Medication Adherence Measurement Methods in Registration Trials Supporting the Approval of New Medicines: A Cross-Sectional Analysis of Centralized Procedures in the European Union 2010–2020

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Medication adherence is a key factor impacting efficacy and safety of medicines, yet how it is dealt with in European registration trials is unknown. A cross-sectional analysis of European Medicines Agency (EMA) marketing authorization dossiers for new medicines approved through centralized procedures in the European Union between 2010 and 2020 was performed. Data were extracted from European Public Assessment Reports and Clinical Study Reports. Clinical trials covering five therapeutic areas were included: diabetes, respiratory conditions, cardiovascular diseases, infectious diseases, and oncology. Outcomes included adherence assessment, measurement methods, and rates. Overall, 102 medicines studied in 253 clinical trials were reviewed. All but one study reported measuring adherence. Two hundred twenty trials (87%) measured adherence using quantitative methods, while 32 (13%) trials monitored adherence but did not further quantify. Reported adherence rates were high (> 90%) across trials yet marked disparities in measurement methods and definitions were found. The most frequently used adherence measurement method was pill/dose count (single method: 52.7%; in combination: 37.7%; with patient diary/report: 17.3%; electronic methods: 1.4%; bioanalytical methods: 4.1%). Patient diary/report (6.4%) and electronic methods (2.7%) were also used as single methods. Electronic methods were more often used in respiratory and anti-infective trials, while bioanalytical methods were more frequently used in diabetes. Overall, adherence is measured in EMA registration trials, yet the methods used and the way in which adherence rates are presented vary widely between trials and therapeutic areas. To better understand and compare efficacy of medicines, standardization of adherence definitions and measurement methods is needed.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Medication adherence is a key factor impacting efficacy and safety of medicines. In daily practice, adherence to long-term therapies is around 50%, i.e., half of the patients do not take their medication as prescribed. While this issue is widely acknowledged and studied in the "real world," the extent to which nonadherence is assessed in clinical trials is less well known.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study aimed to assess how medication adherence is addressed in the main clinical trials supporting the registration of new medicines at the European Medicines Agency (EMA) between 2010 and 2020.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study showed that adherence is measured in most EMA registration trials, yet the methods used and the way in which adherence rates are presented vary widely between trials and therapeutic areas.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Standardization of adherence definitions and measurement methods in clinical registration trials can help better understanding and comparison of efficacy and safety of medicines.

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Adherence to medication is vital for pharmacologic interventions to be effective.[1] Adherence to medication is shortly defined by the World Health Organization (WHO) as "the extent to which the patient follows medical instructions" and involves initiation of therapy, implementation, and persistence with the recommended dosing.[2,3] According to the WHO, adherence to long-term therapies is around 50%, i.e., half of the patients do not take their medication as prescribed.[2] While this issue is widely acknowledged and studied in the "real world," the extent to which nonadherence is assessed in clinical trials is less well known. Generally, medication adherence is thought to be higher in clinical trials which is mostly due to the specific patient selection (strict inclusion criteria and exclusion of nonadherent patients during run-in phases) and the extra attention the patients receive; patients are more closely monitored, and the frequency of hospital visits is higher. However, even in strictly regulated clinical trials medication adherence can be suboptimal, resulting in both clinical and economic consequences, such as failure to show efficacy and less efficient and more costly trials.[5,6]

In the registration process of new medicines, regulators look in particular at the efficacy and safety of the medicine.[7] For a medicine to be registered and to attain marketing authorization, safety and efficacy must be demonstrated by the Marketing Authorization Holder in clinical registration studies. Inadequate assessment of adherence in these confirmatory registration trials can lead to multiple issues, such as inaccurate estimates of the efficacy, safety, and the benefit–risk balance of a medicine.[4,7] Notably, deviations in adherence could have negative regulatory as well as public health consequences.[2] Failure to measure adherence properly could potentially lead to higher sample sizes for studies, unnecessarily high dosages and therefore more adverse effects, underestimation, or failure to confirm the efficacy of the medicine and even emergence of drug resistance regarding antimicrobials.[4,5,8] To date, no studies have systematically assessed medication adherence in clinical registration trials for new medicines. Therefore, it is currently unclear to what extent medication adherence is measured in clinical trials and how accurately and consistently it is measured and calculated.

This study aims to provide an overview of medication adherence in clinical registration studies. In particular, we aimed to assess the extent to which adherence is measured, explore how it is measured, and ascertain the reported rates of adherence in the last decade's registration trials for new medicines in the European Union (EU).

METHODS

Study design

A cross-sectional analysis was performed of the initial marketing authorization dossiers for new medicines approved through centralized procedures in the EU between 2010 and 2020. The study protocol has been prepublished at the Open Science Framework (OSF) Registry https://archive.org/details/osf-registrations-jwcdu-v1.

Therapeutic area selection

The focus of the study was on five therapeutic areas and included diabetes Anatomical Therapeutic Chemical (ATC) codes: diabetes (A10), respiratory conditions (R03, R07), cardiovascular diseases (B01, C), infectious diseases (J04, J05), and oncology (L01, L02). These five areas were selected because each of them represents exemplar areas with specific challenges for adherence: no direct patient notable effect (diabetes), complex inhaled administration route (respiratory), often used in polypharmacy regimens (cardiovascular diseases), public health consequences due to disease spreading and risk of resistance (infectious diseases), and severe adverse effects (oncology).[2]

Data sources

Human medicines within the five therapeutic areas were identified and retrieved from the "table of all European Public Assessment Reports (EPARs) for human and veterinary medicines" available at the website of the European Medicines Agency (EMA).[9] Data extraction took place from three different sources: (i) the EMA webpage, (ii) the Dutch Medicines' Evaluation Board's (CBG-MEB) internal database (Information & Communication Infrastructure), and (iii) the EMA Common Repository (internal database) (**Figure 1**).

Inclusion and exclusion criteria

Self-administered medicines across the five therapeutic areas with an indicated use period of at least 3 months to lifelong were included, given medication adherence issues are most frequently observed in long-term therapies for chronic diseases. Medicines intended for single administration with an intended duration of use shorter than 3 months were excluded. Intravenously administered medicines were excluded as these are administered in the hospital setting by healthcare professionals and therefore are not relevant for the study topic of patients' medication adherence in clinical trials. Only trials lasting at least 3 months were included. Oncology products have special features regarding the duration of treatment in the clinical trials as most cancer treatments should be continued until the disease progression ceases or as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity, i.e., there is no predefined trial treatment duration. Therefore, trials regarding oncology products that have a mean duration of treatment of at least 3 months will be included.

Medicines with a complete and independent Marketing Authorization Application referring to Article 8.3 of Directive 2001/83/EC resulting in marketing approval retrieved from EPARs were included. Biosimilars and generic medicines were excluded because applications for these types of medicines are mainly based on the originator product dossier. In case of combination products with several active substances, only medicines with at least one new active substance with a complete dossier were included. Medicines with a new administration route or significant therapeutic innovation were included as these are factors affecting medication adherence. Furthermore, duplicate dossiers of the same active substance were treated as one.

Data collection procedures

Data were extracted from EPARs available from the EMA's website and internal clinical trial reports (i.e., Common Technical Document, module 5, Clinical Study Reports) using keyword searches (versions of *main studies*, *pivotal*, *key efficacy studies*, *adherence*, *compliance*, and *accountability*) and reviewing specific sections of the documents (**Figure 1**) in order to ensure that all relevant information was collected. All main clinical studies supporting the Marketing Authorization Applications were selected, and medication adherence–related information was retrieved from the EPARs. Additional and more detailed information was extracted from the Common Technical Documents.

Characteristics about the medicine include therapeutic area, route of administration, and dosing regimen. For dosing regimen, the primary dosing regimen for the investigational product was used as the basis for characterization.

Data extraction on adherence information in main clinical studies was done in three tiers. First, it was assessed whether adherence was measured or not. Some studies reported that adherence was monitored

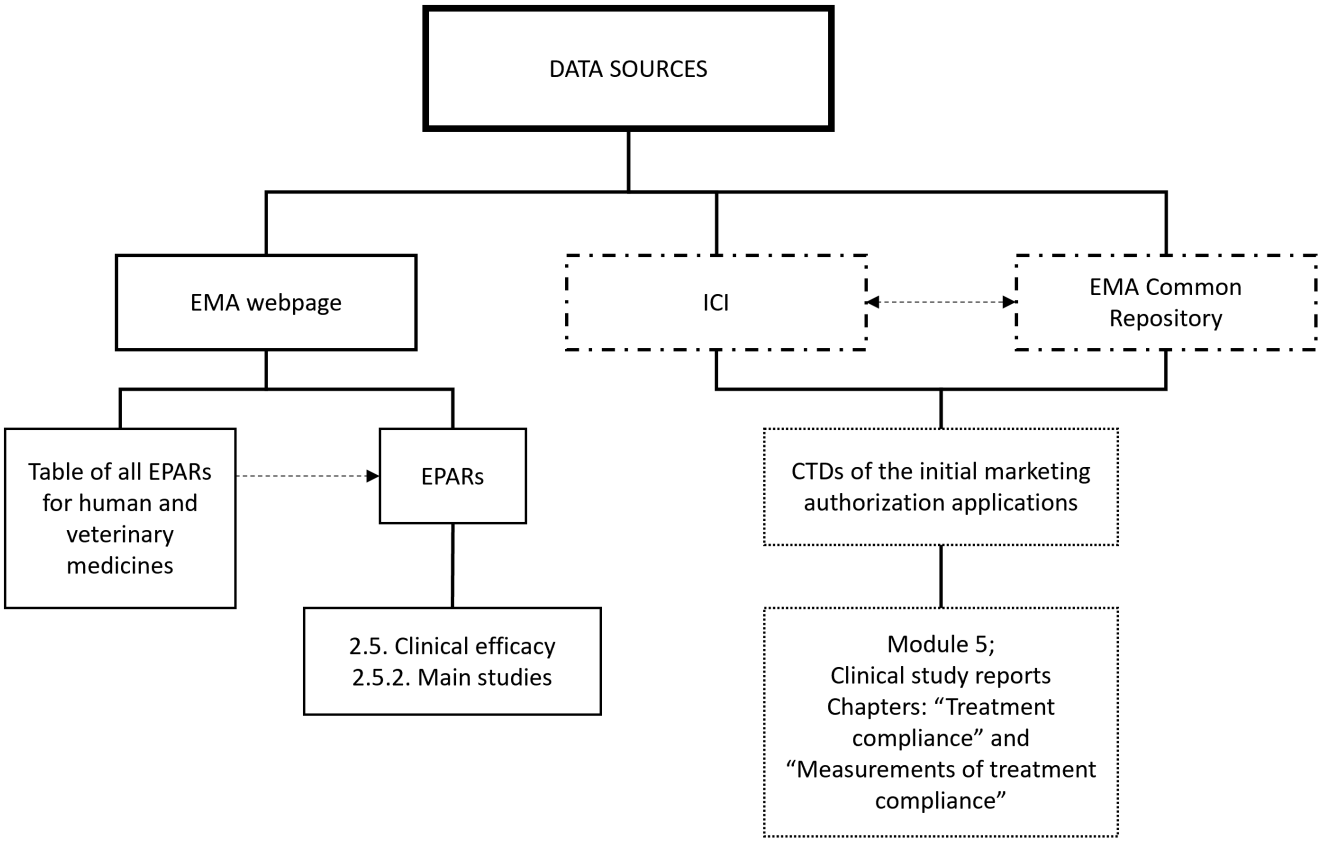

Figure 1 Data sources. CTDs, Common Technical Documents; EMA, European Medicines Agency; EPARs: European public assessment reports; ICI, Information & Communication Infrastructure.

but was not further analyzed and specific data was not provided; this was categorized as "adherence measured but not further quantified." Second, if adherence was measured, the method used for measuring adherence was collected (i.e., pill/dose count, patient diary/report, electronic methods, bioanalytical methods, questionnaire, or other methods). Multiple adherence measurement methods could be used. Third, information about how adherence was defined and reported was collected (descriptive summary statistics, adherence categories, no rates presented). Finally, adherence rates for all studies providing descriptive summary statistics were collected.

Extracted data was collected by one researcher (K.M.M.) and entered in a Microsoft Excel 365 database. For the entered data, regular quality checks with the study team were performed. These checks included consistency, completeness, and uniqueness of the data. Inconsistencies were settled by agreement with other researchers (A.M.G.P., C.E.H., P.G.M.M., J.F.M.v.B.).

Study outcomes

Study outcomes included (i) the percentage of clinical trials where medication adherence was measured, (ii) the method(s) used for measuring adherence, and (iii) the rates of adherence.

Data analysis

The frequency of trials measuring adherence was reported in absolute numbers and percentages for the full study sample and stratified by year of approval, by therapeutic area (diabetes, respiratory conditions, cardiovascular diseases, infectious diseases, and oncology), by route of administration (oral, injection, and inhalation) and by primary dosing regimen (once daily, twice daily, multiple times daily, once weekly, and twice monthly). For the subset of trials measuring adherence, we reported on how frequently different methods were used for measuring adherence (pill/dose count, patient diary/report, electronic methods, bioanalytical methods, questionnaire, or other methods) again in absolute numbers and percentages for all trials and stratified by therapeutic area, by route of administration, and by dosing regimen. Finally, we reported overall adherence rate as the crude pooled mean adherence rates in the subset of trials that reported adherence rate as descriptive summary statistics. Adherence rates were stratified by therapeutic area.

RESULTS

Identification of product characteristics

Of all 862 human medicines authorized between 2010 and 2020, 760 medicines (88%) were excluded based on the exclusion criteria (mainly based on ineligible ATC class, $N = 737$). Finally, 102 medicines were included in the study sample (**Figure 2**). These 102 medicines were assessed in 272 main clinical studies of which 253 (93%) were included based on the inclusion criteria and 19 were excluded. The reason for exclusion of these 19 trials was that the study duration was < 3 months and/or administration at the hospital ($n = 13$) or that the study report was not found ($n = 6$).

Oncology medicines were the largest therapeutic group included (43.1%), however the proportion of clinical trials was only less than a quarter (22.1%). The largest number of clinical trials

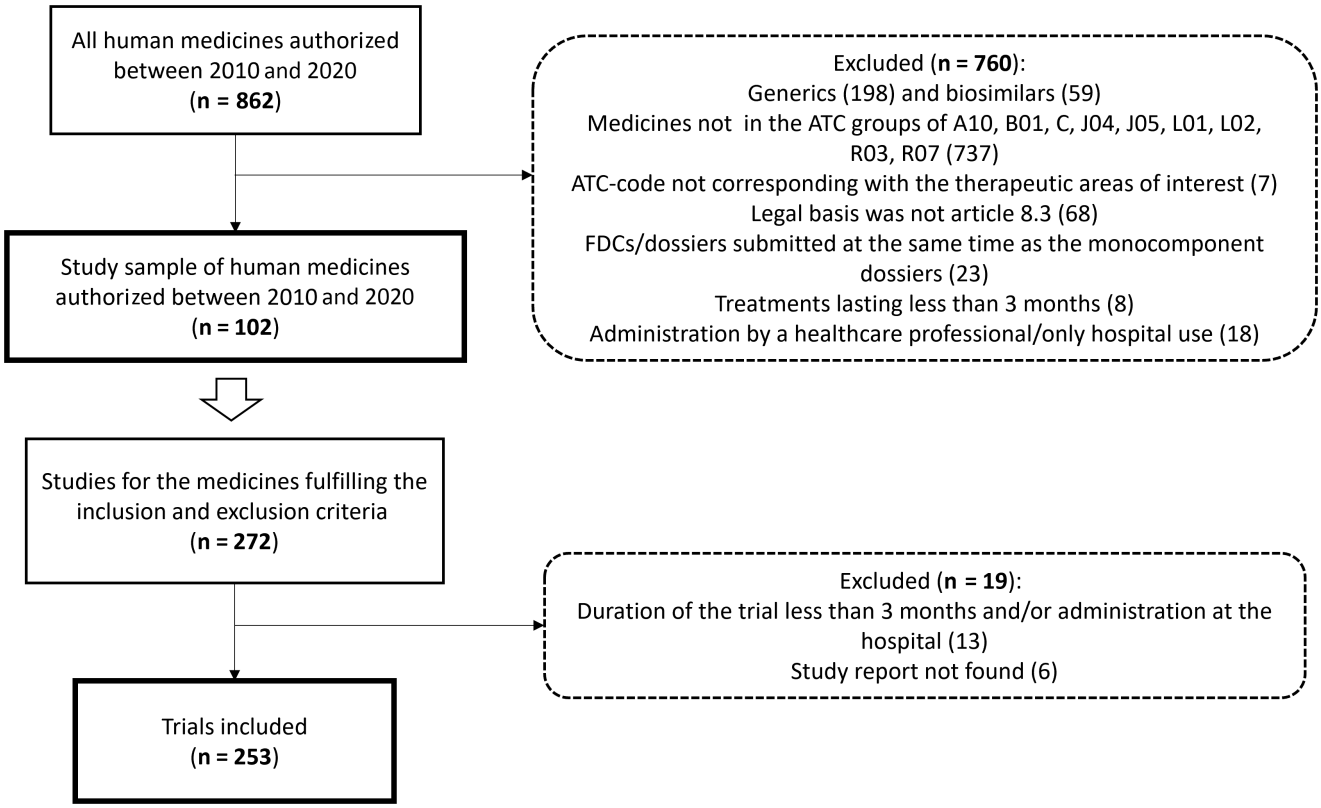

Figure 2 Flowchart of the data selection, description of inclusion/exclusion of medicines/trials. ATC, Anatomical Therapeutic Chemical; FDCs, Fixed Dose Combination Medicines.

Table 1 Overview of product characteristics of included medicines and trials

	Medicines		Trials	
Product characteristics	***n* = 102**	**%**	***n* = 253**	**%**
Therapeutic area and ATC groups				
Diabetes (A10)	16	15.7	90	35.6
Respiratory (R03, R07)	9	8.8	23	9.1
Cardiovascular system (B01, C)	12	11.8	35	13.8
Anti-infectives (J04, J05)	19	18.6	49	19.4
Oncology (L01, L02)	46	43.1	56	22.1
Route of administration				
Oral	87	85.3	175	69.2
Injection	11	10.8	63	24.9
Inhalation	4	3.9	15	5.9
Dose regimen				
Once daily	65	63.7	160	63.2
Twice daily	26	25.5	40	15.8
Multiple times daily	4	3.9	12	4.7
Once weekly	5	4.9	24	9.5
Once monthly	—	—	1	0.4
Twice monthly	2	2.0	16	6.3

ATC, Anatomical Therapeutic Chemical; —, None identified.

were within the diabetes domain (35.6%). The absolute majority of the medicines were orally administered (85.3%), and the most commonly used dosing regimen was once-daily dosing (63.7%). Table 1 presents an overview of the characteristics of all medicines and trials that were included. A full overview of all individual trials and additional study characteristics are provided in **Supplemental Material S1** (Excel document) and **Supplemental Material S2 (Table S2)**, respectively.

Trials

Adherence was measured in almost all trials (> 99%) throughout the study period and there was no clear pattern detected over time (from 2010 to 2020, **Supplemental Material S2**, Table S1 and Figure S1). Of the 253 trials included, 220 trials (87%) measured adherence, while 32 trials (13%) mentioned monitoring adherence but did not further quantify. Trials that did not perform formal adherence measurements shared common features; i.e., the majority of them were injectable medicines (n = 22 of 32), and the trials were mostly for diabetes, oncology, and cardiovascular medicines. Only one trial (0.4%) did not provide any information about adherence (**Supplemental Material S1**, trial No. 253).

Type of method for measuring medication adherence

Adherence measurement methods varied across trials (Figure 3). The most frequently applied method was pill/dose count, which was used in 116 trials (52.7%) as a single method, and in combination with other methods in 83 trials (37.7%). Other methods used as single methods were patient diary/report (6.4%) and electronic methods (2.7%; Table 2). Pill/dose count was used in combination with a variety of "other" methods, including telephone calls (n = 1, 0.9%), and combination of more than one method e.g., patient diary/report + documented conversation/questioning with the patient at the visits (1.8%; Table 2, and **Supplemental Material S2**, Table S3).

Trials that did not further quantify or perform formal adherence measurements (n = 32) and did not collect or analyze the adherence data further used a variety of different methods compared with methods used in trials which formally measured adherence. These methods included reviewing patients' glycemic control, inspecting information provided by the participant of investigational product (IP) administration, and examining further "information deemed important by the Investigators" (**Supplemental Material S1**, trial Nos. 222–253).

Impact of therapeutic area, route of administration, and dose regimen on measuring adherence

Adherence was measured in all five therapeutic areas, the most prominent method being pill/dose count (Table 2). In diabetes, 15 trials (16.7%) assessed adherence but did not use quantitative adherence measures and did not perform further analysis of treatment adherence (**Supplemental Material S1**, trial No. 232–246). All but one of these concerned injectable insulins. Compared with other therapeutic areas, bioanalytical methods (blood/plasma concentration) were slightly more prevalent in trials concerning diabetes (10.7% of 75 trials; **Supplemental Material S1**, trial Nos. 1–2, 162, 197, 203–204, 206, and 208).

Within the respiratory area, dose count was used in 19 trials (82.6% of 23) as a single primary method. Dose count of the inhalation medicines was conducted by either reviewing the dose counter (n = 13; **Supplemental Material S1**, trial Nos. 14–18, 28, and 142–148) or counting capsules of the inhalers (n = 2; **Supplemental Material S1**, trial Nos. 149–150). Electronic methods (e.g., eDiary) were used in three trials (13%) in combination with dose count (**Supplemental Material S1**, trial Nos. 28, 149–150).

The majority of anti-infective trials measured adherence using quantitative measures (98%, n = 48). Electronic methods were used in six trials (12.5%; **Supplemental Material S1**, trial Nos. 99–104). This electronic method was a Medication Event Monitoring System (MEMS) cap attached to a medicine container. MEMS involves an electronic monitor providing information about participant's adherence to medication, achieved by recording the time and date on every occasion that a bottle is opened.[13] Furthermore, anti-infectives were the only therapeutic area where questionnaires (Modified Medication Adherence Self-Report Inventory Questionnaire (M-MASRI), Visual Analog Scale Adherence Questionnaire) were used to assess adherence (**Supplemental Material S1**, trial Nos. 71, 184–185).

Within the oncology trials, 46 (82%) trials measured adherence, while 9 (16%) trials did not provide formal adherence measures. The one trial that did not provide any information about adherence belonged to the oncology group (**Supplemental Material S1**, trial No. 221).

Medication adherence rates

The way of reporting adherence rates in the registration trials varied and was not provided for all the 220 trials that measured adherence (**Supplemental Material S1**). Adherence rates were mainly described as summary statistics, used in 131 trials (60%), providing the mean (minimum, maximum) rates of adherence per treatment arm and/or for the whole trial population. Alternatively, adherence categories were used in 34 trials (15%) showing the division of participants into a variety of predefined classes, for instance the percentage of patients that were > 80% adherent. These adherence categories were not analyzed further in this study as comparison between such categories and different trials was not feasible. Depending on the trial, adherence rates were presented only for the Investigational Product (IP) and/or for the overall study sample. Rates and/or categories were unreported in 55 (25%) trials. Trials that did not quantify adherence further (n = 32) provided no adherence rates.

Despite differences in definitions, the average adherence was high, i.e, over 96% both overall and for each therapeutic group (Table 3). However, while mean rates of adherence were high throughout the study sample, the minimum and maximum rates in individual trials showed marked variation. For example, variation was observed in the way of defining maximum adherence rates. Notably, in 55 trials it was defined that if the calculated adherence rate was > 100%, the rate was capped at 100% (**Supplemental Material S1**). In the rest of the trials, the maximum adherence rates in individual trials were over 100%, and the highest maximum rate observed was 4,500%. Rates over 100% are possible where

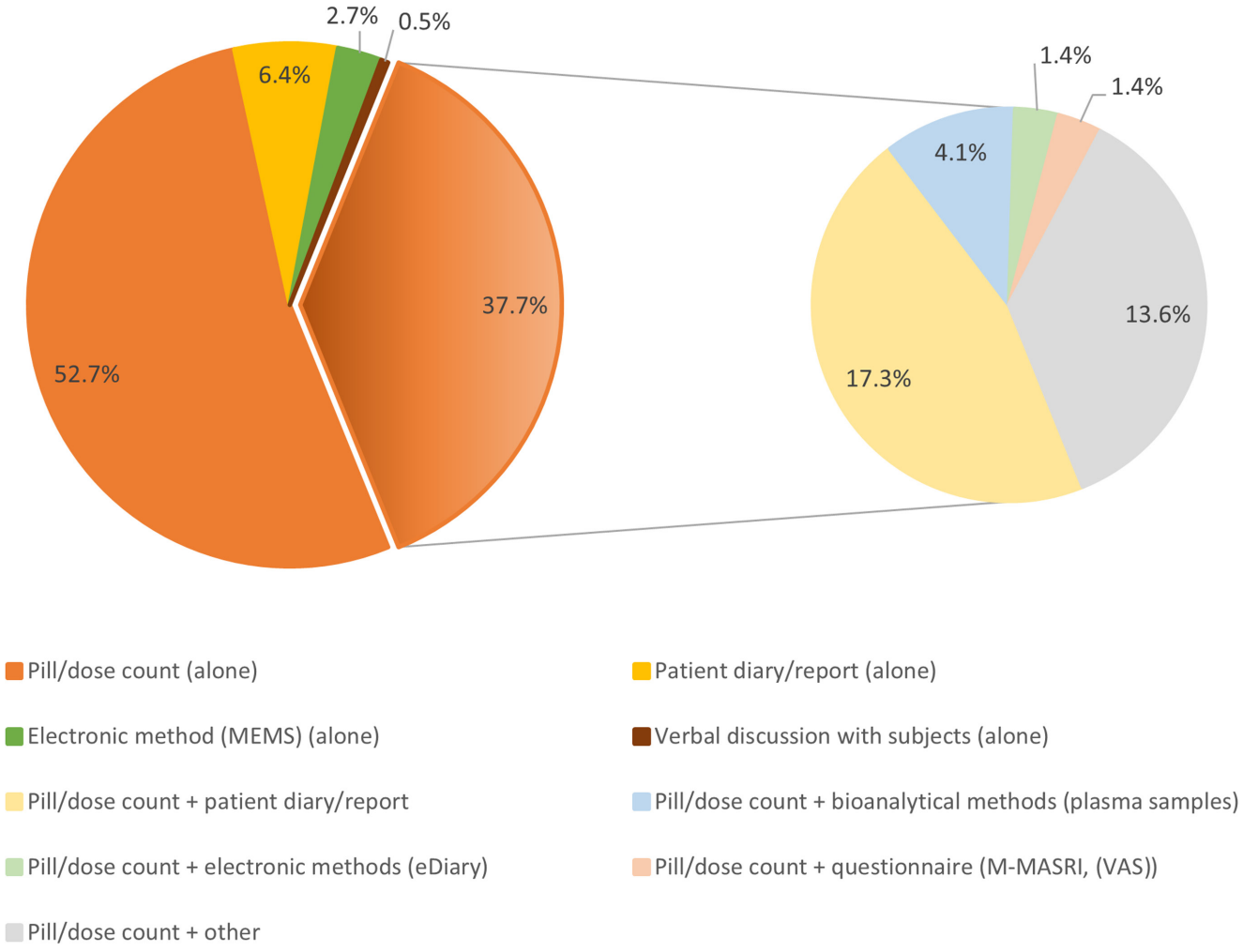

Figure 3 Adherence measurement methods used in trials that had adherence quantitatively measured (n = 220). Pill/dose count was the most prominent method used (orange: as a single method, gradient orange: in combination with a variety of other methods). Electronic methods (MEMS) and patient diary/report were used as single methods a in small number of trials. Pill/dose count + other, see **Supplemental Material S2**. M-MASRI, Modified Medication Adherence Self-Report Inventory Questionnaire; MEMS, Medication Event Monitoring System; VAS, visual analog scale.

the assumption is that all unreturned trial medicines have been ingested. The minimum rates observed varied from 0% to > 90% between individual trials.

DISCUSSION

The purpose of this study was to explore the extent to which medication adherence is measured in clinical registration trials in Europe. This study shows that adherence was measured or monitored in over 99% of the eligible registration trials submitted to the EMA in the last decade. In general, the reported adherence rates were high (> 90%) throughout the study sample; however, marked differences in adherence measurement methods and definitions were found. The most frequently used method was pill/dose count used as a single method (53%) or in combination with other methods (38%). Differences between therapeutic groups were found regarding adherence measurement methods; for example, electronic methods were used in respiratory and anti-infective trials, while bioanalytical methods were more prevalent in those concerning diabetes.

Although not systematically reviewed previously, medication adherence rates in clinical trials are known to be higher than in the "real world," where it averages only around 50%.[2,10] However, note that this number is largely driven by noninitiation and nonpersistence (two issues more common in the real world) and less by the implementation construct of medication adherence.[3] Generally, it is considered that an adherence rate higher than 80% represents appropriate medication adherence, yet this is not supported by firm evidence across disease areas.[11] Furthermore, this adherence cutoff changes per medicine and highly depends on the underlying disease, the medicine's potency, and its pharmacokinetic profile.[11,12] There is no clinically defined threshold for medication adherence that could be universally applied to all medicines across all therapeutic areas.[12,13] For instance, adherence to HIV medication should preferably be ≥ 95% for efficient treatment outcome.[14,15] Clinical trials usually predefine a limit for an acceptable rate of adherence, which varies between trials.[11] The high adherence rates in the registration trials may have multiple explanations: first, patients that provide consent to participate in clinical trials

Table 2 An overview of the percentages of trials measuring adherence by therapeutic area, route of administration, and dose regimen

		Therapeutic area					Route of administration			Dose regimen					
	Total	Diabetes	Respiratory	Cardiovascular	Anti-infectives	Oncology	Oral	Injection	Inhalation	Once daily	Twice daily	Multiple times daily	Once weekly	Once monthly	Twice monthly
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Adherence measured (*n* = 253)															
Adherence was measured in the trials	220 (87)	75 (83.3)	23 (100)	28 (80)	48 (98)	46 (82.1)	164 (93.7)	41 (65.1)	15 (100)	142 (88.8)	38 (95)	7 (58.3)	23 (95.8)	—	10 (62.5)
Adherence measured but not quantified further	32 (12.6)	15 (16.7)	—	7 (20)	1 (2)	9 (16.1)	10 (5.7)	22 (34.9)	—	17 (10.6)	2 (5)	5 (41.7)	1 (4.2)	1 (100)	6 (37.5)
Adherence measures not reported	1 (0.4)	—	—	—	—	1 (1.8)	1 (0.6)	—	—	1 (0.6)	—	—	—	—	—
Methods for measuring adherence (*n* = 220)															
Pill/dose count	116 (52.7)	41 (54.7)	19 (82.6)	13 (46.4)	25 (52.1)	18 (39.1)	91 (55.5)	13 (31.7)	12 (80.0)	88 (62.0)	15 (39.5)	—	13 (56.5)	—	—
Patient diary/ report	14 (6.4)	6 (8.0)	—	—	3 (6.3)	5 (10.9)	13 (7.9)	1 (2.4)	—	12 (8.5)	2 (5.3)	—	—	—	—
Electronic method (MEMS)	6 (2.7)	—	—	—	6 (12.5)	—	6 (3.7)	—	—	—	6 (15.8)	—	—	—	—
Verbal discussion with participants	1 (0.5)	—	—	—	—	1 (2.2)	1 (0.6)	—	—	1 (0.7)	—	—	—	—	—
Pill/dose count+patient diary/report	38 (17.3)	10 (13.3)	—	10 (35.7)	5 (10.4)	13 (28.3)	17 (10.4)	21 (51.2)	—	14 (9.9)	9 (23.7)	3 (42.9)	4 (17.4)	—	10 (100)
Pill/dose count+ bioanalytical methods	9 (4.1)	8 (10.7)	—	—	—	1 (2.2)	5 (3.0)	4 (9.8)	—	5 (3.5)	—	—	4 (17.4)	—	—
Pill/dose count+ electronic methods (eDiary)	3 (1.4)	—	3 (13.0)	—	—	—	—	—	3 (20.0)	—	1 (2.6)	—	—	—	—
Pill/dose count+ questionnaire (M-MASRI, [VAS])	3 (1.4)	—	—	—	3 (6.3)	—	3 (1.8)	—	—	3 (2.1)	—	—	—	—	—
Other[a]	30 (13.6)	10 (13.3)	1 (4.3)	5 (17.9)	6 (12.5)	8 (17.4)	28 (17.1)	2 (4.9)	—	19 (13.4)	5 (13.2)	4 (57.1)	2 (8.7)	—	—

MEMS, Medication Event Monitoring System; M-MASRI, Modified Medication Adherence Self-Report Inventory Questionnaire; VAS, Visual Analog Scale; —, None identified.
[a]Specified in **Supplemental Material**; **Table S3**.

Table 3 Calculated average adherence rates (mean, SD, min, and max)

	Overall adherence rate (%) (main phase)			Overall adherence rate (%) (extension phase)			Adherence rate for placebo (%)			Adherence rate for IP (%) (all arms)		
	n	Mean (SD)	Min, max	*n*	Mean (SD)	Min, max	*n*	Mean (SD)	Min, max	*n*	Mean (SD)	Min, max
All trials that provided adherence rates	125	97.40 (2.80)	84.54, 109.9	10	93.32 (3.15)	89, 98.1	65	97.87 (2.59)	90.15, 107.1	129	97.35 (3.47)	78.09, 111.3
Therapeutic area												
Diabetes	34	97.89 (1.27)	93.41, 100.06	5	94.94 (1.55)	94.07, 97.69	22	98.08 (1.86)	92.75, 101.10	37	97.71 (1.44)	93.49, 101.54
Respiratory	23	97.62 (2.19)	92.7, 99.73	2	90.1 (0.22)	89.94, 90.25	18	97.11 (3.02)	90.42, 100.30	23	97.78 (1.84)	92.6, 100.2
CVD	21	98.18 (1.85)	93, 102	1	98.1	NA	11	97.71 (0.92)	95.95, 99.16	21	98.27 (4.06)	89.3, 114.9
Anti-infectives	35	96.48 (2.89)	90.65, 100.1	1	91.2	NA	5	97.97 (2.13)	94.95, 99.8	35	96.91 (3.86)	78.09, 100.72
Oncology	12	96.93 (6.06)	84.54, 109.9	1	89	NA	9	99.04 (4.33)	90.15, 107.1	13	94.70 (7.71)	78.94, 111.3

Calculated average adherence rates (mean, SD, min, max), overall and by therapeutic area, for the 131 trials that presented adherence rates using summary statistics (i.e., excluding adherence categories).
n = number of trials that presented the rate by using descriptive statistics (mean, min, max).
CVD, cardiovascular disease; IP, investigational product; max, maximum; min, minimum; SD, standard deviation.

may be more intrinsically motivated to adhere to their treatments. Second, the trial inclusion criteria prevent patients being nonadherent in run-in periods being randomized. Third, during a trial, patients are frequently monitored and guided, resulting in higher commitment. Last but not least, the measurement method most commonly applied in clinical trials, i.e., pill count, can lead to an overestimation of actual adherence.

Regarding the measurement method of adherence, marked variations in methods and definitions were observed. Notably, for clinical trials there is no "gold standard" for measuring adherence, nor guidance on specific methods that should be used, and therefore a multimeasure approach might currently be the most appropriate way to capture medication adherence.[6,16] Of note, a single method cannot cover all aspects of adherence. Pill count cannot verify that a patient actually took the medicine and bioanalytical assays cannot determine if a patient has taken the medicine only just before the trial visit (a phenomenon known as "white coat adherence") or continuously.[16,17] The frequent use of pill counts is a legacy from the drug accountability process but is no accurate method. Pill count has higher accuracy than even more subjective measures (i.e., patient self-report), yet it only provides an average proxy measure for intake between trial visits, i.e., it does not create a granular medication-taking pattern like more objective measures such as electronic methods do.[15,16,18] Overestimation of adherence is especially linked to measurement strategies that are subjective and prone to recall bias, for example, patient diaries or questionnaires.[15] Despite this issue of overestimation, patient self-reporting was still used as a single method in 6.4% of the trials assessed in this study. Of note, poor or subjective measurement of adherence in phase III clinical trials, e.g., by pill count or diary, could lead to misinterpretation of the efficacy–safety balance ranging from an underestimation of adverse effects to failure to confirm the efficacy of a new medicine.[4] With more objective and granular adherence measures in place, patients showing suboptimal adherence (being it too poor or too high) could be more easily identified and accounted for in analyses and/or interpretation of overall results.

Although pill/dose count was the most prominent adherence measurement method across all therapeutic groups, some therapeutic area-specific differences were found. For instance, in the anti-infective and respiratory trials, electronic methods were used, whereas bioanalytical methods were more applied in diabetes trials. However, the proportion of these more objective and innovative methods was still relatively small (10–15%) compared with pill/dose count. The efficacy of treatments for infectious diseases is highly dependent on medication adherence and, moreover, nonadherence can cause resistance to the antibiotic. This can explain why electronic methods were more used in this area.[14] Indeed, electronic measures are a much more accurate way to capture and measure adherence than pill count, as it records time and date of each time a bottle was opened and closed, creating dosing histories.[15,19] Electronic monitoring methods provide a reliable and validated drug-dosing history, and the accuracy is 97% compared with pill counts (60%) and self-reporting (27%).[15,17,19]

A study assessing medication adherence of oral oncology medicines in clinical pivotal trials showed that adherence was poorly reported in publications, i.e., adherence was not reported in 33.9%

of the trials published in scientific journals.[20] However, while not being reported in manuscripts, it may still have been measured and reported only in registration dossiers as part of drug accountability. To our knowledge, our study is the first to systematically assess how medication adherence is addressed in registration trials of new medicines using formal registration dossiers. We had access to EMA databases and could thus compile a detailed and comprehensive overview of all relevant registration trials of the last decade. Still, a limitation is the fact that the study sample was limited to only five therapeutic areas. These five chronic conditions comprise, however, a representative set of clinical areas with variable medicine administration routes and dosing regimens. The data sources provided detailed information on all registration trials, and only six trial reports were missing and therefore excluded from the analyses, although we believe it unlikely to have influenced the analysis and results.

Given the differences in measurement methods and definitions of adherence between trials, more guidance could be recommended to allow better comparison and interpretation of drug efficacy and safety across trials and medicines. Current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines (E8, E6(R2), and E9) indicate that adherence should be evaluated, specified, documented in clinical trials, and accounted for in the analysis; however, the way in which adherence should be measured and defined is not included in these guidelines.[21–23] This leaves room for deliberate interpretation and variation in medication adherence measurement in clinical trials. Further specification of measuring adherence, using objective and granular methods where feasible, could improve trial efficiency and allow for better informed decisions on the efficacy–safety balance of new medicines. In addition, information regarding medication adherence in the study reports should be more transparent and made more available. To aid better reporting of adherence measures, increased use of the recently developed EMERGE (European Society for Patient Adherence, Compliance, and Persistence (ESPACOMP) Medication Adherence Reporting Guideline) guidelines is recommended.[24]

CONCLUSIONS

Although medication adherence is measured in over 99% of EMA registration trials, marked variation in the ways of measuring and reporting adherence between trials was detected. Given there is currently no standard guideline on adherence assessment in clinical trials available, multimeasurement methods are suggested in order to effectively capture medication adherence and better enable assessment of efficacy, safety, and risk–benefit. Looking forward, standardization of definitions and measurement methods is recommended.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The institute of Job van Boven (J.F.M.v.B.), i.e., the Medication Adherence Expertise Center of the Northern Netherlands (MAECON) based at the University Medical Center Groningen, has received funding from various companies to study medication adherence management tools. Christine Erikstrup Hallgreen (C.E.H.) is employed by the University of Copenhagen at the Copenhagen Centre for Regulatory Science (CORS). CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, LEO pharma) as well as patient organizations (Rare Diseases Denmark). The centre is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus, and the research is not company-specific product or directly company related. Katerina Maria Mantila (K.M.M.) was during the study period, from February 2021 to August 2021, a master's thesis student at the University of Copenhagen at the CORS, with an internship at the Dutch Medicines Evaluation Board (CBG-MEB)/University of Medical Centre Groningen (UMCG). Since February 2022, K.M.M. has been working at PharmaLex. PharmaLex was not involved in any aspects of this study. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

K.M.M., A.M.G.P., C.E.H., P.G.M.M., and J.F.M.v.B. wrote the manuscript. J.F.M.v.B., A.M.G.P., C.E.H., and P.G.M.M. designed the research. K.M.M. performed the research. K.M.M. analyzed the data.

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