COLLECTING BETTER QUALITY PATIENT REPORTED OUTCOMES IN MIGRAINE: BASELINE PATIENT UNDERSTANDING OF HOW TO RECORD A HEADACHE DAY

Liangfang Zhao[1], Rinah T. Yamamoto[1], Ellen M. Durand[1], June Tuller[1], Laura Khurana[1], Susan M. Dallabrida[1]

[1]ERT, Boston, MA USA

BACKGROUND

The quality of patient-reported outcomes (PROs) play a critical role in endpoint collection in clinical trials. Authorities have discovered that patient variability in interpreting the measurement parameters and reporting the PROs has led to many disparities in clinical trial data. Therefore, regulatory documents from several agencies, including the FDA and EMA, have specified a standardized order by which PRO is administered. The regulatory agencies, as well as scientific and educational organizations, also recommended training and instructions to patients for self-administered PRO instruments as a mechanism to minimize inconsistencies in trial conduct.

Migraine is a chronic neurovascular disorder characterized by recurrent attacks of often severe headache, typically presenting with nausea and sensitivity to light and/or sound. In adults, migraine attacks usually last from 4 to 72 hours[1]. Clinical trials for migraine often use changes in duration and/or frequency of migraine as primary or secondary endpoints and to classify clinical and pathological features of migraine. Based on the International Classification of Headache Disorders 3rd edition (beta) headache diagnosis is often determined by a minimum number of days with the headache[2]. However, without training to define days, patients may not always define days with a headache in the same way. For example, if one patient counts days as a 24 hour period, they are likely to report a headache that begins at 8 in the evening and lasts through 8 the next morning, as one headache day. If another patient with the same headache duration counts this as headache lasting two days, the resulting data will be inconsistent and unreliable. Therefore, it is very important for the patients to report the same physical reactions consistently. In this study, we examined the baseline interpretation of migraine patients.

METHODS

78 migraine patients were recruited via the Clinical Connection website (https://www.clinicalconnection.com), an online patient recruitment resource. Patients were given a scenario of overnight headache, "If you were participating in a clinical trial that asked you to report how many days you had a headache in a week and you had a headache from 8:00 pm Sunday night to 8:00 am Monday morning, does it count as 1 or 2 days with a headache", and were asked to select 1 answer from 4 choices.

Considering the potential complexity of this scenario for naïve patients, they were also asked to select an answer for another situational question, "If you participated in a clinical trial and the doctor asked you to complete a questionnaire every day for 6 months and you had questions about how to respond to a particular question, what would you do?" as an indication of patients' trial compliance behavior. In addition, demographic data (age, gender, education and income), as well as whether patients have ever participated in clinical trials, was also collected.

Number of headache days is defined as a day with headache pain that lasts for 4 hours or more, based on common headache study designs and as reviewed by Silberstein *et. al*[3].

RESULTS

- 74 partipicants responded to the headache question.
- The average age of participants was 46, with youngest participant at age of 16, oldest participant at age of 80 and a standard deviation (STD) of 15.2 (Figure 1A).
- 91.0% of participants were female (n=71) and 9.0% were male (n=7, Figure 1B).
- Most participants reported a highest education level of "High school graduate/GED" or "Some college/Technical degree/AA/AS" (69.2%, categorized under "High school/Some college" on Figure 1C).
- 18 patients reported a household income of below 20k, 29 reported income of 20-49k. Additionally, 23 patients reported a household income of 50-99k and 7 reported 100k or above (Figure 1D).
- Only 25.7% (19 patients) answered the question correctly ("2 days. I had a headache on Sunday and Monday", Figure 2, navy bar). The majority of respondents (56.8%, 42 patients) chose the wrong answer, "1 day. The sum of hours that I had a headache is fewer than 24" (Figure 2, green bar). The rest 17.6% of respondents either chose "It depends on how bad my headache was at each occurrence. I would need more information to answer this question" (2 patients, Figure 3, orange bar), or "It depends on how bad my headache was at each occurrence. I would need more information to answer this question" (11 patients, Figure 2, sky-blue bar).
- It is noteworthy that, 17 (21.8% of total patients) reported they have participated in clinical trials at some point. Among this group of patients, only 4 (23.5%) answered the question correctly.
- 74 patients responded to the compliance question (Figure 3). However, only 54.1% (40 patients) would check with the doctor's office before responding to uncertain questions, while 45.9% would either use their best judgements (10.8%, 8 patients) or refer to non-physician resources such as online or dictionary (35.1%, 26 patients).

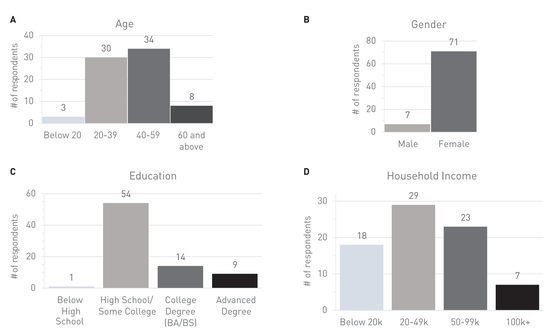

Figure 1. Demographic data of participants, including age (Panel A), gender (Panel B), highest education (Panel C) and household income (Panel D).

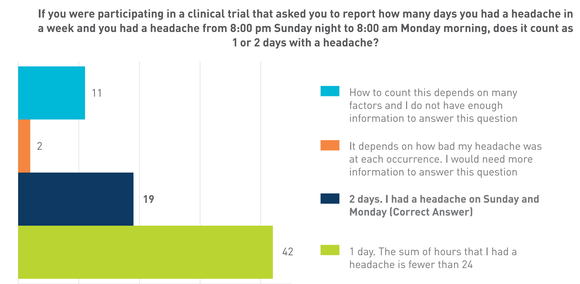

Figure 2. Patient answer count towards a given scenario of headache. The correct answer (Navy bar, "2 days. I had a headache on Sunday and Monday) is highlighted in bold.

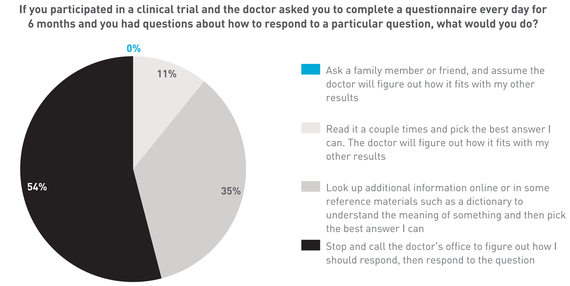

Figure 3. Patients' response count towards a given scenario of trial compliance behavior, as percentage of total respondents.

CONCLUSION

Our findings suggest that:

- When presented with a specified overnight headache scenario, patients provided a diverse range of answers among all possible choices, suggesting that patients were not clear on how the length of a headache was defined and have a diversified baseline.
- Without training on terminology such as how one "headache-day" is defined, more than 56% of respondents might have answered in a way that would invalidate the results of a clinical trial. Additionally, training would have provided the information needed to answer the question appropriately for those subjects who answered that they would either need more information or that their response would depend on the severity of their headache.
- Such diversified headache-day interpretations pose a significant risk towards the quality of clinical outcome data collection. When migraine patients entered clinical trials that involve headache-day counts, they could be likely reporting in a similar pattern comparing to the ones who participated in our survey, and therefore compromise the results of actual clinical trials. This conclusion is further reflected through the responses from the subset of patients who have participated in clinical trials. Regardless of the limitations in this subset of data, for example, the sample size of this subset of participants was relatively small, and that we did not specifically collect information to distinguish clinical trials for migraine versus other disease indications, our study still suggested a necessity for proper patient training to mitigate such risk of data quality compromise.
- When patients encounter unclear situations during an actual clinical trial, they may not consult with the site to put in an appropriate answer. Instead, almost half of the patients would either refer to non-clinical resources, or not refer to anything at all. This trial compliance behavior could cause even more deterioration of data quality if the patients were not properly trained and encountered such complex scenarios during a migraine trial.
- Our findings are also in accordance with the FDA migraine treatment guidance, as described in the 2014 draft, which explicitly states that "The headache diary should be shown to be well defined and reliable for the target population based on the recommendations described in FDA guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*[4].
- Providing consistent training to migraine subjects who are in a clinical trial to help them understand expectations and how to accurately complete a headache diary may be a helpful method to improve clinical trial data quality and to comply with FDA regulation.

DISCLOSURE

The authors are employees of ERT.

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