Author's response to reviews

Title: Adherence to hormone therapy among women with breast cancer

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Author's response to reviews: see over
Dear Editor,

In response to the request of Dr. Volker Ziller, this letter aims to clarify the definition and the way we calculated adherence in the study. We underline points addressed in the text submitted, and propose some text inclusions in the article to make it clearer.

With regard to his comment about the need of an English review, we agree, in the case of the article being accepted, to make arrangements to have the whole text reviewed by a British native speaking editor, according to the British English standard.

**Definition of adherence:**

Adherence is defined in the article in the following paragraphs of Methods:

> Adherence was calculated according to the recommendation of a daily hormone therapy (HT) pill for five years. The drugs that INCA distributed free of charge were TMX and AIS.

> Adherence was calculated as a medication possession ratio (MPR) [17], and patients with an MPR ≥ 80% were considered adherent. This reference value has been widely used in the literature [18-20]:

\[
MPR = \frac{\text{Total pills dispensed to the patient}}{\text{Last dispensing date for HT (LD) – HT starting date} + \text{supply delivered at LD}} \times 100
\]
We highlight that this formula has been recommended by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) to increase the reliability, quality and comparability of medicine adherence studies. It is presented in reference 17 of the article (Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. Value Health 2008; 11: 44-7), and is employed in other published articles, that are now added as references in the text:


In operational terms, for each woman we summed up all pills dispensed, and divided the sum by her cohort time (days). The cohort time, in turn, was defined by the difference between the last and the first data of medicine dispensation, added to the last quantity of pills received, when the patient did not die. When the patient died, the cohort time was given by the difference between the death date and the first date of medicine dispensation.

**Question regarding the need of applying a fixed time frame:**

“In the methods section MPR calculation is described with the time period calculated based on last dispensing date minus first dispensing date. If this was truly the way it was done it would lead to severe overestimation of adherence. The time period should be e.g. twelve months or five years or some other fixed time frame and this should be compared to the time patients were supplied. The provided way of calculating would e.g. not detect non-adherent patients that received there last dispensing after 12 months but should have been treated for 60 months, they would be classified adherent and 48 months would be missed. As this flaw would influence all consecutive analysis this should be clarified before further review can be continue.”

We agree that the reviewer’s doubt is pertinent, and his argument is logic. However, the concepts of adherence and persistence have been treated in distinct ways, as may be verified in diverse publications. It is likely that some misunderstanding is related to their distinction, despite their close relation. ISPOR defines adherence as the degree or the extent that the treatment prescribed day by day is respected with regard to time, dose, and frequency, while persistence takes into account the duration of time since the beginning of the treatment until its discontinuation:

**Medication compliance.** Medication compliance (synonym: adherence) refers to the act of conforming to the recommendations made by the provider with respect to timing,
dosage, and frequency of medication taking. Therefore medication compliance may be defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.” Compliance is measured over a period of time and reported as a percentage (Fig. 1). This definition is operationalized in prospective assessments as dose taking in relation to what was prescribed Table 1 shows compliance patterns for a patient prescribed a once-daily medication. Electronic monitoring provides sufficient details to calculate the number of doses taken daily as well as whether the doses were taken at appropriate intervals (e.g., approximately 12 hours apart for a twice-daily dosing). Additional details can be obtained as number of days with extra doses or without any doses. The definition is operationalized in retrospective assessments as the number of doses dispensed in relation to the dispensing period, often called the “medication possession ratio (MPR)” [28]. Compliance with the prescription is assumed when the medication is dispensed.

Medication persistence refers to the act of conforming to a recommendation of continuing treatment for the prescribed length of time. Therefore, medication persistence may be defined as “the duration of time from initiation to discontinuation of therapy” (Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. Value Health 2008; 11: 44-7).

Therefore, it is really possible that a patient is considered non-persistent in the treatment, because she discontinued it before five years, but she is considered adherent while taking the medicine.

Alterations in the text to make it clearer:

The following paragraphs of Methods

Adherence was calculated according to the recommendation of a daily hormone therapy (HT) pill for five years. The drugs that INCA distributed free of charge were TMX and AIS.

Adherence was calculated as a medication possession ratio (MPR) [17], and patients with an MPR \(\geq 80\%\) were considered adherent. This reference value has been widely used in the literature [18-20].

were replaced by

Adherence is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen, and is operationalized, in a retrospective assessment, as the number of doses dispensed in relation to the dispensing period, often called the “medication possession ratio (MPR)” [12, 17-19].

It was calculated, for each woman, by summing up all quantities dispensed, and dividing the sum by her time in the cohort, that, in turn, was given by the difference between the last and the first dispensing date summed to the last quantity, for those that did not die, and between the death and the first dispensing
date, for those that died [12, 17-19]. We considered the recommendation of a daily hormone therapy (HT) pill for five years. The drugs that INCA dispensed free of charge were TMX and AIS.

Patients with an MPR $\geq 80\%$ were considered adherent, which is a criterion widely applied [20-22].

Finally, in the Discussion, the bolded text was added:

The method employed in this study and in others accounted for medication delivery as a proxy for medication use; however, this could result in an overestimation of adherence rates. This bias can be attenuated when estimations are made on the basis of secondary data from large populations [23]. Moreover, we underline the difference between the concepts of treatment adherence and persistence, indicating that adherent patients may be non-persistent if they interrupt the treatment before the recommended period of five years.

With the clarifications here provided, we hope that the peer-review process may advance.

Best Regards,

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