

# Addressing the Patient Factor in ePRO to Improve Compliance

Patient-reported outcomes (PROs) are commonly used by biopharmaceutical companies to support regulatory filings, formulary submissions, and product marketing. Sponsors of PRO research have learned that patient compliance is dramatically improved when data is collected electronically from patients rather than by paper. Electronic patient-reported-outcomes (ePRO) compliance rates, however, can also be improved if Sponsors understand the reasons for non-compliance and patient preferences for PRO data collection. This article reviews the literature on patient compliance relating to ePRO and summarises recent research conducted with patients to provide a broad picture of how Sponsors can improve patient compliance during trials involving PRO.

## ePRO in Clinical Trials

PROs are often used in clinical trials to measure treatment efficacy and endpoints. Unlike laboratory tests and other physical assessments that require interpretation from a secondary source such as a clinician, PROs are measures that come directly from patients. Hence, PROs provide a unique window into how patients perceive the investigational drug and the state of their health during treatment.

As PROs are essential data points in many clinical trials, obtaining high levels of patient compliance is extremely important to the success of studies. Evidence shows that higher compliance can be achieved if data is collected by electronic means rather than paper.<sup>1,2</sup> Higher compliance with ePRO is directly related to special features that electronic technologies provide, such as reminders for patients to complete diary entries, mechanisms to facilitate data completion (e.g., not allowing patients to skip questions), alerts to investigators and the study team of non-compliance, and time-stamped data that assures diary entries were made in a timely manner. As a result of such electronic facilitators, the quality of patient data is greatly enhanced over traditional paper-based methods.

Since ePRO allows for efficient data collection globally and high rates of compliance, it is extremely important that Sponsors, investigators, and key study personnel play roles in assuring that ePRO systems and procedures are convenient and user-friendly for patients. This article will help Sponsors along those lines by providing a literature review on patient compliance in trials involving ePRO and contributing proprietary Almac research data collected via surveys and interviews.

## Addressing the Patient Factor in ePRO Compliance

While ePRO helps to improve compliance, it cannot force patients to consistently comply. Patients are people, after all, and can choose whether or not to adhere to study protocols. Hence, when designing and implementing ePRO systems, Sponsors need to understand why patients are not compliant and make use of technology features that encourage patients to stay active in the study. By doing so, Sponsors will improve compliance and the overall quality of trial data.

To provide insight on patient compliance in ePRO, the authors conducted a literature review of 132 articles (published 1995-2011) that reported on the results of studies utilising ePRO. From that literature review, we identified and analyzed 25 articles that focused on reasons for non-compliance and 20 that reported on patient preferences (in comparing paper to ePRO).<sup>3,4</sup>

Lessons learned from the literature were combined with insights collected directly from patients through blinded proprietary research sponsored by Almac. The study was conducted to better understand the challenges patients face when participating in trials involving ePRO. Subject inclusion criteria consisted of having been enrolled in at least one clinical trial within the past two years in which keeping a diary was required. In total, 307 patients responded to a 10-minute internet based survey that contained both quantitative and qualitative questions. Additionally, 10 patients were interviewed to provide qualitative insights. Respondents were based in the United States and the gender of the sample was generally balanced (55% female and 45% male). Females had previously participated in an average of four clinical trials with diaries and males in an average of three studies.

## Patient Compliance Rates

Almac's patient survey revealed compliance with diary completion during clinical trial participation was very high (96%). Since this number was reported by patients themselves, it is possibly inflated due to overly positive self-reporting. By contrast, the average ePRO compliance rate overall in the literature review was lower (86%), yet still moderately high when compared to paper collection (79%).<sup>4</sup>

It is important to recognise that compliance varies among studies due to several factors, including the nature of the illness, patient population, study design, and patient experiences, among others. Ultimately, even if it seems impossible, researchers should strive to achieve 100% compliance to obtain full representation of the study population by attempting to prevent non-compliance whenever possible.

## Addressing Reasons for Patient Non-Compliance

Uncovering reasons why patients are not compliant leads to identifying ways that ePRO systems and study designs can improve compliance. Ten major reasons for non-compliance were identified in the literature review. Listed in order by highest frequency, they include<sup>3</sup>:

1. Time
2. Reminder issues
3. System issues
4. Personal reasons
5. Health
6. Equipment loss
7. Study design
8. No/limited access to input data
9. Length of study
10. Other.

As time to complete diaries is the top reason for non-compliance, it can be concluded that burden is likely a major underlying cause of non-compliance. The survey further supports this explanation as 58% of patients indicated that shorter diaries are associated with more favourable diary experiences. Hence, study designs and protocols should be sensitive to the amount of time required by patients to complete diaries – choose shorter diaries where possible, check with the diary author to see if an appropriate short form is available, limit frequency of required diary completion, and reduce frequency of lengthy questionnaires whenever possible.

To address another important reason for non-compliance (system issues), Sponsors and vendors should develop glitch-free technologies that are reliable and user-friendly, as this will likely reduce patient burden and frustration. Moreover, since personal reasons (e.g., going to bed early, technophobia, confidentiality concerns, major life change, being on vacation, and lack of interest) are main factors contributing to non-compliance, it is important to make it as easy and convenient as possible for patients to complete their entries. On this theme, Almac's survey research indicates that 59% of patients prefer to have multiple data collection modalities (e.g., phone, web, handheld device) that provide flexibility and convenience for completing diaries. However, it is important to note that use of multiple modalities should only be employed in trials where it is appropriate and feasible both clinically and in a regulatory sense.

Given that reminder issues were identified as a main reason for non-compliance in the literature review, one way to improve compliance involves providing patients with effective reminders to complete their diaries. The key insights identified relating to reminders included: no reminders were provided, phone call reminders were not received, and current reminders were not sufficient. To better understand these challenges, Almac's survey asked patients to identify what kind of reminders they wished to receive and how they preferred to receive them. The two top items for which patients wanted reminders were “anything they

should take action on as part of the clinical trial” (76%) and “when they needed to record their ePRO entries,” (60%). In terms of mode of reminder, the majority of patients preferred email (80%) or a SMS/text message (55%).

Compensation is often thought to be associated with increased patient adherence to PRO requirements. Within the literature review it was found that compensating patients did not impact compliance; however training them was associated with higher rates of compliance<sup>5</sup>. Additionally, in the Almac survey, when patients were asked why they would consider dropping out of a diary study, a main reason was having difficulty in understanding directions. These results indicate that providing patients with proper training and guidance allows for higher comfort levels in the use of ePRO systems, thus alleviating frustration and burden. Furthermore, when patients are trained, they require less support throughout the duration of the study. Therefore, Sponsors should plan to include patient training in the start-up phase of the trial and work with ePRO vendors to create effective training tools for patients and sites.

## Patient Preferences in ePRO

In addition to identifying reasons for non-compliance, learning what patients like about ePRO may also lead to identifying ways to increase adherence to protocols. In the patient survey, the top responses reported for positive patient diary experiences were ease of use (66%), simplicity of questions (60%), and reducing the time spent to make daily entries (58%). In the literature review on patient preferences, the most common positive aspect identified was ease of use. Thus, anything Sponsors can do to reduce time and improve the user experience is essential. As indicated in the patient survey, such things would include providing multiple electronic technology options where appropriate (e.g. phone, web, handheld devices), offering frequent reminders, and making diaries easy to complete.

Patient views of the negative aspects of ePRO, while reported less than positive aspects, are just as valuable, if not more so,



because they may directly relate to reasons for non-compliance. In the survey, almost half of the participants (48%) did not report any unfavourable diary aspects. But for those who did offer responses, the most common were: entries were too frequent, lack of multiple data entry options, and inconvenience. In the literature review focusing on preferences, most of the negative aspects that contributed to non-compliance were related to the development and design of ePRO systems.<sup>3</sup>

## Patient Recommendations for Improvement

Insights generated from Almac's patient survey reveal other ways to improve compliance. To seek out suggestions from patients on how Sponsors can improve the diary collection process, patients were asked to report three of the most important things that can be done to improve their experience with ePRO. The patients' suggestions were (ordered by highest response):

1. Provide multiple technology options for completing diaries (59%)
2. Shorten the time needed to make an entry (58%)
3. Make it easier to make an entry (54%)
4. Provide automated reminders (54%)
5. Provide an easy way to get help with making entries/directions when needed (42%)
6. Provide better instructions for making entries (30%).

Patients were also asked to report the single most important thing that would improve their experience participating in a clinical trial involving ePRO. The most common themes represented in their open-ended responses were ease of use, reminders, and convenience and clarity of what is expected of them relating to study procedures.

## Summary and Conclusions

Since high levels of patient compliance are critical to successfully collecting and analysing PRO data, Sponsors of clinical trials must understand the reasons for non-compliance and take actions to address them. This article points out that understanding

patient preferences for technologies and improving the patient's experience with keeping a diary is essential to driving higher compliance rates. Throughout this investigation into the factors affecting compliance, several common challenges facing patients came to light. These are summarised along with recommendations on how to address them in Table 1.

## References

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**Table 1:** Patient Factor Recommendations to Improve ePRO Compliance

Patient Factor	Recommendations
Time	<ul style="list-style-type: none"> <li>✓ Use short instruments (when possible)</li> <li>✓ Require low frequency of administration (if appropriate)</li> </ul>
Burden	<ul style="list-style-type: none"> <li>✓ Try to limit the burden on patients – ask necessary questions in an efficient way</li> </ul>
Frustration / Ease of Use	<ul style="list-style-type: none"> <li>✓ Try to prevent patient frustration through making systems simple, straightforward, and easy to use</li> </ul>
System Issues	<ul style="list-style-type: none"> <li>✓ Develop high quality systems supported by Help Desk assistance</li> </ul>
Convenience	<ul style="list-style-type: none"> <li>✓ Provide ePRO options that make it convenient for patients to respond, such as internet and email</li> <li>✓ Offer multiple technology options and flexibility where possible, feasible, and appropriate</li> </ul>
Reminders	<ul style="list-style-type: none"> <li>✓ Remind patients to complete ePRO tasks</li> <li>✓ Ensure patients are equipped to receive reminders</li> <li>✓ Allow patients to select their preferred reminder type (e.g., email, text message)</li> </ul>
Training	<ul style="list-style-type: none"> <li>✓ Train patients to use ePRO technology at the start-up phase of the trial</li> <li>✓ Provide patient with clear instructions</li> </ul>
Support	<ul style="list-style-type: none"> <li>✓ Provide patients with a help/user guide, web site support, and help desk</li> </ul>



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