Food and Drug administration (FDA), adherence strategies designed to enrich clinical trials have become a regulatory priority.[9,22,23] Imprecision in assessing and classifying non-adherence, and the lack of a consistent approach to incorporating adherence data in the analysis of study results, may lead to imprecision in the calculated perceived efficacy of a drug in clinical trials. Thus many trials may not accurately answer the question posed by the sponsors and regulators, who seek an accurate estimate of the true efficacy of treatment, or the question posed by payers who seek a reliable estimate of the effectiveness of treatment in the marketplace after approval.

For all these reasons, it is timely to consider a structured approach to the classification, collection, and interpretation of data related to non-adherence in cardiovascular clinical trials.

Non-adherence Academic Research Consortium composition, methodology, and goals

See Supplementary material online, *Section S2*.

General considerations regarding adherence definition and classification

A major challenge in correctly defining and understanding adherence and its potential clinical implications lies in the inconsistent terminology historically used throughout the medical literature (e.g. compliance, persistence, concordance, etc.). However, this semantic confusion in terminology has been largely resolved. While 'patient compliance' and 'medication adherence' have been the most widely used terms, each serving as indexing terms in the Index Medicus of the US National Library of Medicine, 'compliance' has been increasingly replaced by 'adherence',[24] as the latter term has been thought to evoke more the idea of cooperation between prescriber and patient, rather than passive obedience to the physician's instructions. The shift from 'compliance' to 'adherence' reflects a fundamental change in understanding relationships between patients and practitioners. The 2003 WHO definition of adherence—the extent to which a person's behaviour taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations for a health care provider—has been widely adopted.[10] In 2012, the Ascertaining Barriers to Compliance (ABC) project, defined medication adherence as 'the process by which patients take their medication as prescribed' while emphasizing that it encompassed three major components: initiation, implementation, and discontinuation.[24] Initiation of treatment occurs when the patient takes the first dose of the prescribed medication. Implementation is defined as the extent to which actual behaviour corresponds to the prescribed dosing regimen. Discontinuation marks the end of therapy. The concept of 'persistence' is defined as the length of time between initiation and discontinuation of treatment. Thus, optimal adherence in the context of a clinical trial comprises *initiation* (a binary variable),

implementation (adherence to medication based on dosing history), and *persistence* until recommended *discontinuation*.

While medication initiation and discontinuation pose relatively minor difficulties, the challenges derived from the complex nature of implementation have been well documented as have the shortcomings of traditional methods (mostly based on patient self-reporting or returned pill counts) of measurement.[21] The introduction of electronic monitoring combined with even more sophisticated analytic techniques has provided a potential solution,[25] the vast majority of publications still classify patients in a dichotomous fashion based on an 80% adherence cut-off rule derived from pill count or pharmacy refill databases, depending on the setting. Although as a crude measure, it is associated with clinical outcomes across all therapeutic areas,[26–29] the 80% threshold should not be interpreted as a measure of daily implementation of the dosing regimen but rather a cut point that correlates with treatment discontinuation. More accurate measures of adherence, predominantly reflecting implementation, have potential to enhance our understanding of its effects on outcome in different disease states.[30]

Hence, a newly designed classification for non-adherence should account for the three main elements of adherence (i.e. initiation, implementation, and discontinuation), including detailed information on dosing implementation and timing of discontinuation as well as the reasons underlying deviations from the prescribed medication.

Non-adherence Academic Research Consortium non-adherence classification

Based on the aforementioned principles, the proposed four level classification of non-adherence captures a gradient of non-adherence, in a hierarchical fashion, from initiation through implementation to the discontinuation of treatment (*Table 1* and *Figure 1*). Since the clinical implications of non-adherence largely depend on the incremental value on health-related outcomes of any investigational pharmacological treatment (i.e. lack of adherence to a toxic drug may actually improve outcomes as compared to perfect adherence), the severity of non-adherence patterns is best standardized based on the expected degree of over- or more frequently under-exposure to study medication for any given experimental drug. Three additional layers of information characterize the decision-process and circumstances underlying non-adherence, the clinical scenario and, where relevant, the timing relative to treatment initiation.

The gradient of adherence ranges from optimal adherence to the study protocol (Type 0), through suboptimal treatment implementation (Type 1) to treatment discontinuation classified as temporary (Type 2), where the period exceeds the pharmacological effect of the study drug but treatment is recommended, or permanent (Type 3). Optimal adherence, classified as Type 0, allows for 5% tolerance, during the study timeframe, from that defined per protocol.

Incorrect implementation of the study regimen is classified as Type 1. This implies deviation from the prescribed regimen to a greater extent than the 5% tolerance allowed for optimal adherence, but without fulfilling the criteria for temporary or permanent discontinuation

described below (i.e. non-consecutive, relatively sparse, and rare intake errors). Type 1 is further classified into three subtypes; Type 1a—continuous exposure to a different dose of the study drug; Type 1b—intermittent under-exposure to study drug resulting from a decreased frequency of drug intake, resulting in total exposure <95% of pre-specified doses; Type 1c—over-exposure owing to an increased frequency of drug intake, resulting in total exposure >105% of pre-specified doses. These thresholds reflect the 5% tolerance allowed in Type 0.

Sustained discontinuation of the study regimen for a period longer than the pharmacological life (defined as the time from last drug intake to the termination of the pharmacological effect) of the drug is classified as Type 2, if temporary, and Type 3, if permanent. The pharmacological life is used as the discriminator to clearly distinguish two potential scenarios. In one scenario, despite the deviations from implementation there is still some pharmacological activity of the study drug; in the other scenario, the deviations result in effective temporary or permanent discontinuation of the study drug. The duration of the pharmacological life of the study drug, based on scientific evidence, should be pre-specified in the study protocol. Examples of pharmacological lives for out-of-hospital cardiovascular drugs are provided in Supplementary material online, *Section S3*. When study drug is permanently discontinued (Type 3) and another drug, from the same class or a different class, is substituted, the adherence information for the new drug is collected as described above.

The second layer classifies the decision-making process that underlies non-adherence. There are three subtypes: non-adherence on the initiative of the study investigator or delegated representative (e.g. study nurse); non-adherence on the initiative of a non-investigator physician (e.g. general practitioner (GP) or insurance doctor) or other health care professionals (e.g. nurse practitioners, physician assistants, and dentists); non-adherence on the initiative of the patient or legally deigned guardian.

The third layer, summarized in the acronym RESULT, classifies the most common clinical scenarios underlying non-adherence, where R stands for risk profile change, E for events, S for surgery, U for other unlisted reasons, L for logistical issues, and T for trauma (*Table 1*).

The fourth layer classifies the timing of non-adherence relative to treatment initiation. Three categories namely early, late, and very late are proposed. The time intervals for each category should be pre-defined by protocol. The single longest non-adherence event (in days) and cumulative non-adherence in days should also be reported. While the NARC classification has been developed to capture adherence and lack thereof to study medication, the metrics proposed below can similarly be applied to non-study drugs (i.e. ancillary/concomitant medications recommended within the protocol). This would allow categorization of study patients based not only on gradients of adherence to study drug but also for pre-defined concomitant medications which may have either major prognostic implications or potential interaction with the study medication itself.

Principles underlying the non-adherence classification

Gradient/pattern of non-adherence (Layer 1)

In order to account for inevitable occasional lapses by even the most motivated subjects, the NARC accepts a 5% tolerance as a

Table 1   Non-adherence Academic Research Consortium Consensus Classification

Level 1: Captures the type of non-adherence

Type 1: Deviations from the prescribed regimen.

  Intermittent variability in medication dose/exposure that does not fulfil criteria for non-adherence Types 0, 2, or 3 definitions.

  a. Change in dose not pre-specified by protocol

  b. Under-exposure: intake of <95% of the prescribed doses

  c. Over-exposure: intake of >105% of the prescribed doses

Type 2: Temporary discontinuation

  Omission of ≥1 dose of prescribed medication resulting in loss of pharmacological effect, within the protocol-defined time frame, followed by resumption of the prescribed regimen

Type 3: Permanent discontinuation

  Permanent discontinuation of prescribed medication (resulting in loss of pharmacological effect based on a drug-specific pharmacological life within the protocol-defined time frame).

Level 2: Captures the decision-maker responsible for non-adherence

Medically driven—investigator: change initiated by the study investigator (or delegated representative)

Medically driven—other medical professional: change initiated by another medical professional (non-investigator physician, dentist, pharmacist, etc.).

Patient driven: change initiated by the patient.

Level 3: Captures the reason(s) underlying non-adherence

Risk profile change:

  Newly diagnosed/recognized medical conditions

  Newly introduced/withdrawn concomitant medication

  New information related to the study drug

  Perception that medication not needed (patient/caregiver driven only)

Events: adverse events (anticipated or unanticipated) related to the study drug such as bleeding or ischaemic events or other drug-specific side effects
  (e.g. dyspnoea, hyperkalaemia, and abnormal liver function).

Surgery:

  Non-cardiac surgery (e.g. cholecystectomy and cancer surgery)

  Coronary artery bypass or other cardiac surgery

  Percutaneous coronary intervention

  Endoscopy

Unlisted: reason not captured by the other categories such as cost of medication, lack of symptoms.

Logistic: issues related to prescription, (forgotten medication) or complexity of the pharmacotherapy (including misunderstanding of the prescribed
  regimen),

Trauma: temporary or permanent discontinuation as a direct result of trauma.

Level 4: Captures the timing of non-adherence

Early: pre-defined by protocol

Late: pre-defined by protocol

Very late: pre-defined by protocol

Given the historical importance of using 80% as arbitrary cut-off point for assessing adherence or lack thereof across studies, the NARC task force favours separately reporting this information calculated as the number of prescribed drug intakes minus the number of missed intakes divided by the number of prescribed drug intakes throughout the study duration. Detailed examples for the practical application of the NARC classification are provided in the case-based example section and in the Supplementary material online.

reasonable threshold to define optimal adherence. The 5% cut-off point to define optimal adherence is based on evidence originating outside the cardiovascular field, where it was shown that a >5% non-adherence pattern to thiopurines was associated to higher risk of replaces in children affected by leukaemia.[31] The majority of clinical trials classify patients who have taken >80% of doses (generally based on pill counts) as 'adherent'. The choice of this threshold is based on pharmacy refill data, which showed the best prognostic discrimination with this threshold irrespective of the medication studied.[21,26–29] However, a relatively low binary threshold forces patients with different non-adherence patterns into the same

category (*Figure 2*). Critically, it does not permit a distinction between those who implement the regimen in a suboptimal fashion, while still being continuously exposed to a potentially therapeutic concentration of the study drug from those who, with the same level of 'adherence' based on pill counts have a different non-adherence pattern, that includes truly off-drug time periods.

Patients whose cumulative intake of study drug is <80% are likely to have interrupted the treatment, with loss of the pharmacological effect, at some point during the study (*Figure 3*). Hence, this 20% tolerance seems more suitable as a prognostic rather than an adherence marker, as it essentially captures, potentially unreported, treatment
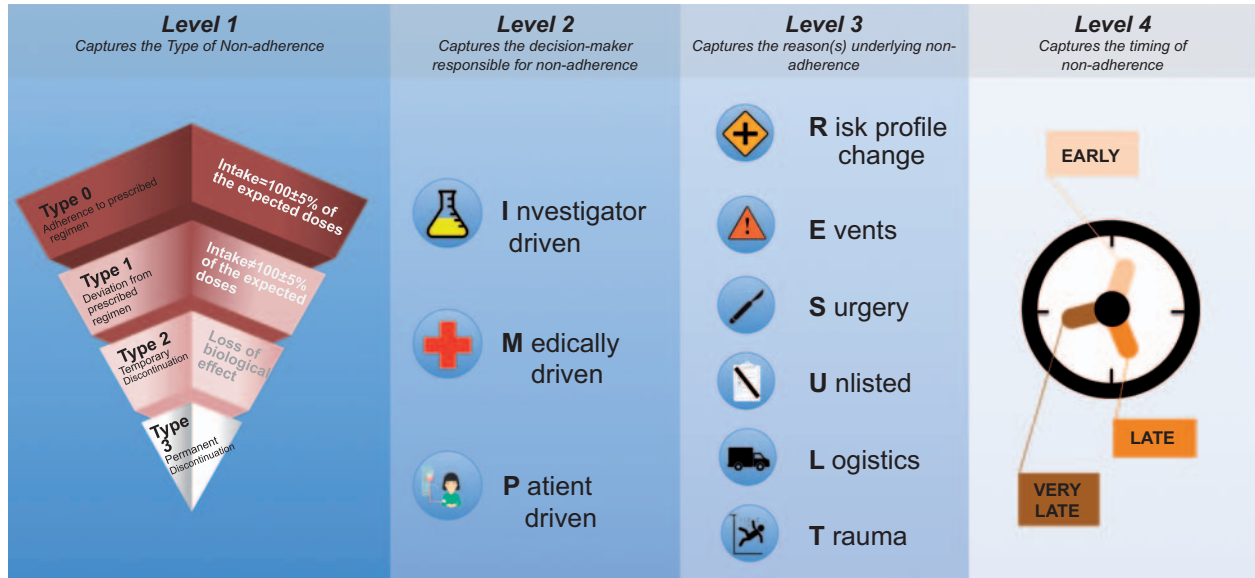
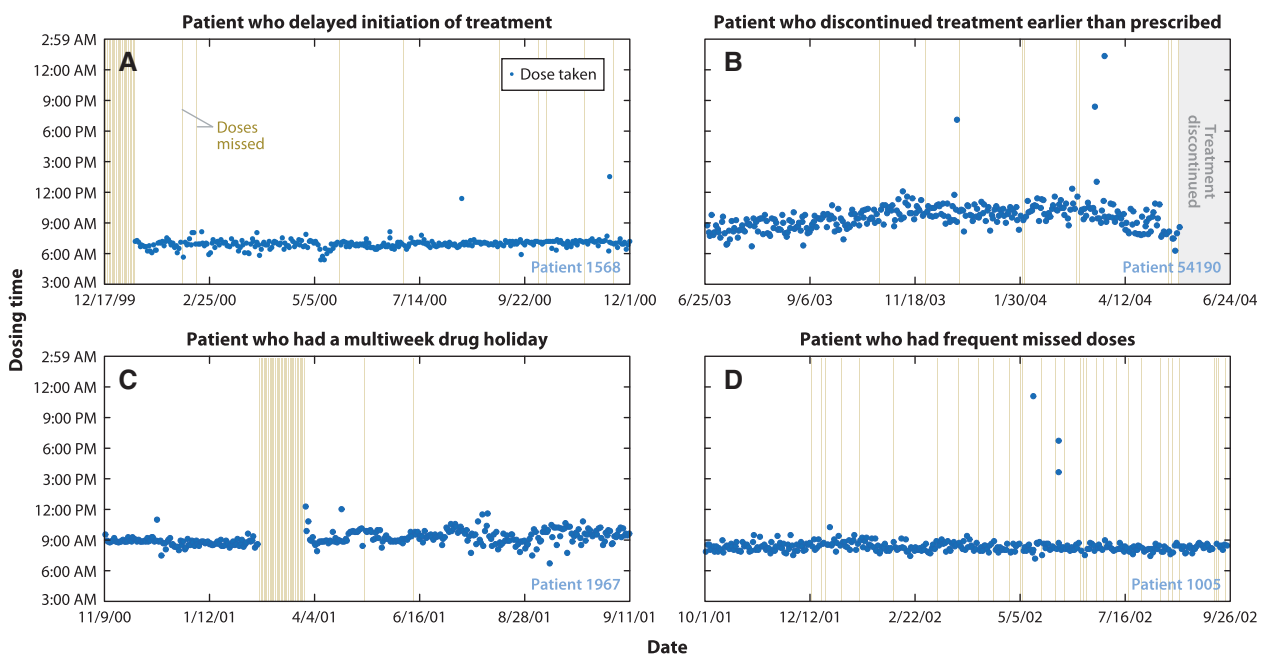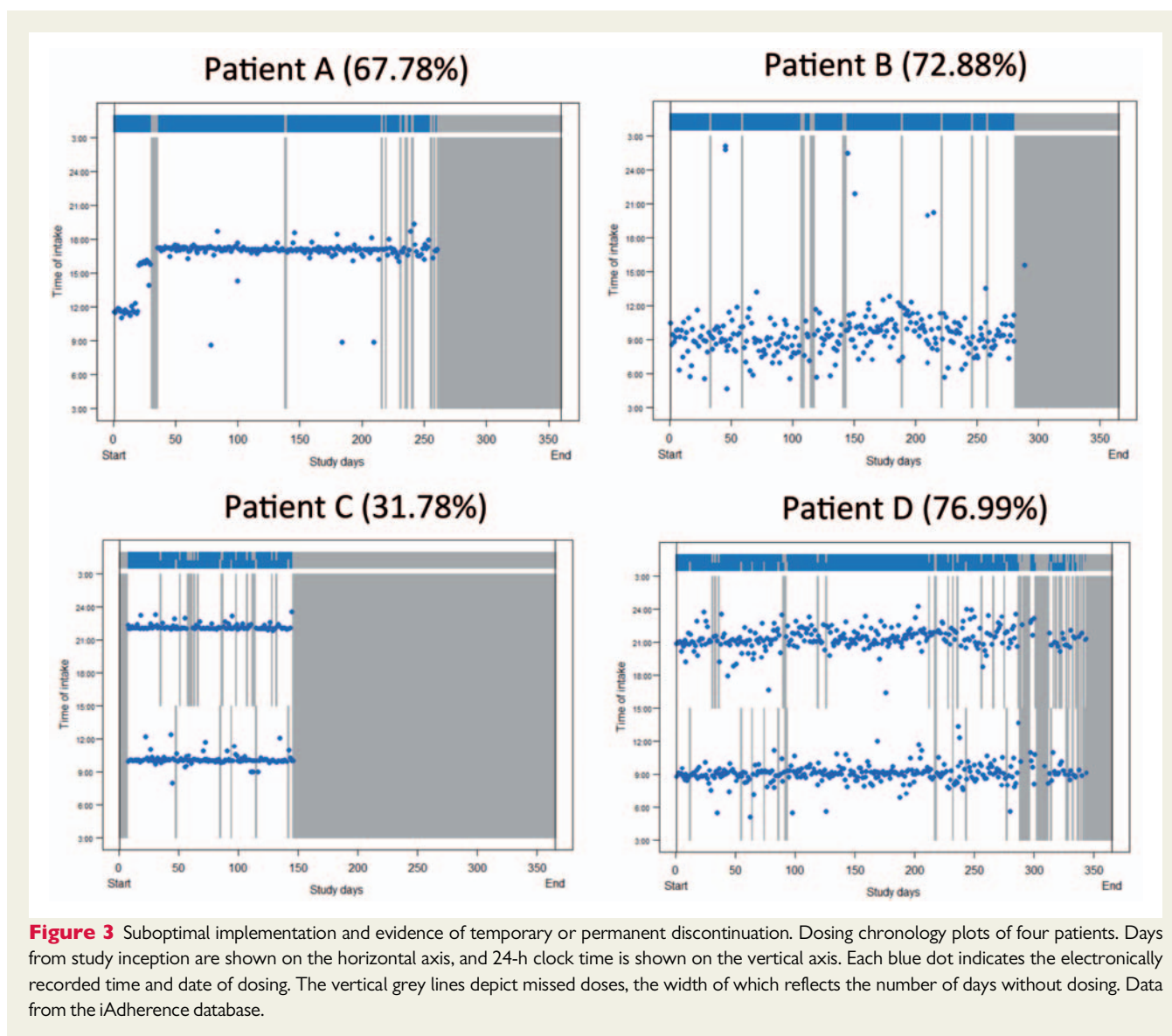**Figure 1** Levels of the Non-adherence Academic Research Consortium Classification.

Figure 2 Dosing chronology plots of four patients. Calendar date (mm/dd/yy) is shown on the horizontal axis, and 24-h clock time is shown on the vertical axis. Each blue dot indicates the electronically recorded time and date of dosing. The vertical tan lines depict missed doses, the width of which reflects the number of days without dosing. During the depicted periods of study, each patient took 90–91% of prescribed doses, with the indicated wide variations in the temporal patterns of dose omissions. Data from the iAdherence database (From Blaschke *et al.*[21]).

discontinuation. In addition, a stricter adherence regimen demonstrated a superior efficacy in studies outside the cardiovascular field, especially for treatments with a narrow therapeutic window or a short pharmacological half-life.[31,32]

Unlike previous approaches to capture and categorize adherence, the NARC proposes a refinement based on the documented pharmacological half-life of the study drug, in an attempt to distinguish non-adherence patterns which result in under- or over-

Figure 3 Suboptimal implementation and evidence of temporary or permanent discontinuation. Dosing chronology plots of four patients. Days from study inception are shown on the horizontal axis, and 24-h clock time is shown on the vertical axis. Each blue dot indicates the electronically recorded time and date of dosing. The vertical grey lines depict missed doses, the width of which reflects the number of days without dosing. Data from the iAdherence database.

exposure to drug effect from those where patients, for variable periods, have no exposure whatsoever to a pharmacologically relevant concentration of the study drug. Specific considerations apply for placebo-controlled studies. As a placebo has no pharmacological life by definition, one reasonable approach might be to arbitrarily assign a pharmacological life to the placebo equivalent to that of the study drug.

The Type I category may pose specific challenges. In order to distinguish Type I from other categories, a highly reliable method to capture adherence pattern is required, for example electronic monitoring. Hence, the reliability of this category within trials cannot be disentangled from how adherence is assessed and captured during the study conduct. Type 1A may not be applicable to blinded studies where only one regimen of the investigational drug is assessed. Moreover, a physician-guided change in the prescribed dose of an investigational drug should not be perceived as a non-adherence pattern as long as the protocol pre-specifies the possibility to up or down-titrate the investigational regimen based on tolerability or other factors, such as for example concomitant medications.

Similarly, a change in drug dose in the setting of a dose finding study where multiple investigational drug regimens are compared may be regarded as Type 3 rather than Type 1A. Hence, the protocol should pre-specify the applicability of Type 1A and if so clarify which drug regimen(s) would fulfil this entity. The NARC task force suggests that adherence be also examined on a continuous scale, as the percentage of prescribed doses actually taken. Given the historical importance of using 80% as arbitrary cut-off point for assessing adherence or lack thereof across studies, the NARC task force favours separately reporting this information calculated, over the entire study duration, as the number of prescribed drug intakes minus the number of missed intakes divided by the number of prescribed drug intakes (expressed as a percentage).

Decision-making process and context underlying non-adherence (Layers 2 and 3)

While many studies have reported the effect of treatment cessation on subsequent cardiovascular events, few captured precisely the

decision-making processes or the clinical scenarios that led to cessation. Treatment discontinuation may result in an adverse event or treatment may be discontinued as a result of an adverse event. Capturing the exact timing of adverse events and treatment discontinuations generally helps in the ascertainment of the cause–effect nature of this relationship; however, this may not always be possible or reliable. The PARIS registry has shown that risk of cardiovascular events following discontinuation of antiplatelet treatment after coronary stent implantation is highly dependent on the circumstances surrounding treatment discontinuation.[33] For example, compared with patients who remained on dual antiplatelet therapy (DAPT), those who had physician-guided discontinuation were at significantly lower risk of major adverse cardiovascular events compared with those where DAPT cessation was not physician-guided.[33] In the context of a clinical trial, the NARC consensus was to clearly differentiate whether physician guidance on treatment discontinuation originated from the investigator or an authorized representative—who would be expected to have a more in-depth knowledge about study design, procedures, and the study drug—or from another source, including primary a care physician or other subspecialty physicians, such as for example gastroenterologists or dentists. The setting leading to lack of adherence was felt to potentially be as important as the non-adherence pattern. Outside the randomized trial setting where costs are generally funded by the clinical investigation, some of the decisions resulting in non-adherence may be arrived at after discussion between the patient and his primary physician. Where such decisions are agreed by both parties they will be classified as physician driven.

The RESULT acronym has been developed to help memorize and easily categorize the most frequent clinical scenarios resulting in non-adherence (Table 1). Trauma might be conceptually included in the risk profile change category. However, based on growing recognition of the importance of trauma as a potential treatment modifier, especially for but not limited to antithrombotic drugs,[33] the NARC recommends capturing it as a distinct entity.

Timing of non-adherence (Layer 4)

The time threshold to define these categories should be pre-specified in the protocol as the definition of a fixed time window for different medications is not appropriate and may not be relevant for some cardiovascular trials. In fact, the temporal impact of non-adherence varies significantly based on the context of the study and the indication for and/or type of medication studied (e.g. antihypertensive drug vs. antiplatelet agents). Thus, the NARC proposes this fourth layer depending on the nature of the study and the investigated drug.

Non-adherence Academic Research Consortium classification: case-based examples

An overview of case examples for the application of the NARC classification is provided in Table 2. An additional comprehensive library of explanatory patient case examples is provided in Supplementary material online, Section S4.

Collecting and analysing non-adherence

The various approaches to collect adherence information are rarely or inconsistently incorporated in current major randomized trials (see Supplementary material online, Section S5). Moreover, even when adherence data are collected, they are rarely utilized in the statistical analysis to test the consistency of the primary endpoint(s) (see Supplementary material online, Section S1 and Table S1).

The imprecision introduced by the inconsistent assessment of non-adherence in clinical trials makes estimating the efficacy of the study drug difficult.[34] Hence, clinical trials may not accurately answer the scientific question posed by regulators, who seek an accurate estimate of the efficacy/method-effectiveness/causal effect (i.e. the effect if all participants were to be fully adherent) and safety of treatment, or the question posed by payers who seek a reliable estimate of the use-effectiveness (i.e. the effect with typical use) of treatment in the marketplace after approval.[35–39]

Variability in implementing a dosage regimen can result in toxicity or lack of effect that may differ among drugs and dose regimens (e.g. once daily vs. twice daily) in an unpredictable fashion.[17] An example, outside the cardiovascular field, relates to human immunodeficiency virus (HIV) pre-exposure prophylaxis with tenofovir/emtricitabine.[23] While the effectiveness of tenofovir/emtricitabine in some clinical trials was null,[40,41] one study, which maximized adherence to the study medication, resulted in efficacy approaching 100%.[23] Based on an adherence-adjusted analysis, the drug was subsequently approved for its prophylactic effectiveness against infection with HIV.[42]

Yet, adherence data have not often been used as an explanatory variable in registration trials as there is widespread agreement among clinical trialists that intention-to-treat (ITT) analysis should be the primary analysis of randomized controlled trials. However, ITT ignores the situation, now acknowledged as common, where a substantial fraction of trial patients fail to take the medicine as prescribed. Supportive, adherence-informed analysis, complementing the ITT analysis with an appropriate adherence-adjusted analysis, would deliver:

- A robust estimate of method-effectiveness for drug efficacy when taken correctly.
- A more accurate and cost-effective analysis of collected clinical data (PK and PD)
- Define dosing errors that have the greatest potential to undermine effectiveness
- Define dosing errors that have the greatest potential to create hazard (e.g. rebound effects after sudden cessation of dosing, recurrent first-dose effects, emergence of resistance to anti-infective agents)

Collection of non-adherence in clinical trials: recommendations for the case report form

See Supplementary material online, Section S6.

Analysis of non-adherence in clinical trials: statistical analysis considerations

The NARC classification aims to improve validity and reliability in comparing rates of non-adherence across studies and to increase

Table 2   **Non-adherence Academic Research Consortium Classification case examples**

Definition	Case examples
Level 1: Type of non-adherence event	
Type 0: Complete adherence to medication as specified in the study protocol and in any case not fulfilling criteria for non-adherence Types 1, 2, and 3. This requires an exposure to medication of 100 ± 5% of the doses prescribed in the study protocol.[a,b]	Patients with pulmonary embolism, already treated with oral anticoagulants for 6 months after the event, are randomized to treatment with dabigatran or placebo for an additional period of 12 months. The primary endpoint is evaluated after 12 months of treatment. The study protocol specifies a dose of 150 mg twice daily for those with normal renal function reduced to 75 mg twice daily in patients with renal impairment (creatinine clearance 15–30 mL/min). Patient 1 has normal renal function and was treated with dabigatran 150 mg twice daily. At follow-up, he had taken 98% of the expected doses. Patient 2 has a creatinine clearance of 18 mL/min and was treated with dabigatran 75 mg twice daily. At follow-up, he had taken 96% of the expected doses. Both patient fulfil NARC 0 criteria.
Type 1: Intermittent variability in medication dose/exposure from protocol prescription not fulfilling non-adherence Types 2 and 3 definitions.	Patients are included in an open label randomized study comparing losartan 100 mg vs. an active antihypertensive treatment. Losartan is administered once per day. Only if systolic blood pressure at two different ambulatory measurements is confirmed to be less than 100 mg, losartan 50 mg q.d. can be administered. Follow-up visits are scheduled every 3 months. Patients are expected to use 90 ± 4 pills between follow-up visits.
a. change in the dose specified in the protocol	Patient 1 reports at a follow-up visit two episodes of mild dizziness. He felt these episodes were related to the study medication. Systolic blood pressure measurements showed values consistently above 100 mmHg. Yet, the physician decided to down-titrate the prescribe losartan regimen to 50 mg, to avoid the risks the patient will self-discontinue the investigational treatment. This patient fulfils NARC Type *1a criteria*.
b. under-exposure: less than 95% of the doses expected by the protocol	Patient 2 had used 75 pills (83% of expected doses) at a follow-up visit. This patient denies having interrupted study medication at any time but reports having forgotten some non-consecutive pills. This adherence pattern fulfils NARC Type *1b* criteria.
c. over-exposure: more than 105% of the doses expected by the protocol	Patient 3 did not understand the physician's instructions and took study medication twice daily for 1 week. At the follow-up visit, 97 pills have been used (107% of expected doses). This patient has been overexposed to the study drug fulfilling NARC Type *1c* criteria.
Type 2: Temporary discontinuation of the medication causing the termination of its pharmacological effect based on a drug-specific pharmacological life and followed by a return to the original regimen	Patients are included in a randomized study testing ticagrelor 90 mg twice daily vs. placebo. The pharmacological life of ticagrelor/placebo was defined in the study protocol as 5 days. Follow-up visits are scheduled every month. Patients are expected to use 60 ± 3 pills between follow-up visits. Patient 1 had a nosebleed and decided to discontinue study medication until the next follow-up visit (12 days later). At that time the investigator reinitiated study medication. This patient discontinued study medication for longer than its pharmacological life and fulfils NARC Type *2* criteria. Patient 2 developed respiratory symptoms and discontinued study medication for 3 days (six doses). This patient did not discontinue study medication for longer than the pharmacological life of the drug, but he did not implement the treatment correctly as he omitted more than the tolerated three doses. This patient fulfils NARC Type *1b* criteria.
Type 3: Permanent discontinuation of the medication within the study	Patients presenting with an acute coronary syndrome and treated with drug-eluting stents are randomized to rivaroxaban 2.5 mg or placebo in addition to the standard of care dual antiplatelet therapy regimen. The pharmacological life of rivaroxaban/placebo was defined in the study protocol as 24 h. The primary endpoint is evaluated after 12 months of treatment.

Continued

Table 2 *Continued*

Definition	Case examples
	Patient 1 was randomized to rivaroxaban 2.5 mg and after 4 months of treatment had an intracranial bleed. Study drug was immediately discontinued and never restarted. This patient fulfils NARC Type *3* criteria.
	Patients with clinically evident atherosclerotic vascular disease were randomized to a treatment with evolocumab 140 mg or placebo. The pharmacological life of evolocumab/placebo was defined in the study protocol as 15 days. The primary endpoint is evaluated after 36 months of treatment.
	Patient 1 was randomized to evolocumab and after 4 months of treatment had a severe muscle pain with significant increase of creatine kinase. Study drug was immediately discontinued and never restarted. This patient fulfils NARC Type *3* criteria.
Level 2: Decision-making process around the non-adherence event	Patients presenting with an acute coronary syndrome and treated with drug-eluting stents are randomized to rivaroxaban 2.5 mg or placebo in addition to the standard of care dual antiplatelet therapy regimen. The primary endpoint is evaluated after 12 months of treatment.
Investigator driven: change on the initiative of a study investigator	Patient 2 was randomized to rivaroxaban 2.5 mg and after 6 months of treatment had gastro-intestinal bleeding requiring blood transfusion. The study investigator decided to discontinue the study drug based on his clinical assessment of the risk of further bleeding. The drug was never restarted. This patient fulfils NARC Type *3*, sub-type*I* criteria.
Other medical doctor driven: change on the initiative of any other physician	Patient 3 was randomized to rivaroxaban 2.5 mg and after 2 months of treatment had a scheduled hip replacement. The surgeon decided to discontinue all antiplatelet and anticoagulant medications, including the study drug. The drug was restarted after 20 days, at the time of the next scheduled follow-up visit. This patient fulfils NARC Type *2*, sub-type *M* criteria.
Patient driven: change on the initiative of the patient	Patient 4 was randomized to placebo and after 8 months of treatment had a nosebleed. He did not contact his physician. He decided on his own initiative to discontinue the study drug. The drug was restarted 2 days later at the time of the next scheduled follow-up visit. This patient fulfils NARC Type *2*, sub-type *P*.
Level 3: Clinical scenario underlying non-adherence	
Risk profile change: including but not limited to new conditions or pharmacotherapy that increase patient's risk to receive the previously prescribed therapy.	Patients presenting with an acute coronary syndrome and treated with drug-eluting stents are randomized to rivaroxaban 2.5 mg or placebo in addition to the standard of care dual antiplatelet therapy regimen. The primary endpoint is evaluated after 12 months of treatment.
	Patient 4 was randomized to rivaroxaban 2.5 mg and after 6 months of treatment was diagnosed with a cerebral neoplasm. The oncologist discontinued the study drug because of concern related to the potential risk of an intracranial bleed. The drug was never restarted. This patient fulfils NARC Type *3*, sub-type *M*, sub-type R criteria.
Events: including but not limited to expected or not expected events related to the study drug, adverse side effect, bleeding, or ischaemic events.	Patients are included in a randomized study of ticagrelor vs. clopidogrel. Ticagrelor (90 mg) twice daily was prescribed. Follow-up visits are scheduled every month. Patient 4 was randomized to ticagrelor and attended his general practitioner (GP) due to severe dyspnoea. The GP decided to discontinue ticagrelor and switch to prasugrel. This patient fulfils NARC Type *3*, sub-type *M*, sub-type *E*.
	Patients are included in a randomized study of evolocumab vs. ezetimibe. Evolocumab (140 mg) once every 2 weeks was prescribed. Follow-up visits are scheduled 3 months. Patient 4 was randomized to evolocumab and suffered an infection of the puncture site 1 month after study inception, which was treated by the general practitioner. The patient skipped the following four injections and after attending the follow-up visit decided to restart the study drug. This patient fulfils NARC Type *2*, sub-type *P*, sub-type *E*.

Continued

Table 2   *Continued*

Definition	Case examples
Surgery: including but not limited to surgery, endoscopic or other type of invasive procedures inducing drug withdrawal	Patients are included in a randomized study of ticagrelor vs. clopidogrel. The pharmacological life was defined in the study protocol as 5 days for ticagrelor and 7 days for clopidogrel. Follow-up visits are scheduled every month. Patient 6 was randomized to clopidogrel and discontinued study drug for 9 consecutive days for a planned surgical procedure on the direction of the surgeon. The drug was then restarted. This patient fulfils NARC Type 2, sub-type M, sub-type S criteria.
Uncertain: including all those reasons that might result in deviation from the prescribed study drug regimen that are not captured by the other categories of the RESULT acronym.	A patient is included in an open label phase III study testing the efficacy/safety profile of a new antiplatelet agent. The patient decided to stop the study medication because he became convinced that the experimental drug was poison. Soon after he was diagnosed with a psychotic illness and study drug was not restarted. This patient fulfils NARC Type 3, sub-type P, sub-type U criteria.
	Patients with symptomatic heart failure and iron deficiency are randomized to i.v. ferric carboxymaltose or placebo once per month. The pharmacological life of the drug was defined in the study protocol as 90 days. The primary endpoint is evaluated after 12 months of treatment.
	Patient 7 was randomized to placebo. At attending the follow-up visit the investigator noted that patient was prescribed with ciprofloxacin by the general practitioner. Due to a possible drug-interaction patient was discontinued to the study drug until the end of antibiotic treatment (skipped two doses of study drug and then reinitiated treatment). This patient fulfils NARC Type 2, sub-type I, sub-type U criteria.
Logistical issues: including but not limited to issues related to prescription, cost, or complexity of the pharmacotherapy. It may also include non-adherence due to misunderstanding or patient forgetfulness.	Patients presenting with an acute coronary syndrome and treated with drug-eluting stents are randomized to rivaroxaban 2.5 mg or placebo in addition to the standard of care dual antiplatelet therapy regimen. The pharmacological life of rivaroxaban/placebo was defined in the study protocol as 24 h. The primary endpoint is evaluated after 12 months of treatment.
	Patient 7 was randomized to rivaroxaban 2.5 mg. The patient could not attend the scheduled follow-up visit and ran out of study drug. As a result, the patient discontinued study treatment for 3 consecutive days and was then resupplied with drug. This patient fulfils NARC Type 2, sub-type P, sub-type L criteria.
Trauma: leading to impossibility to take or concerns over the possible increased risk of side effects of a given treatment	Patients presenting with an acute coronary syndrome and treated with drug-eluting stents are randomized to rivaroxaban 2.5 mg or placebo in addition to the standard of care dual antiplatelet therapy regimen. The primary endpoint is evaluated after 12 months of treatment.
	Patient 8 was randomized to placebo. After a car accident a brain computed tomography (CT) scan, did not show any evidence of bleeding. However, the patient was admitted to the intensive care unit and the intensivist together with the investigator decided to stop the study drug. The patient was discharged after 8 days and the study drug restarted. This patient fulfils NARC Type 2, sub-type I, sub-type T criteria.
	Patients with symptomatic proximal deep-vein thrombosis and active malignancy are randomized to subcutaneous dalteparin 200 IU/Kg or oral warfarin (target International normalized ratio (INR) 2.5). The primary endpoint is evaluated after 12 months of treatment.
	Patient 8 was randomized to dalteparin. After a car accident a brain CT scan, did not show any evidence of bleeding. However, the patient was admitted to the intensive care unit and the intensivist together with the investigator decided to stop the study drug. The patient was discharged after 8 days and the study drug restarted. This patient fulfils NARC Type 2, sub-type I, sub-type T criteria.

Continued

Table 2   *Continued*

Definition	Case examples
Level 4: Timing of the non-adherence event[c]	
Early: a deviation from prescription that occurs early after initiation	Patients are included in a randomized study of ticagrelor vs. clopidogrel. Ticagrelor (90 mg) twice daily was prescribed. Follow-up visits are scheduled every month. The timing of non-adherence is defined in the protocol as follows: non-adherence occurring in the first month is defined as early; non-adherence occurring after the first month but before 12 months is defined as late; non-adherence occurring beyond 12 months is defined as very late. Patient 4 was randomized to ticagrelor and after 15 days consulted his general practitioner with severe dyspnoea. The GP decided to discontinue ticagrelor and switch to prasugrel. This patient fulfils NARC Type *3*, sub-type *M*, sub-type *E*, timing *Early*
Late: a deviation from prescription that occurs late after initiation	Patients are included in a randomized study comparing losartan 100 mg vs. placebo. Losartan is prescribed once daily. Follow-up visits are scheduled at the first month after randomization and every 3 months thereafter. Patients are expected to use 90 ± 4 pills between follow-up visits. The timing of non-adherence is defined in the protocol as follows: non-adherence occurring in the first month is defined as early; non-adherence occurring after the first month but before 6 months is defined as late; non-adherence occurring beyond 6 months is defined as very late.
	Patient 4 was randomized to losartan 50 mg. Adherence was documented as NARC 0 at 1-month follow-up. However, the patient misunderstood the instructions of the physician and took study medication twice daily after the first follow-up visit for 1 week. At the second follow-up visit, at 4 months, 97 pills have been used (107% of expected doses). This patient fulfils NARC Type *1c*, sub-type *P*, sub-type *L*, timing *Late*.
Very late: a deviation from prescription that occurs very late after initiation	Patients presenting with an acute coronary syndrome and treated with drug-eluting stents are randomized to rivaroxaban 2.5 mg or placebo in addition to standard of care dual antiplatelet therapy. The primary endpoint is evaluated after 12 months of treatment. The timing of non-adherence is defined in the protocol as following: non-adherence occurring in the first month is defined as early; non-adherence occurring after the first month but before 12 months is defined as late; non-adherence occurring beyond 6–12 months is defined as very late.
	Patient 4 was randomized to rivaroxaban 2.5 mg and after 7 months of treatment was diagnosed with a cerebral neoplasm. The oncologist felt there was a high bleeding risk and discontinued the study drug. The drug was never restarted. This patient fulfils NARC Type *3*, sub-type *M*, sub-type *R*, timing *Very late*

[a]If the protocol pre-specifies a dose adjustment for specific patient categories (e.g. those with renal impairment, older age, high/low weight and so forth) a reduction/increase in dose during the study according to protocol criteria will not be considered as non-adherence (NARC 1) but as complete adherence (NARC 0).
[b]If the protocol pre-specifies a washout period, this will not be considered as a temporary drug discontinuation (NARC 2) but as complete adherence (NARC 0).
[c]In studies where timing of nonadherence pattern is felt to play a crucial role (e.g. for DAPT adherence in stent studies), follow-up visits or adherence monitoring tools should be planned according to the pre-defined time frames for non-adherence patterns (e.g. at 30 days to capture events occurring early (within 30 days) from those occurring lately (after 30 days).

analytic efficiency. At a minimum, simply describing the overall burden and different types of adherence in a uniform manner represents an important advance from the disparate approaches commonly used across studies. From an analytic perspective, we propose several general guiding principles that may be followed or should be considered in clinical studies examining therapeutic pharmacologic interventions. We suggest the following elements as important considerations when designing data collection tools and analytic plans for clinical studies with potential adherence implications (*Table 3*).

Statistical analyses in the setting of non-adherence

General principles of censoring

Kaplan–Meier (KM) analyses with logrank test or Cox regression analysis under the proportional hazards (PH) assumption is the conventional analytic approach in randomized clinical trials with a time-to-first-event primary endpoint, e.g. the composite of death, myocardial infarction, or stroke. Kaplan–Meier and Cox regression analyses allow censoring of follow-up if censoring is an event that has

> **Table 3   Principles surrounding the collection and analysis of adherence for valid statistical analysis**
>
> - Pre-specify the definition of adherence
> - Determine if adherence information will be collected in a static (at follow-up visits only) or in a dynamic fashion (throughout the study duration)
> - Profile occurrences of medication discontinuation at a minimum by:
>   - Underlying reason;
>   - Duration;
> - Pre-specify analytic plan for adherence
>   - Sample size/power considerations
>   - Must take into account primary trial hypothesis (efficacy vs. safety)
> - Pre-specify the different analytic sets, in particular the per-protocol population

no relationship whatsoever with the patient's risk (after accounting for characteristics in the Cox model) at the time of censoring. This condition is met if censoring occurs at a pre-defined study termination date, e.g. 730 days after randomization of the individual patient (i.e. a fixed duration of follow-up for all patients), or a fixed date (e.g. 365 days after randomization of the last patient), or when the primary endpoint has occurred in a pre-specified number of patients or a pre-specified number of events has occurred (provided the characteristics of the participants when enrolled remains constant over time for the last two scenarios). The first scenario pre-specifies a fixed duration of follow-up for all patients; the latter two involve a variable duration of follow-up. Non-adherence or permanent discontinuation of trial medication may frequently be related to prognosis. Therefore, naively censoring of follow-up at the time of non-adherence or permanent discontinuation of trial medication without further appropriate accounting for the relationship between time of non-adherence and patient's risk, in principle, introduces bias in a KM or Cox regression analysis. If non-adherence and then censoring occurs in patients with a relatively poor prognosis, KM curves underestimate the event rates over time. If non-adherence or permanent discontinuation is asymmetrical in the two treatment groups, censoring of follow-up typically biases the estimation of the treatment effect.

Intention-to-treat analysis

Analysis according to the ITT principle was introduced to address the issue of (selective) withdrawal from treatment in a randomized setting. An ITT analysis is based on two tenets. First, the outcome status until pre-defined study termination (as defined above) is known for all patients. Second, in the actual KM or Cox-PH analysis, events are counted based on randomization rather than actual treatment at the time of the event. In the presence of similar non-adherence in the treatment arms, an ITT analysis is generally associated with a diminution of treatment differences that might have been evident if all patients had been treated according to the study protocol. In an ITT analysis, preservation of the comparability of the treatment groups, as created by randomization, prevails over treatment adherence.

Since ITT is likely biased towards the null, its use for safety points is generally discouraged. The ITT analysis assumes that an important component of the treatment efficacy is the ability to comply with the protocol-mandated regimen. Therefore, non-adherence is an intrinsic component of the overall treatment effect. In other words, an ITT analysis does not estimate the pharmacological effect of a treatment but a combined effect of treatment efficacy and adherence. However, when the rate of non-adherence is high, effect estimation by ITT could become less clinically meaningful, and the benefit of preserving comparability ensured by randomization may not offset the issues. Without supplementing ITT analysis with additional information such as adherence rate, the interpretation of ITT result is difficult and questionable. Furthermore, an ITT analysis pre-supposes that follow-up and event collection is not affected by actual treatment status.

On-treatment analysis

On-treatment (OT) analyses were introduced to accommodate that notion that study treatments should not take into account events that occur while the patient is off treatment. Historically, these types of analyses have been particularly important in safety assessments. In an OT analysis, follow-up is censored at the time of permanent discontinuation of trial medication, which implies that only events that occur while the patient in on the randomized study treatment are taken into account. An OT analysis excludes events that occurred off treatment. An OT analysis requires a precise definition of the off-treatment period relative to the last exposure to trial medication. Conventional choices utilize clearance of drug concentrations in the blood or a fixed time interval, e.g. of 28 days.

A newer variant of OT analysis allows interval censoring. This approach introduces censoring for the duration of temporary interruptions of trial medication. Events that occur during the censored interval are excluded from the analysis, whereas events that occur after resumption of treatment are again included in the analysis.

In an OT analysis, whether with permanent or interval censoring, censoring cannot be assumed to have occurred at random. Non-adherent patients may be sicker and hence at higher risk for the primary outcome. In fact, it was recently shown that even non-adherence to placebo worsens outcomes.[7,43] Thus, censoring for non-adherence (similar to any form of loss to follow-up) could lead to biased treatment comparisons, diminishing or exaggerating the underlying treatment effect. The direction and magnitude of the bias is determined by the degree to which treatment withdrawal is selective and its association with the risk for the primary endpoint. In an OT analysis, adherence prevails over the preservation of the balance of the treatment groups.

Modified intention-to-treat analysis

The term modified intention-to-treatment (mITT) analysis (or population) is commonly used in clinical trial reports, but has no universally accepted meaning.[44] Sometimes it is a variant of an OT analysis. The term usually refers to the complete removal of non-adherent patients (or other groups of patients) from the statistical analysis. Post-randomization exclusions should be avoided as much as

possible. Justifiable exclusions comprise technical failures of the randomization process, ineligible patients incorrectly randomized, and, in double blind trials, patients who did not receive a single dose of study drug.[44] Exclusion of patients who actually started randomized treatment should be avoided. Thus, exclusion of non-adherent patients from the statistical analysis is strongly discouraged, even where non-adherence commences shortly after randomization.

Per-protocol analysis

The term per-protocol analysis (or population) is also commonly used in clinical trials reports, but, once more, has no universally accepted meaning. The per-protocol designation sometimes refers to the process of entry into the trial. A per-protocol analysis then implies complete removal from the analysis of patients who violated inclusion or exclusion criteria. Quite often, a per-protocol analysis also implies censoring of follow-up as soon as treatment substantially deviates from the study protocol. In those circumstances, a per-protocol analysis is similar or may even be identical to an OT analysis.

Statistical analysis applied to the Non-adherence Academic Research Consortium non-adherence classification

Analyses might be performed that exclude different populations of non-adherent patients by degree of severity, ranging from exclusion of Type 3 non-adherence as the most stringent entity, to exclusion of any non-adherent patients (e.g. Types 1, 2, or 3) as the most conservative and inclusive formulation. Alternatively, an intermediate approach for accounting for minor types of non-adherence patterns, (e.g. Types 1 or 2) is to exclude patients in whom more than 1 episodes of minor non-adherence pattern has occurred or further stratifying the patient population based on the decision-maker (e.g. Layer 2 of the classification) and/or the reason (e.g. Layer 3 of the classification) for non-non-adherence. We in fact propose each study protocol to pre-specify which degree(s) and entity(ies) of non-adherence is/are critical and factor those into the statistical analyses plan, taking the study the type and objectives of study protocol as well as the anticipated characteristics/effects of the study medication. Examining the treatment effect in these different populations may be informative to not only confirm the overall results but also to assess the influence of non-adherence on the treatment effect. In this context, pre-specifying the relevant analyses in the setting of non-adherence is important to ensure that the observed treatment effect does not deviate substantially with varying levels of adherence. For example, instead of claiming superiority or lack thereof of a given treatment strategy in the various sub-populations identified by the NARC classification, heterogeneity testing should better inform the interpretation of study results.

As discussed above, other studies may be focused on estimating the causal effect of a treatment in the presence non-adherence itself. In addition to a temporal dimension, the construct of adherence can also vary in severity. As such, previous approaches quantifying adherence as a binary variable (i.e. on- vs. off-treatment) at fixed follow-up time points, do not fully represent the fluctuating nature of non-adherent behaviour. As shown by the PARIS study, both temporal and contextual dimensions are crucial to linking the occurrence of non-adherence with subsequent cardiovascular risk.[33] The NARC scheme is consistent with this observation as the different levels of non-adherence should ideally be measured at repeated time intervals thereby allowing a natural hierarchy from less severe (Type 1) to most severe (Type 3). The implication of this approach is shown below in a hypothetical study where an individual's follow-up time is categorized into different time intervals. We assume that the trial is designed to test the superiority of a novel drug vs. placebo in reducing risk for MI. A patient is randomized to the experimental drug, experiences a myocardial infarction (MI) on Day 21 and then permanently stops the study drug on Day 31. For purposes of addressing the question of the trial, namely whether or not the new drug is associated with a reduction in risk for MI compared to placebo, the event in question will be included in both the ITT and per-protocol analyses as the event occurred while the patient was receiving protocol-mandated study drug. However, a separate but related question is whether or not non-adherence to the study drug increases risk for MI. A naïve analysis would categorize this patient as non-adherent (which did occur on Day 31) and evaluate the time to MI. This approach, however, ignores the temporal link between the timing of drug cessation and MI. Additional statistical considerations on non-adherence in the setting of clinical trials are discussed in Supplementary material online, Section S7.

Case-based examples for statistical considerations on non-adherence

See Supplementary material online, Section S8.

Summary and conclusions

Patient adherence represents the crucial link between prescribed effective medication and successful management or prevention of disease and comprises three distinct elements, initiation, implementation, and persistence. Despite the recognition that adherence is a complex multifaceted phenomenon, many publications still classify patients in a dichotomous fashion as 'adherent' or 'non-adherent', and it is rarely accounted for in the statistical analysis of trials.[14,21] This is generally based on an 80%[29] adherence rule derived from pill counts or pharmacy refill databases.[14,26–28] Although it appears overly simplistic, this dichotomous classification does have prognostic significance. Data obtained from pharmacy refill databases show that the 80% threshold predicts prognosis because it identifies primarily patients who discontinue treatment. Treatment discontinuation is highly associated with prognosis as discontinuation is often the consequence of a clinical event or results in an event. However, lesser degrees of non-adherence, short of discontinuation, have major implications from the early phases of drug development through the post-marketing phase. These gaps in adherence, largely undetected by the pre-electronic methods, can be the primary reason for a failed trial (as a result of a Type 2 error), and can result in an underestimate of the effectiveness of a drug at doses typically administered in Phase 2 trials leading to the selection of suboptimal, usually overestimated, dose regimens in Phase 3 trials. In clinical practice, unrecognized non-adherence may be interpreted as drug resistance and can

invalidate assessments of therapeutic and pharmaco-economic benefits.

In line with the original Academic Research Consortium mission, The NARC task force has developed a series of pragmatic consensus definitions and methodologies to classify, record, and account for non-adherence patterns in clinical trial settings. Consistent application of these definitions across cardiovascular clinical trials will result in a more reliable and more efficient estimates of the efficacy and effectiveness of drugs in regulatory and post-marketing settings. While this standardized classification and framework has been developed to capture, classify, and report any possible degree of medication non-adherence in clinical trials, protocol-specific adaptations based on expected outcomes of over- or under-exposure to study medication or depending on the pre-defined method(s) to capture adherence patterns in a specific clinical trial is warranted. For example, it is anticipated that reliable collection of Type 1 non-adherence pattern will require electronic monitoring systems to be in place during the study. In settings where the anticipated clinical consequences of Type 1 non-adherence are considered not to be relevant for the objectives of the study, Type 1 category may be omitted. On the other hand, Types 2 and 3 categories by definition expose patients to off-drug periods. As such, every effort should be made to capture these entities as here described irrespective of the availability of more sophisticated monitoring systems. A proposal on how these entities may be recorded in a standardized care report form is provided. This will still preserve cross comparability of adherence terms among different studies while allowing detection and characterization of more subtle non-adherence behaviours. In the same way, capturing the timing frame of non-adherence, as proposed in the Level 4 of the NARC classification, might not be relevant/applicable in all clinical trial settings.

Finally, consistent with the Academic Research Consortium charter, this process and the definitions provided rely heavily on consensus and integration of previously developed definitions, with adoption and adaptation. Continuous refinement of adherence endpoints and of their proposed categorization into a structured hierarchical classification is envisioned as a critical step in order to move from a consensus- to an evidence-based approach.

In conclusion, given the high prevalence of suboptimal adherence in clinical trials combined with its deleterious clinical and societal implications, we propose a continuous, hierarchical, and standardized classification and framework for reporting, collecting, and analysing medication non-adherence in clinical trials and provide a critical appraisal of methodologies for adherence collection in view of the newly proposed adherence endpoints.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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