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Estimation of adherence to medication treatment in presence of censoring

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Aims: The purpose of this study is to provide a theoretical framework for the analysis of medication adherence based on longitudinal data from electronic medication monitors and to suggest methods for unbiased estimation of the effect of time and covariates on adherence.

Methods: After defining the statistical summaries involved in adherence analyses and the assumptions necessary for their estimation, we address the issue of bias encountered when adherence is estimated on censored data. We suggest 2 unbiased methods to estimate adherence: (i) indirect combining implementation and persistence; and (ii) based on weights, allowing estimation of the effect of time and covariates on adherence via generalized estimating equations models.

Results: We applied the proposed methods to investigate the effect of sex on adherence in a sample of 43 oncology patients followed 1 year. Implementation was higher for men than for women at baseline (98.8 *vs*. 97.5%, odds ratio [OR] 2.08, 95% confidence interval [CI]: 1.00–4.35), whereas the relationship was reversed at 1 year (94.5 *vs*. 96.4%, OR 0.65, 95%CI: 0.28–1.52). Adherence declined faster in men, with year-end values of 46.3% for men and 92.2% for women (OR 0.07, 95%CI: 0.02–0.26).

Conclusion: Estimation of adherence is a complex statistical issue with longitudinal and duration data, possibly censored, interleaving. This study provides a theoretical framework and suggests methods for unbiased estimation of adherence as a function of time and covariates. This allows the effect of an intervention to be estimated in clinical trials, and helps healthcare providers reframe adherence programmes to address covariates such as sex.

KEYWORDS
censoring, electronic monitors, generalized estimating equations models, implementation, longitudinal data, medication adherence, persistence, pharmionics, survival analysis

1 | INTRODUCTION

A correct medication intake is an important prerequisite for the effectiveness of a treatment. Pharmionics is the biopharmaceutical subdiscipline studying how well or poorly patients actually use prescribed medicines.[1] This topic is 1 of many aspects of drug therapy that has been largely neglected for long. One of the main reasons was the poor state of available methods for compiling and analysing medication

histories in ambulatory patients. In recent years, medication event monitoring systems (MEMS Adherence Hardware and Software, Aardex Group) have been developed that are capable of recording the daily medication intake of a sample of patients over time.[2] MEMS monitors are electronic pillboxes that record the date and timing of each opening. The compiled number of daily openings, considered a good approximation of the number of pills actually taken on a given day, is compared with the prescribed regimen to obtain a daily assessment of the patient dosing history.[3–7] In general, a correct dosing at a given day is defined when the number of drug intakes is at least equal to the number prescribed on that day, resulting in a binary longitudinal variable (dosing, correct/incorrect). By summarizing over all patients this binary longitudinal variable, one can obtain an estimate of *adherence* to a given drug as a function of time.

In a population having started a treatment, adherence is a concept combining 2 separate dimensions[8]: (i) patient *persistence* to the treatment, i.e. a summary of the length of time patients continue to take the drug; and (ii) patient *implementation* of the treatment, i.e. a longitudinal summary of the individual dosing (correct/incorrect) among patients still under medication (persistent) at each date. For example, a patient having initiated a treatment, and who is supposed to take a pill twice a day for 3 months may show very good implementation by not missing any pill for 2 months and then decide to stop the medication by discontinuing the treatment that day. A second patient with the same prescription may show fluctuating behaviour, missing 1 or 2 pills on some days, but persisting on the medication until the end of the prescription. Persistence and implementation summarize these 2 aspects of the individual behaviour in a patient, the former describing the length of time until discontinuation of treatment, and the latter the quality of medication intake during that time.

Discontinuation of treatment is generally defined as the patient's unilateral decision to stop treatment prematurely. Although this definition is fairly straightforward for many long-term conditions such as hypertension or diabetes, it is less obvious for cancer treatments, where treatments are often stopped and sometimes resumed. Thus, while discontinuation is sometimes entirely the patient's decision, the decision to discontinue cancer treatment may also be shared between the oncology team and the patient. From a statistical point of view, persistence is a notion related to a duration variable, the time until discontinuation. More precisely, it is defined as the distribution of this duration variable, i.e. the probability of being still under treatment at each follow-up time. When estimating such a function, one should be aware of the possible presence of censoring. In this context, a censoring time can be represented by an interruption in follow-up that is not (or not necessarily) due to a cessation of treatment. The patient is lost on a certain day, e.g. they move to another city or decide to interrupt the MEMS monitor, so that it is impossible to know whether they continue to take the treatment (no information on persistence), regularly or not (no information on implementation), from that day on. But censoring may also be due to medical, prescriptive reasons, such as a planned switch to another medication or treatment strategy (e.g. surgery) or a drug interruption due to treatment failure or toxicity.[9] Classical survival analysis techniques, such as the Kaplan–Meier survival estimate, can be applied to estimate the distribution of the time to discontinuation in presence of censoring.[10–12] By contrast, implementation is a notion related to a binary outcome (correct/incorrect dosing) measured repeatedly over time (e.g. each day) until discontinuation of a patient.[13] Since implementation is defined at a given day among persistent patients, the presence of censoring has no impact on its estimation (at least under given assumptions). On the contrary, censoring can become a problem when both dimensions are summarized in the concept of adherence, which is defined at each day as the probability of a correct dosing among *all* subjects initially enrolled into the study (i.e. including subjects discontinuing before a given time).

The purpose of this paper is 2-fold. Firstly, we wanted to provide a theoretical framework for the numerous adherence analyses in the field of pharmionics, with an accurate definition of the quantities studied, their estimation on MEMS data, and the assumptions supporting this estimation. Secondly, we aimed to address the specific issue of the bias encountered in the presence of censoring when adherence is estimated empirically from the data. We present here a simple way to correct such a bias by combining estimates of persistence and implementation,[9,14] and also provide a new method based on weighting each observation, that allows modelling of adherence as a function of time and potential covariates. In particular, this methodology will make it possible to estimate and test the effect of an

What is already know about this subject

- Adherence analyses based on longitudinal data have been conducted since the new ABC taxonomy in the 2010s defining persistence, implementation and adherence. The most recent of these analyses adopted generalized estimating equations (GEE) modelling to estimate the pattern of implementation over time and to compare trends in different population groups. In its current state, the topic still required the definition of a theoretical framework and the development of a method for unbiased estimation of adherence via GEE models.

What this study adds

- The present study provides a theoretical framework for adherence analyses by specifying the 2 independence assumptions underlying the estimation of adherence quantities. This study also suggests a method based on a system of weights that allows unbiased estimation of adherence as a function of time and possible covariates via GEE modelling. The proposed method will facilitate the comparison of adherence between population groups, for example in adherence clinical trials.

intervention on adherence patterns over time in adherence observational and interventional studies, which has so far been virtually impossible.[15–18] Methods presented in this paper are illustrated on data from a routine care medication adherence programme using MEMS monitors to estimate the 12-month persistence, implementation and adherence to oral anticancer medications[9] (OAMs).

2 | METHODS

2.1 | Notation, definitions and assumptions

Let $(A_t)_{t\geq 1}$ be the time-dependent binary variables defining the daily dosing (correct/incorrect) of a patient during the monitored period: $A_t = 1$ if the patient takes at least *all* the prescribed doses on day t (e.g. ≥1 for a once-a-day regimen, ≥2 for twice-a-day regimen), and $A_t = 0$ otherwise. Let T and C be the random variables defining the time until discontinuation and the time until censoring, respectively. If $T \leq C$, a discontinuation is observed (event); if $C < T$, a censoring is observed. The longitudinal binary variables $(A_t)_{t\geq 1}$ are related to the time variables T and C in the following way: if a duration for a given patient ends with a discontinuation ($T \leq C$), their dosing will be incorrect ($A_t = 0$) for all $t \geq T$ by definition; if for a patient the duration is censored ($C < T$), their dosing will be missing for all $t \geq C$.

We can now define the following summaries. *Persistence* at time t, $p(t)$, is defined as the probability of a discontinuation time larger than t (probability that a patient is still under medication in t):

$$p(t) = P(T > t). \tag{1}$$

Implementation at time t, $i(t)$, is defined as the probability of correct dosing in t among patients still on treatment (persistent) at that time:

$$i(t) = P(A_t = 1 | T > t). \tag{2}$$

Adherence at time t, $a(t)$, is defined as the probability that a patient among those initially included into the study has a correct dosing in t:

$$a(t) = P(A_t = 1). \tag{3}$$

To estimate the quantities $p(t)$, $i(t)$ and $a(t)$, we need to make 2 independence assumptions. First, we assume that discontinuation time T is independent of censoring time C (assumption (i)). This is the assumption of *noninformative censoring* that is made in the classical survival analysis setting and underlies all standard survival technics (e.g. the Kaplan–Meier estimate). We need this assumption to estimate (1) and (2). The estimation of (2), and (3) also requires a second independence assumption, i.e. independence between time to censoring C and the binary variables A_t, $\forall t \geq 1$ (assumption (ii)).

2.2 | Estimating persistence, implementation and adherence

Following the literature,[7–10] the nonparametric Kaplan–Meier survival estimate (here noted as $\hat{p}(t)$) is adopted to estimate persistence. This gives an unbiased estimate of the probability defined in (1) in the presence of censoring (thanks to assumption (i)).

To estimate implementation, we observe that:

$$i(t) = P(A_t = 1 | T > t) = P(A_t = 1 | T > t \cap C > t). \tag{4}$$

This result can be shown using elementary probability properties on the basis of assumptions (i) and (ii) and noting that a correct dosing at day t implies necessarily a discontinuation time larger than t: $(A_t = 1) \subseteq (T > t)$. Based on (4), implementation can be estimated as the observed proportion $\hat{i}(t)$ of correct dosing at day t among patients not having discontinued *nor being censored* before this date (patients under observation in t).

$$\hat{i}(t) = \hat{P}(A_t = 1 | T > t \cap C > t). \tag{5}$$

Define a time dependent binary variable $(O_t)_{t\geq 1}$ taking value $O_t = 1$ if dosing A_t is observed at day t and value $O_t = 0$ if it is missing at that day. Dosing is observed in t, $O_t = 1$, if censoring time C is larger than t or discontinuation time T is smaller or equal to C:

$$(O_t = 1) = (C > t) \cup (T \leq C). \tag{6}$$

When estimating adherence (3) on the data, the proportion of correct dosing on a given day t can only be calculated among dosing observed (not missing) on that day: $P(A_t = 1 | O_t = 1)$. It can be shown that this conditional probability does not correspond to the (absolute) probability $a(t) = P(A_t = 1)$. More precisely, the former is less than or equal to the latter:

$$P(A_t = 1 | O_t = 1) \leq P(A_t = 1), \tag{7}$$

so that the adherence calculated on observed dosing systematically underestimates the true adherence. The inequality (7) is proven in Appendix 1. The source of this bias can be explained heuristically considering that dosing can be incorrect on day t ($A_t = 0$) for 2 reasons: a zero may be due to an incorrect dosing on that day or to the fact that the patient stopped taking the drug on a given day before t. This second type of zeros cannot be missing because once a discontinuation has occurred, censoring can no longer occur. Thus, while a value of $A_t = 1$ can always be missing, a value of $A_t = 0$ is sometimes *protected* from being missing. Therefore, the probability of a nonmissing dosing if the (underlying) dosing is correct ($A_t = 1$) is lower than the probability of a nonmissing dosing if the (underlying) dosing is incorrect ($A_t = 0$), and the following holds:

$$P(O_t = 1 | A_t = 1) \leq P(O_t = 1 | A_t = 0). \tag{8}$$

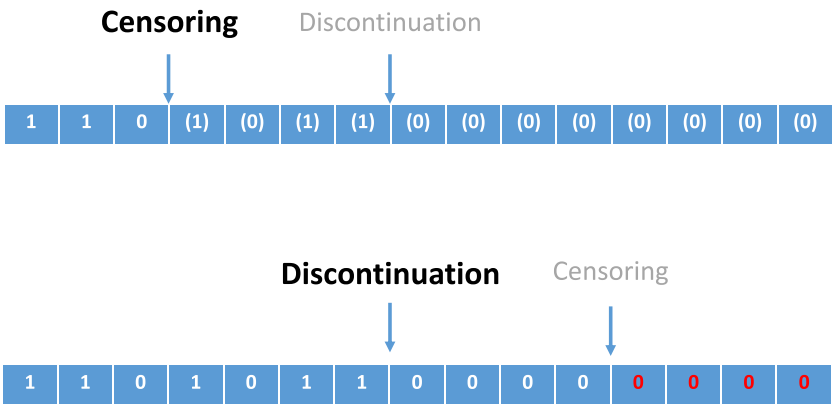

FIGURE 1 Diagram of missing daily dosing (longitudinal variable) when a discontinuation or a censoring is observed. Missing dosing are indicated in brackets. In red, some incorrect dosing (zeroes) that are protected from being missing

The diagram depicted in Figure 1 shows a situation where, being a discontinuation observed (T < C), the incorrect dosing after this event do not become missing after (unobserved) censoring. Result (7) can then be easily derived from (8) using the Bayes theorem.

One way to correct this bias is via an *indirect* estimate of adherence obtained relating the latter to persistence and implementation.[11] Using the total probability theorem one can write: $a(t) = P(A_t = 1) = P(A_t = 1|T > t)P(T > t) + P(A_t = 1|T \le t)P(T \le t)$. The second term being zero ($A_t = 1 \subseteq T > t$), the following relation holds:

$$a(t) = i(t) \cdot p(t), \tag{9}$$

and adherence can be estimated by:

$$\widehat{a}(t) = \widehat{i}(t) \cdot \widehat{p}(t). \tag{10}$$

2.3 | Modelling adherence

If one wishes to model adherence (a longitudinal binary variable) with respect to time, one can adopt longitudinal models such as generalized linear mixed effect models or generalized estimating equations (GEE) models. The latter allow the introduction of a correlation between daily measurements for a given patient within the framework of logistic modelling for binary data. However, modelling directly $(A_t)_{t \ge 1}$ data would result in an estimate of the biased adherence $P(A_t = 1|O_t = 1)$. Here we provide a system of time-dependent weights for the binary outcome $(A_t)_{t \ge 1}$ able to correct this bias. One can show the following result (Appendix 2):

$$a(t) = \frac{w_1(t)P(A_t = 1|O_t = 1)}{w_1(t)P(A_t = 1|O_t = 1) + w_0(t)P(A_t = 0|O_t = 1)}, \tag{11}$$

with:

$$w_0(t) = P(O_t = 1|A_t = 1) = \frac{P(A_t = 1 \cap O_t = 1)}{a(t)}, \tag{12}$$

$$w_1(t) = P(O_t = 1|A_t = 0) = \frac{P(A_t = 0 \cap O_t = 1)}{1 - a(t)}. \tag{13}$$

We observe that, according to (8), the weight assigned to correct dosing on a given day t is greater than that attributed to the incorrect dosing on the same day ($w_1(t) \ge w_0(t)$, $\forall t \ge 1$), allowing to counterbalance the greater probability of observing a missing value in the case of $A_t = 1$ than for $A_t = 0$. The numerator of (12) and (13) can be estimated on a given day t as the percentage of nonmissing *and* correct (respectively nonmissing *and* incorrect) dosing among all the patients initially included, while denominator is estimated using (10):

$$\widehat{w}_0(t) = \frac{\widehat{P}(A_t = 1 \cap O_t = 1)}{\widehat{i}(t) \cdot \widehat{p}(t)}, \tag{14}$$

$$\widehat{w}_1(t) = \frac{\widehat{P}(A_t = 0 \cap O_t = 1)}{1 - \widehat{i}(t) \cdot \widehat{p}(t)}. \tag{15}$$

Models are then applied to the weighted data $(A_t)_{t \ge 1}$, i.e. attributing weight $\widehat{w}_0(t)$ to $A_t = 0$ and $\widehat{w}_1(t)$ to $A_t = 1$. A basic model will contain the time or some function of the time as a covariate (polynomials, splines). If other covariates X are added to the model, weights will also be covariate dependent:

$$w_0(t|X = x) = P(O_t = 1|A_t = 1 \cap X = x) = \frac{P(A_t = 1 \cap O_t = 1|X = x)}{a(t|X = x)}, \tag{16}$$

$$w_1(t|X = x) = P(O_t = 1|A_t = 0 \cap X = x) = \frac{P(A_t = 0 \cap O_t = 1|X = x)}{1 - a(t|X = x)}. \tag{17}$$

3 | SIMULATIONS

We performed simulations in order to show adherence bias due to censoring and to demonstrate our correction using weights (14) ad(15). We compared different scenarios in which we considered

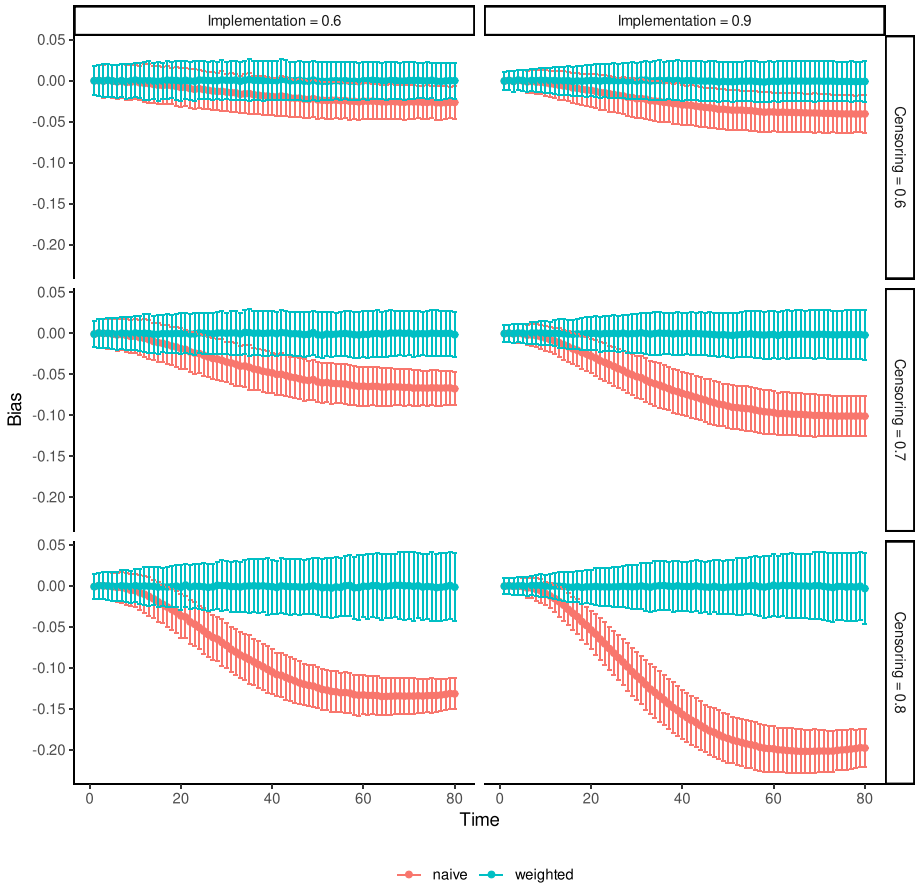

FIGURE 2 Simulations of the bias of a naïve and a weighted corrected estimate of adherence for different amounts of censoring and implementation levels

different levels of censoring and implementation. All scenarios share the same lognormal distribution of discontinuation times:

$$T \sim LogN(4.0, 1.0)$$

Three different lognormal distributions were compared for censoring times:

$$C \sim LogN(2.5, \sigma); \quad \sigma = 4.9, 2.3, 1.3$$

The value of σ determines here the amount of censoring after a follow-up of 80 days, with 60, 70 and 80% censoring for $\sigma = 4.9, 2.3$ and 1.3, respectively. Implementation was assumed constant over the time:

$$A_t \mid T > t \sim Bernoulli(i_0), \; i_0 = 0.6, 0.9$$

The true adherence pattern of our experiment was then $a(t) = i_0 \cdot P(T > t)$. We made $N = 1000$ simulations with $n = 1000$ patients each. In each simulation, patient i ($i = 1, ..., n$) has a value of discontinuation time T, t_i, generated from (1), and a value of censoring time C, c_i, generated from (2). The daily dosing pattern of patient i ($i = 1, ..., n$), $a_i(t)$, is simulated according to 3) until time $t = \min(t_i, c_i)$. After that time, daily dosing is zero if $t_i \leq c_i$, while it is missing if $c_i > t_i$. For each simulation, adherence is then estimated by averaging $a_i(t)$ for $i = 1, ..., n$, first with a simple mean (naïve estimate) $\widehat{a}_n(t) = 1/n \sum_{i=1}^{n} a_i(t)$, and then using weights (weighted estimate) $\widehat{a}_w(t) = \sum_{i=1}^{n} \widehat{w}_i(t) a_i(t) / \sum_{i=1}^{n} \widehat{w}_i(t)$, where $\widehat{w}_i(t) = a_i(t)\widehat{w}_1(t) + (1 - a_i(t))\widehat{w}_0(t)$, and $\widehat{w}_0(t)$, $\widehat{w}_1(t)$ are weights defined in (14) and (15).

The mean and the standard deviation of the bias of estimates $\widehat{a}_n(t)$ and $\widehat{a}_w(t)$, $b_n(t) = \widehat{a}_n(t) - a(t)$ and $b_w(t) = \widehat{a}_w(t) - a(t)$, are represented in Figure 2 for each scenario ($\sigma = ...$, $i_0 = 0.6, 0.9$). The higher the level of censoring, the greater the bias in the naïve estimate. For a given level of censoring, larger bias is associated with higher levels of implementation. The proposed solution using weights is virtually unbiased.

4 | RESULTS

Here we consider data from an electronic monitoring study conducted with 43 patients with cancer taking OAM at the pharmacy of the Center for Primary Care and Public Health (Unisanté) in collaboration with the department of Oncology, Lausanne University Hospital and University of Lausanne, Lausanne (Switzerland). This 1-centre, observational, longitudinal study was approved by the Ethics Committee of Canton de Vaud, Switzerland (Protocol Nr: 261/07).[9] The study lasted 12 months, but more than half of the sample (23 patients) stopped the medication adherence programme before the end of the 12-month

	Men		Women	
	Discontinuation	Censoring	Discontinuation	Censoring
1st quarter	3	4	0	1
2nd quarter	0	6	0	3
3rd quarter	0	3	1	1
4th quarter	1	0	0	0
12 mo	0	3	0	17

TABLE 1 Distribution of discontinuations and censoring among sexes and across the time (by quarters of the year). Oncology patient data at Unisanté, Lausanne

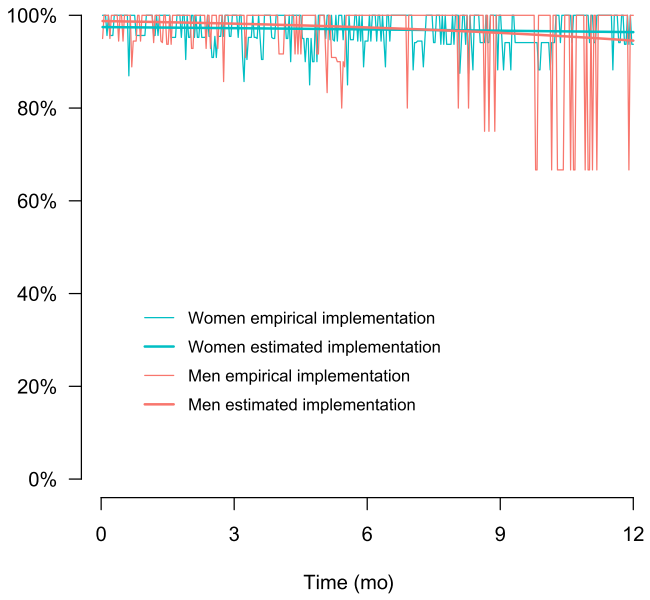

FIGURE 3 Empirical implementation and implementation predicted by a generalized estimating equations model (Table 1) for women and men. Oncology patient data at Unisanté, Lausanne

study period. Reasons for stopping included 5 discontinuations of the OAM, all due to adverse effects, and 18 censoring before the end of the year, due to the monitoring interruption, to planned end of OAM, or to OAM failure. The sample was almost sex balanced (53% women) and an interesting question might be to compare medication behaviour (implementation, persistence and adherence) across sexes. Table 1 presents the number of discontinuations and censoring for men and women for each quarter of the year. Only 1 discontinuation and 5 premature censoring occurred for women during follow-up, while the majority of women (17) are observed through the end of the year. Among men, we observed 4 discontinuations, while only 3 men were observed until the end of the year (13 of them are censored before).

Figure 3 shows the empirical implementation (5) for men and women. A GEE model with an auto-regressive correlation structure (ar1), including time, sex and the interaction between the 2, was estimated to predict for both sexes the underlying implementation across the time, using the *geeM* package of the program R (R Core Team, 2021). The predictions were added to the graph and the model results are given in Table 2. A cross effect was observed for sex: men had better implementation at the beginning of monitoring (98.8% for men and 97.5% for women, odds ratio [OR] 2.08, 95% confidence interval [CI]: 1.00–4.35), but their implementation decreased during follow-up (OR of time 0.91, 95%CI 0.81–1.02) while staying approximately constant for women (OR of time 0.97, 95%CI 0.92–1.03). This led to an opposite result at the end of 12-month monitoring period (implementation 94.5% for men and 96.4% for women, OR 0.65, 95%CI: 0.28–1.52).

Figure 4 shows the empirical persistence and adherence obtained separately for men and women. Persistence was estimated via the Kaplan–Meier survival function calculated for each group; empirical adherence was obtained separately for men and women using (10). A GEE model with autoregressive correlation structure (ar1) including a power 3 polynomial of time, sex and interactions between the 2 is estimated on the weighted (nonmissing) 0/1 daily dosing using weights (16) and (17). The model results are provided in Table 2 and the predictions for both sexes are added to Figure 4. Persistence was worse in men than in women, with 94.7% persistent among women and 63.3% among men at the end of the monitoring period (persistence difference 31.4%, 95%CI: −8.5 TO 71.4%). Adherence trends were different across sexes (Figure 4), with a lower adherence for men than for women at the end of the 12-month monitoring period (46.3% for men and 92.2% for women, OR 0.07, 95%CI: 0.02–0.26).

Figure 4 also shows the predicted adherence that would be obtained for both sexes without using weights, i.e. without correcting for bias related to missingness. Due to the large number censoring, the bias on these data is substantial, for men, with a predicted adherence of 33.7% instead of 46.4% (13% absolute bias). The bias is near to zero for women since they only had 1 discontinuation and few censoring.

5 | DISCUSSION

Adherence to the prescription of a drug, for instance to OAMs, is crucial for the effectiveness of the treatment. In patients having initiated a treatment, the study of the patient's medication behaviour is an assessment to be carried out over time, with interest in both the duration of individual persistence with treatment, and the quality of medication taking during the persistence period.[1–11] From a statistical point of view, we are faced with 2 different processes, interacting with each other: a binary variable with repeated measurements qualifying the daily dosing (correct/incorrect) during the individual follow-

TABLE 2 Results of a generalized estimating equations model (auto-regressive correlation) for implementation and a weighted generalized estimating equations model (auto-regressive correlation) for adherence. Covariates are sex (reference = women), time (polynomials) and interactions between the 2. Oncology patient data at Unisanté, Lausanne

	Implementation			Adherence		
	OR	95%CI		OR	95%CI	
Intercept	38.43	26.02	56.76	44.96	14.28	141.5
Men	2.080	0.996	4.345	0.316	0.084	1.192
Time[a]	0.970	0.918	1.025	1.134	0.532	2.419
$Time^2$	-	-	-	0.942	0.821	1.080
$Time^3$	-	-	-	1.003	0.996	1.011
Time · men	0.909	0.812	1.018	0.466	0.188	1.156
$Time^2$ · men	-	-	-	1.194	1.007	1.417
$Time^3$ · men	-	-	-	0.990	0.981	0.999

[a]All time effects are expressed for 1-month (30 d) increase.

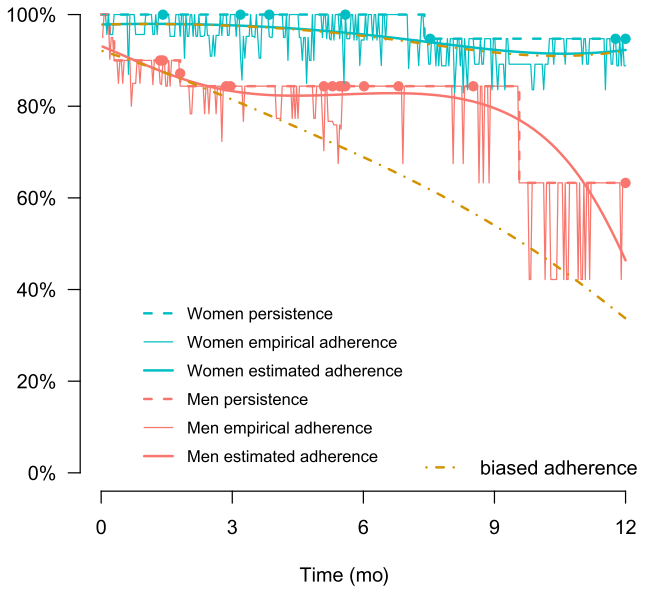

FIGURE 4 Kaplan–Meier estimate of persistence, empirical adherence and adherence predicted by a weighted generalized estimating equations model (Table 1) for women and men. Circles on the Kaplan–Meier curve represent censoring data. Oncology patient data at Unisanté, Lausanne

up, and a continuous duration variable indicating the time until the drug is stopped, the latter being subject to censoring.[12,13]

In this paper, we aimed to clarify the theoretical framework of such adherence analyses, indicating the assumptions that need to be made in order to estimate the desired quantities. Achieving unbiased estimates of medication persistence, implementation and adherence, besides being a general condition in statistics, also fulfils a requirement of the ESPACOMP Medication Adherence Reporting Guideline (EMERGE).[19] Particularly, we need an assumption of noninformative censoring stipulating the independence of time to discontinuation and time to censoring, and a second assumption of independence between time to censoring and daily dosing. The first assumption is necessary to obtain an unbiased estimate of persistence, i.e. the distribution of the time until the drug is stopped; both assumptions are necessary to obtain an unbiased estimate of treatment implementation, i.e. mean daily dosing among persistent patients.

When implementation and persistence are summarized in the concept of adherence, i.e. mean daily consumption among all initially included patients, the presence of censoring in drug discontinuation times (and thus missingness in the longitudinal dosing variable) generates a bias in the intuitive (empirical) estimation of adherence, due to a higher probability of missing data when the underlying dosing is correct. The second objective of this paper was to understand this bias statistically and to give a solution allowing to model adherence as a function of time and possible covariates. A response was found in a system of time-dependent weights to be assigned to individual binary data before entering them into a longitudinal model. The method was demonstrated on an oncology treatment adherence dataset to address the question of the role of sex on the time trend of adherence.[9] We showed on this data that adherence pattern was significantly worse among men. Several clinical trials have been conducted in the past to assess the impact of an intervention on medication intake[15,16] and others are planned for the future.[17,18] The method we have proposed will allow evaluation (estimate and test) of the effect of the intervention on the adherence trends, by introducing the intervention variable into the (weighted corrected) longitudinal adherence model. Ultimately, it will also help healthcare providers reframe medication adherence enhancing programmes to address more specifically significant covariates in adherence, such as gender issues.

The results presented in this article are therefore based on the 2 independence assumptions above. Although such assumptions are in fact implicit in all adherence analyses performed to date, it is clear that they represent a limitation of our work. In particular, the assumption of independence between daily dosing, a longitudinal binary variable (correct/incorrect), and censoring time is a strong assumption. While it is reasonable to assume that the quality of daily implementation is not related to censoring time in the case of the patient moving to another city or a planned switch to another drug or treatment

strategy, this assumption may be questioned for patients with treatment failure or toxicity. In this case, one may suspect that early censoring is related to or even due to suboptimal implementation, but this is not necessarily true. Other parameters come into play such as genetics or other uncontrolled clinical and environmental factors. Regarding censoring due to interruption of MEMS monitoring, clinical experience shows that it can be related to 2 opposite situations in terms of implementation. A patient may interrupt adherence monitoring with very good implementation, feeling that they no longer need the monitoring to maintain the desired level of adherence. Other patients, conversely, will discontinue MEMS because they are having difficulty with the treatment and their implementation is deteriorating. However, this phenomenon is less often observed in relatively small studies, such as that in our application, in which patients are closely monitored and recalled several times when their implementation worsens and they no longer attend follow-up interviews. Finally, the clinical context may also play a role in the plausibility of this hypothesis. Indeed, one can assume that the dependence between the quality of implementation and the duration of censoring, for whatever reason, will be less strong in cancer, where patients are fighting for their lives, than in other contexts where patients might be less engaged in their treatment and thus more exposed to suboptimal implementation. It is important to note that the independence assumptions (i) and (ii) cannot be verified on the observed data. On 1 hand, the discontinuation time and the censoring time, assumed to be independent (i), are never both observed on the same patient; on the other hand, when a censoring occurs, the implementation is unknown from the censoring date, which prevents the independence between the censoring time and the daily implementation (ii) to be verified. Nevertheless, as an indication, we verified that in our data, where several reasons of censoring coexist,[9] the time of censoring correlated weakly with the quality of implementation *before* censoring for the 38 censored patients, i.e., excluding the 5 discontinuations (correlation coefficient <0.2).

Statistically speaking, the independence assumption between censoring time and daily dosing (correct/incorrect) corresponds to an assumption of *noninformative dropout*,[20–22] generating missing data that are missing completely at random.[23] Different solutions have been proposed in the literature to account for *informative* dropout, among others by random-effect mixture models or selection models,[24] allowing a dependence between the dropout variable (our censoring variable) and the longitudinal process (our daily dosing). However, in our case, the task would also be made harder by the presence of a second (competing) time variable, the time to discontinuation, related to the longitudinal process in that the daily dosing will be incorrect once a discontinuation occurs, by definition. In other words, correcting for informative dropout would not prevent us from correcting for the bias induced by the simultaneous presence of discontinuation and censoring (dropout), for example by using the weights proposed in this paper. This complex exercise could be the subject of future work.

A second limitation that this article shares with the majority of adherence analyses conducted to date is the definition of correct dosing on a given day as taking *at least* the prescribed number of pills, resulting in a binary longitudinal process. Of course, this dichotomization represents a loss of information that does not allow penalizing of over-dosing. Nevertheless, this choice stems from the clinical observation that under-dosing, a public health threat, is much more common than over-dosing, with the exception of addictive treatments. Further analyses of adherence as a continuous or ordinal variable could be the subject of future work.

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COMPETING INTERESTS

We have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The code and a blurred version of the data are available on the GitHub repository: https://github.com/jpasquier/adherence-bjcp

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APPENDIX A

Bias in empirical adherence in presence of censoring

Be $(O_t)_{t\geq 1}$ a binary variable taking value 1 if the dosing is known (not missing) in t. The following holds:

$$(O_t = 1) = (C > t) \cup (T \leq C)$$

Using the disjoint union $\sqcup$ the event $(O_t = 1)$ can be written as:

$$(O_t = 1) = (C > t) \sqcup (T \leq C) \cap (C \leq t)$$

which implies:

$$P(O_t = 1) = P(C > t) + P(T \leq C \cap C \leq t)$$

Consider the event of a correct and nonmissing dosing in t. It can be written as follows:

$$\begin{aligned}(A_t = 1) \cap (O_t = 1) &= [(A_t = 1) \cap (C > t)] \sqcup [(A_t = 1) \cap (T \leq C) \cap (C \leq t)] \\ &= (A_t = 1) \cap (C > t).\end{aligned}$$

The second event of the disjoint union above is empty since dosing cannot be equal to 1 in t if a discontinuation occurs before t. Consider now the probability of a correct dosing among nonmissing:

$$\begin{aligned}P(A_t = 1 | O_t = 1) &= \frac{P(A_t = 1 \cap O_t = 1)}{P(O_t = 1)} \\ &= \frac{P(A_t = 1 \cap C > t)}{P(C > t) + P(T \leq C \cap C \leq t)} \leq \frac{P(A_t = 1 \cap C > t)}{P(C > t)}\end{aligned}$$

Thanks to the assumption of independence between A_t and C, the probability at the numerator is the product of $P(A_t = 1)$ and $P(C > t)$. The last simplifies with the denominator leading to the result:

$$P(A_t = 1 | O_t = 1) \leq P(A_t = 1)$$

Time-dependent weights correcting the bias

We observe that the probability of a correct dosing at day t (adherence) can be written as:

$$P(A_t = 1) = \frac{P(A_t = 1)}{P(A_t = 1) + P(A_t = 0)}$$

Applying to each term properties of a conditional probability and simplifying one obtains:

$$P(A_t=1)=\frac{\frac{P(A_t=1|O_t=1)}{P(O_t=1|A_t=1)}P(O_t=1)}{\frac{P(A_t=1|O_t=1)}{P(O_t=1|A_t=1)}P(O_t=1)+\frac{P(A_t=0|O_t=1)}{P(O_t=1|A_t=0)}P(O_t=1)}$$
$$=\frac{P(O_t=1|A_t=0)P(A_t=1|O_t=1)}{P(O_t=1|A_t=0)P(A_t=1|O_t=1)+P(O_t=1|A_t=1)P(A_t=0|O_t=1)}$$

We thus define weights:

$$w_0(t)=P(O_t=1|A_t=1)=\frac{P(O_t=1\cap A_t=1)}{a(t)}w_1(t)=P(O_t=1|A_t=0)$$
$$=\frac{P(O_t=1\cap A_t=0)}{1-a(t)}$$

These weights can be empirically estimated by:

$$\widehat{w}_o(t)=\frac{\widehat{P}(O_t=1\cap A_t=1)}{\widehat{p}(t)\cdot\widehat{i}(t)}\widehat{w}_1(t)=\frac{\widehat{P}(O_t=1\cap A_t=0)}{1-\widehat{p}(t)\cdot\widehat{i}(t)}$$

where $\widehat{P}(O_t=1\cap A_t=1)$ (respectively $\widehat{P}(O_t=1\cap A_t=0)$) is the proportion of nonmissing and correct dosing in t among all patients initially included (respectively the proportion of non missing and incorrect dosing in t among all patients initially included), and $\widehat{p}(t)$ and $\widehat{i}(t)$ the estimated persistence and implementation at time t, respectively. The above defined weights can be used to reconstruct adherence:

$$\widehat{a}(t)=\frac{\widehat{w}_1(t)\widehat{P}(A_t=1|O_t=1)}{\widehat{w}_1(t)\widehat{P}(A_t=1|O_t=1)+\widehat{w}_0(t)\widehat{P}(A_t=0|O_t=1)}$$

being $\widehat{P}(A_t=1|O_t=1)$ (respectively $\widehat{P}(A_t=0|O_t=1)$) the proportion of correct dosing in t among nonmissing in t (respectively the proportion of incorrect dosing in t among nonmissing in t).

OR, odds ratio, CI, confidence interval