**Impact of assessment frequency of patient-reported outcomes: an observational study using an eHealth platform in cancer patients.**

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## Abstract

*Background and Aim:* The evaluation of patient-reported outcomes (PRO) in cancer has proven relevant positive clinical impact on patients' communication with healthcare professionals, decision-making for management, wellbeing and overall survival. However, the optimal

frequency of PRO assessment has yet to be defined. Based on the assumption that more frequent sampling would enhance accuracy, we aimed at identifying the optimal sampling frequency that does not miss clinically relevant insight.

*Methods:* We used pilot data from 31 advanced cancer patients who completed once daily the 19-item MD Anderson Symptom Inventory at home. The resulting dataset allowed us to compare different PRO assessment frequencies to daily sampling, i.e.: alternate days (q2d), every third day (q3d) or once a week (q1w). We evaluated the sampling frequencies for two main outcomes: average symptom intensity and identification of severe symptoms.

*Results:* The majority of the differences between corresponding averages of daily data and those for q2d, q3d and q1w datasets were close to 0, yet the extremes exceeded 5 Clinically meaningful differences i.e., >1, were observed in 0.76% of patient-items for q2d, in 2.72% for q3d, and in 11.93% for q1w. Moreover, median values of missed instances of a severe symptom (i.e., >6) were 14.6% for q2d, 27.8% for q3d, and 55.6% for q1w.

*Conclusions:* Our analysis suggests that in patients receiving chemotherapy for advanced cancer, increasing the density of PRO collection enhances the accuracy of PRO assessment to a clinically meaningful extent. This is valid for both computation of averages symptom burden and for the recognition of episodes of severe symptom intensity.

**Keywords**

Cancer; patient-reported outcomes; mHealth; digital oncology; domomedicine; MDASI; symptoms

*Text*

The evaluation of patient-reported outcomes (PRO) in cancer has proven relevant positive clinical impact on patients' communication with healthcare professionals, decision-making for management, wellbeing and even overall survival [2, 3, 18]. Recent technological advances have further allowed the use of digital systems for systematic PRO collection to monitor cancer patients' symptoms in routine clinical practice [4, 14, 17]. However, the optimal frequency and method of PRO assessment has yet to be defined. Indeed, common sampling frequency varies from daily to weekly in recent literature using electronic PRO collection by cancer patients on treatment [1, 3, 9, 16]. This issue is particularly critical for patients receiving anticancer treatment, since the elicited toxicity acutely affects patients' perception of wellbeing, with variations in symptoms severity from one day to the next [9, 12, 13, 15,

16]. Most frequently, however, weekly electronic PRO remote monitoring has been adopted in oncological studies and practice [1, 3, 11]. Notwithstanding, based on the assumption that more frequent sampling would enhance accuracy, we aimed at identifying the optimal sampling frequency that does not miss clinically relevant insight. In order to evaluate the importance of sampling frequency on PRO-related results, we used data from 31 patients with advanced cancer receiving systemic anticancer treatment, enrolled in a monocentric pilot study performed at Paul Brousse Hospital (Villejuif, France). Patients completed once daily the 19-item MD Anderson Symptom Inventory (MDASI) [7] at home using a touch-screen computer connected to the internet and data were uploaded on an eHealth platform [12]. The resulting dense longitudinal dataset allowed us to compare different PRO assessment frequencies to daily sampling, allegedly the most accurate evaluation of patients' symptoms. We selected alternate days (q2d), every third day (q3d) or once a week (q1w) sampling. We evaluated the chosen sampling frequencies based on two main outcomes: (1) average symptom intensity and (2) identification of severe symptoms. The rationale behind this choice was that average PRO measure is frequently used as an endpoint in randomised trials [8, 10], whilst the occurrence of a symptom above a defined threshold can be used as a trigger for dedicated interventions or define clinical deterioration [6, 9]. MDASI items range from 0 (no symptom) to 10 (worse possible symptom severity) [7]. For our exploratory analysis, we used the initial 42 days on-study (least common multiple of 2, 3 and 7). Overall data availability was 72.7% out of 24,738 potential individual data points (19 items on 42 days for 31 patients). No imputation was performed for missing data. Each MDASI item was considered separately, and two separate series for q2d with 21 data points each, three separate series for q3d with 14 data points, and seven independent 6-timepoint datasets for q1w were retrieved, alongside the 42-day reference series with daily assessments for each patient. Data availability was comparable among all series (ranging between 65.6% and 79.0%; data not shown).

For the first outcome, the average symptom intensity, we calculated the mean intensity of all daily ratings for all 19 MDASI items in individual patients (N=31). Thus, we obtained 589 average symptom intensity scores for at least 42 daily ratings, and the values for every patient-item were considered the reference. We then calculated all down-sampled matching mean symptom intensity in each patient-item, and computed the differences between corresponding averages of daily reference data and those for each of the two q2d, three q3d

or seven q1w datasets. While the majority of these differences were close to 0 (Figure 1A), the extremes exceeded 5 (on a 0 to 10 range scale). Importantly, clinically meaningful differences, i.e., defined as MDASI difference >1 [19], were observed in 0.76% of patient-items for q2d, in 2.72% for q3d, and in 11.93% for q1w (Figure 1A).

As expected, the 19 assessed symptoms displayed different variabilities in average severity when assessed less frequently than daily. To explore this, we computed the coefficients of variation of each symptom mean rating within the down-sampled series. We observed that the average values for 'fatigue' and 'interference with activity' were least dependent of sampling frequency, whilst average 'nausea', 'vomiting' and 'interference with mood' exhibited larger variation when recorded at different sampling intervals (Figure 1C). This suggests that more frequent sampling can more accurately capture the variability of episodic symptoms but also the relevant dimension of irregular emotional dysregulation that could otherwise be missed, as not necessarily seized by the more stable sadness and distress.

For the second outcome, the identification of severe symptoms, we used daily data throughout the 42-day recording period to retrieve 589 time-series of daily assessments and determined the proportion of symptom intensity ≥7, i.e., rated as severe [20]. Amongst these time-series datasets, we observed 223 instances (37.9%) with severe symptoms. We subsequently compared the occurrence of daily instances with symptom intensity ≥7 to that of the down-sampled datasets. For each time-series obtained with less frequent sampling, it would be expected that some instances of severe symptom would have been missed, in spite of the fact that the assessment was completed during the same timeframe, since the day in which the symptom intensity was ≥7 was not part of that less dense dataset. Thus, we calculated the rate of instances whose rating of a severe symptom was not found when lower frequency of assessment was used. Thus, increased PRO collection frequency systematically improved the accuracy of identifying patients with severe symptoms: median values of missed instances were 14.6% for q2d, 27.8% for q3d, and 55.6% for q1w (Figure 1B). This finding implies that more than half of the instances when a patient experienced a day with one symptom being severe (i.e., ≥7 on a 0 to 10 scale) could have potentially been missed if the PRO sampling was performed on a weekly rather than a daily basis.

We acknowledge the limitations of this exploratory and simulated study: we have a fairly small number of patients, and we assumed that the PRO scores and the compliance would have been the same if the patients were asked to complete the questionnaire less frequently than once a day. Notwithstanding, our assumptions are partly supported by the recall period for the MDASI questionnaire limited to the last 24 hours [7], and by similar figures of compliance reported in studies with weekly symptoms assessments [1, 3].

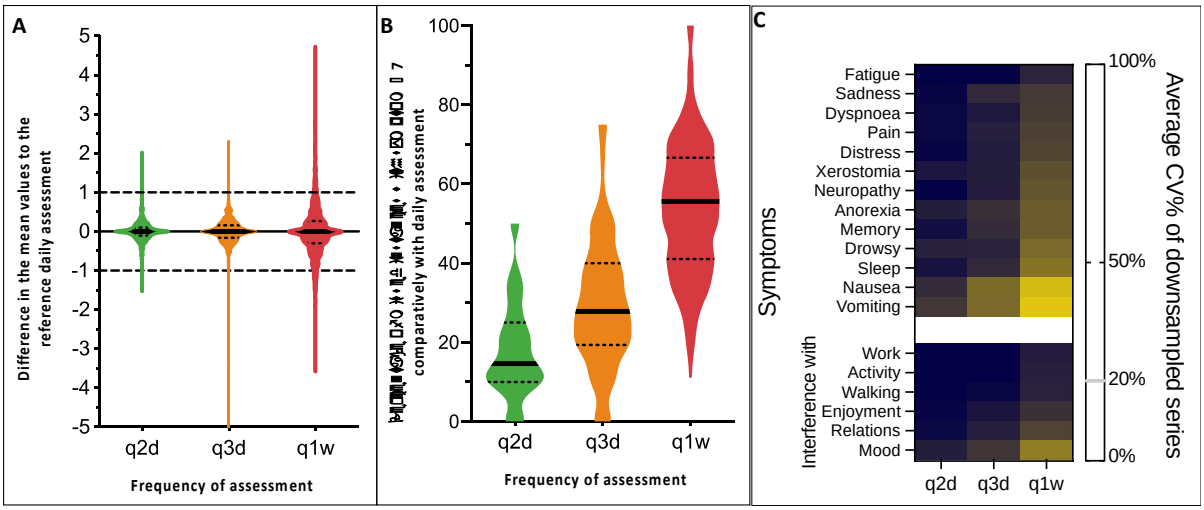
In conclusion, our analysis suggests that in patients receiving chemotherapy for advanced cancer, increasing the density of PRO collection enhances the accuracy of PRO assessment to a clinically meaningful extent. This is valid for both computation of averages symptom burden and for the recognition of episodes of severe symptom intensity. Our findings therefore support the use of mobile technology (like dedicated smartphone apps) to remote monitor cancer patients, ideally on a daily or at least alternate days basis. Validation of our findings, however, is warranted using existing datasets (e.g., [9, 16]) and those from ongoing prospective studies from our group [5] taking advantage of mHealth platforms with dense PRO collection.

**Figure 1.**

Panel A: Violin plots depicting the distributions of the differences in means between daily (reference) and less frequent (q2d; q3d; q1w) symptom assessments. Positive values indicate lower average symptom severity with less frequent than daily sampling. Dotted lines display interquartile range.

Panel B: Violin plots displaying the distributions of the missed instances of items indicating severe (i.e., ≥7 on a 0 to 10 scale) intensity when assessing PROs less frequently than daily. Thick line indicates the median, and dotted lines show interquartile range.

Panel C: heat maps depicting the mean coefficient of variations (CV), expressed as percentage, in average MDASI [7] item ratings calculated with less frequent than daily assessment. We ranked the symptoms and the interference items from the least to the most variable ones.

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**Declarations:**

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**Conflicts of Interests:**

None to disclose.

**Availability of data and material:**

The data that support the findings of this study are available from the corresponding author, PFI, upon reasonable request.

**Code availability:**

N/A

**Authors' contributions:**

PFI: conception and design; data acquisition, analysis and interpretation; figure plotting; manuscript drafting and final editing;

SK: data analysis and interpretation; manuscript drafting and final editing;

RD: data interpretation; figure plotting; manuscript final editing;

NIW: data interpretation; manuscript final editing;

MB: data acquisition; manuscript drafting and final editing;

AK: data acquisition and analysis; manuscript final editing;

AU: data acquisition; manuscript final editing;

CPS: data interpretation; manuscript final editing;

DS: conception and design; data interpretation; manuscript drafting and final editing;

FAL: conception and design; data acquisition, analysis and interpretation; manuscript drafting and final editing.

**Ethics approval:**

No specific ethical approval was necessary for this study. The patient-generated dataset was part of a pilot study (inCASA: Integrated Network for Completely Assisted Senior Citizen's Autonomy), which was approved by the local institutional review board (Villejuif, France).

**Consent to participate:**

N/A

**Consent for publication:**

N/A

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