Zifo
SCIENTIFIC INFORMATICS

A Zifo White paper

ePRO: THE SUBJECT CENTRIC APPROACH

Introduction

Imagine you are participating in a clinical trial, and as the clinical trial progresses, the site wants you to answer a few very personal questions.

For instance, take the **Columbia-Suicide Severity Rating Scale (C-SSRS)** - a questionnaire which collects information on the suicidal behavioural patterns of a person.

Any average person would be hesitant to reveal such personal information face to-face with a site person. That's where Patient Report Outcomes (PRO) come into action, Where the subject can fill in the data independently.

By having a glance into the past...

The first publication of 'PRO' in the title came out in 1976.

With almost 3,000 mentions in 2013[1], PRO data started to get attention through its inclusion in the publications.

To illustrate this, what if the site asked you what did u have for dinner last Friday?

Not very easy to recollect, right?

See how PROs are helpful.

PRO can be traced from paper PRO to Specialized PRO devices to modern-day apps and webpages which function as the ePRO instruments. There are several standardized questionnaires implemented on ePRO (e = electronic) devices, such as:

- Insulin treatment satisfaction questionnaire
- Brief pain inventory short form
- SF-36v2™ health survey
- EuroQol-5 dimensions (EQ-5D)
- McGill pain questionnaire
- Neuropathic pain scale
- SF-36v2™ health survey
- Profile of mood states-brief

ePRO is for everyone

Looking back, earlier studies that replaced paper-based methods with a LINC-2 minicomputer facilitated the entry of ePRO systems into the clinical industry.

As the technology grows, accessibility of the e-diary systems to the participants and its implementation across clinical studies is increasing.

From a LINC-2 minicomputer, desktops to laptops, and finally smartphones, ePRO usage is on the hike.

Let's use a common life scenario: how do you all write down the list of groceries you want to buy?

On paper with a pen, right? I have to get some paper and a pen now. Wait, why search for it when you have Notes on your smartphone? Grab your phone and make your notes. It's that simple. For younger participants, recording everything electronically without having to depend on paper notebooks is very typical.

Let's now assume this is the 1960s. A clinical trial of 1000 participants is ongoing, and the site is busy distributing paper diaries to the participants, which they have to fill out from their homes.

Consider the work site has to put in for distributing paper forms to the participants, which is thousands in number. Imagine the burden of work on the participants to fill it out and understand what to fill in and what not. The font size of the questionnaires also could be a potential drawback since older people might find it difficult to read smaller fonts.

EPRO methods can overcome all these hurdles. Participants don't have to focus on what not to fill, as it would be disabled by the system from the back end. Also, participants can zoom in and zoom out the text as per their preference. On the other hand, sites don't have to put much effort into distributing the paper forms since they will be taken care of online, which won't be a burden, irrespective of the number of participants.

Nevertheless, it is essential to consider different age groups while implementing ePRO into a study, those factors along with age will be explained in the upcoming sections.

ePRO VS Paper PRO

As mentioned earlier, compared to the initial years of PRO, we are now heading towards electronic modes of data collection. Why would paper data acquisition be replaced with electronic data capture in a clinical study? Simple - a study's data variability was reduced by 33 % when paper forms were replaced by electronic forms1.

By agreeing to the fact that all trials are different with different budgets, it is recommended to take a close look at your budget before deciding to use ePRO. ePROs are not yet very common, contrary to what one may think. In 2015, almost half of the trials were still using paper PROs.

Much of this growth might be attributable to the population's massive increase in mobile phones and tablets. According to reports from statista2, the Worldwide smartphone sales in 2015 of 1609 million was almost double that of 843 million in 2012.

Studies on compliance differences between paper diaries and e-diaries have been performed for several years now. Clinical researchers were curious to run an off-site survey when a trial participant was spotted in the site's car park nervously filling out their paper diary just before an appointment; this incident led to the coining of the term "Parking lot compliance."

Several studies have reported that participants are more comfortable using electronic devices to record outcomes when compared to paper diaries. Also, e-diaries are better suited to human nature. Features like alarms, notifications, and reminders help trial subjects fill in the data correctly. Also, e-dairies are password protected, which can provide privacy to the subjects entering sensitive information.

Online and Offline modes

In general, ePRO instruments can be designed in offline and online modes. Application-based and Web-based ePROs require validation for each operating system version (iOS, Android, Windows) and each browser version (Safari/ Chrome/ Internet Explorer, etc) they are used on.

The offline ePRO approach is beneficial in network-restricted areas - as the subject does not require internet connectivity during data entry - and data will be saved once connected to the internet later. One disadvantage of offline mode is that if the device is damaged before data upload, the data could be lost.

ePRO Advantages

One of the most significant advantages that ePRO offers is direct patient feedback at data collection, which turns out to be time-saving as transferring paper data into a database is no longer required. It also reduces data discrepancy and transcription errors by enabling mandatory fields, dependent fields, format checking, real-time data checking, etc.

3 Advantages of Modern ePRO

Top 3 Advantages of Modern era ePRO

1 Supply

The supply of the patient-reported outcome modules is not necessary, as the subject has their own device. The site need not handle any device at all.

2 Training

No additional training is required, as the subject is already trained in accessing the webpages and applications from the mobile. Probably less than the training they would receive if the PRO instrument had been on paper.

3 Maintenance

Any repairs/maintenance works needed for the device will be handled by the subject. Neither the sponsor nor the site need to be involved in this.

In a word, the advantages of modern ePRO include:

Supply: In most cases, sites allow subjects to bring their own electronic device to run trial applications – the approach, commonly known as BYOD (Bring Your Own Device), will drastically reduce a study's cost overall. This strategy has risen alongside the Decentralized clinical trial - where subjects can fill out diaries from the comfort of their own homes.

In a nutshell, BYOD would increase the subject's flexibility in filling out the data since they are familiar with their own device, which they use daily – especially the elderly, who will be uncomfortable with a new device.

Training: Not much additional training is required as the subject is already trained in accessing the webpages and applications from their own device.

On the other hand, even though the subjects are familiar with their own devices, they'll likely be unfamiliar with the ePRO application – for which site staff should put additional efforts in making them comfortable with the app usage. However, these training sessions would likely consume much less time- Probably less than the training they would receive if the PRO instrument had been on paper.

Maintenance: In the event of any damage to the device, the subject shall be taking care of it.

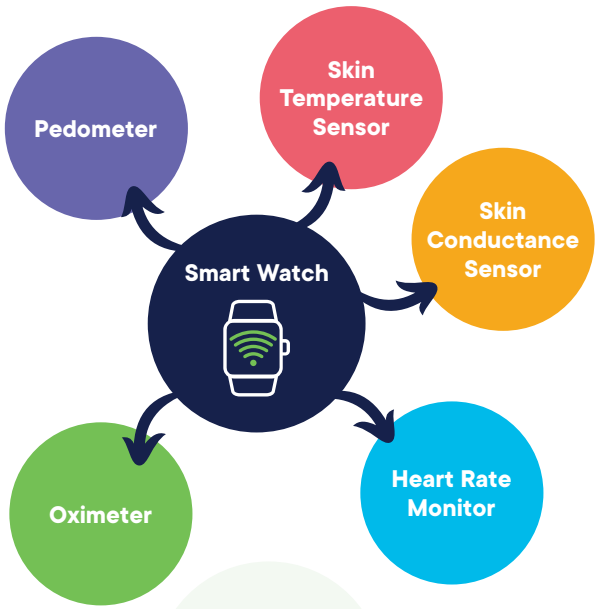
At the same time, the site must troubleshoot the device's security features, capability and performance even before the study starts. The subject is not confined to using their own device solely. There could be scenarios where the subject's device is not up to the study standards. In such cases where the device's performance is compromised, subjects are given the choice to opt for the sponsor-provided device.

Telemedicine in assisting ePRO

Telemedicine devices are essential for the existence and expansion of ePRO. The systems such as Blood pressure monitors, Pulse oximeters, Glucometers, Smart ECGs and, most of all Smart watches aid in the betterment of automatic data collection.

As the telemedicine industry grows, the ePRO industry directly benefits. As new devices are introduced into the industry, sponsors look forward to their implementation in their studies.

Taking smartwatches, the industry is in a rapid growth phase incorporating most of the diagnostic systems within them.



To be clear, there have been scenarios where smartwatches have saved lives.

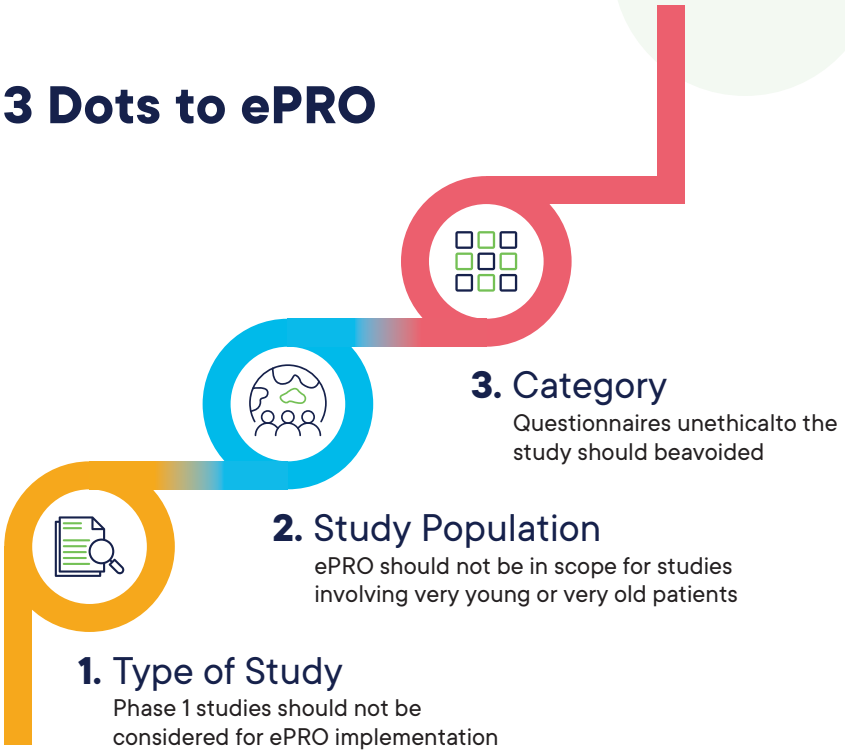
Not so long ago, as the reports say - a 36-year-old with an undiagnosed heart condition got frequent alerts from his Apple smartwatch because of the irregular heartbeat he was having. Soon, he called the UK medical helpline -111, where they advised him to go to the hospital right away.

What's intriguing is that he wouldn't have gone to the hospital if it wasn't alerted by the device. Ideally, the device should send alerts to the hospital, given the information is synced correctly in the smartwatch.

In brief, data acquisition is important in the same way as the data syncing process. Many scenarios have been replicated worldwide, with the endpoint being that devices can save lives! Looking at this from a clinical perspective, the data syncing from smartwatches/telemedicine devices to EDC systems could be better by establishing better integration between the device and the corresponding EDC systems. In such a way, the investigator's work can be reduced to an extent where a monitor would check whether the synced data is valid and up to the regulatory standards. Such modern developments and innovations in the telemedicine devices industry generate a similar uplift in ePRO industry as well.

Predicting the outcomes and fetching real-time data can create a big difference here. Such predictive modelling methods analyze historical and live data to create a 'statistical outcome' predicting how the patient exhibit a specific behaviour in future. The model will be updated as the data is collected. Often, these models combine demographic and lifestyle information from external sources to help create a fault-free, accurate system. These advancements make the ePROs more suitable for clinical studies of various domains and enhance their implementation as well.

Factors in implementation of ePRO into a study



Type of study: Since phase 1 studies focus on safety, ePRO implementation is a strict No! Even minute errors in such information could significantly impact the study output. Such information should be collected on-site, in person, where it is best to use in observational studies.

Study population: The study population is one of the significant factors to consider in the implementation of ePRO. ePRO should not be in scope for clinical studies involving 'Very old subjects', 'Kids/infants', or 'Patients at risk'.

Very old subjects: Participants in the very old age group with little technical knowledge will find it difficult to answer the ePRO questionnaires online.

Kids/infants: Participants in very young age groups would need parents' support in filling out the ePRO forms; in such scenarios, ePRO implementation is not recommended.

Patients at risk: Patients under high risk, such as suffering from severe illnesses, should be excluded from using ePROs.

Category: The category of the Questionnaires should be considered while designing ePRO in a study.

While a major portion of the standard questionnaires are good to go with ePRO implementation, a few questions can be seen as a distress signal, e.g. the quality of life questionnaire – initially, the questionnaire is very typical until it is asked on a patient with very few days left in their life. Such scenarios should be carefully considered while implementing ePROs.

Things to consider

Amidst all the advantages of modern ePRO, certain things must be considered:

i) Prevent the subject from modifying the data entered into the app after a certain period.

ii) Prevent subjects from installing any apps that might affect the ePRO app or the data collected by it.

iii) Prevent the subject from deleting the ePRO app.

These pitfalls can be overcome by implementing certain features on the smartphone/tablet where the ePRO app is installed.

Smartphone distribution can be managed by the clinical team so that the security features can be implemented successfully in the device - thereby preventing data loss or misusage by any unauthorized app installations or the subject mistake itself. This can ensure the integrity and security of the data collection process.

If it's BYOD (Bring Your Own Device), the site can install security features to support data integrity and security. An alternative to this would be locking the data once entered, thereby ensuring data modification at another point in time.

The industry demands an ePRO instrument to have certain features:

ePRO Features

Industry demands an ePRO to have the following features

Easy to use for participants

Easy to use for site staff

Cost effective

Flexible

Regulatory compliance (21 CFR Part 11)

However, given that ePRO applications would comply with the General Data Protection Regulations, surveys3 indicate that almost 30 % of the subjects were concerned about their data privacy.

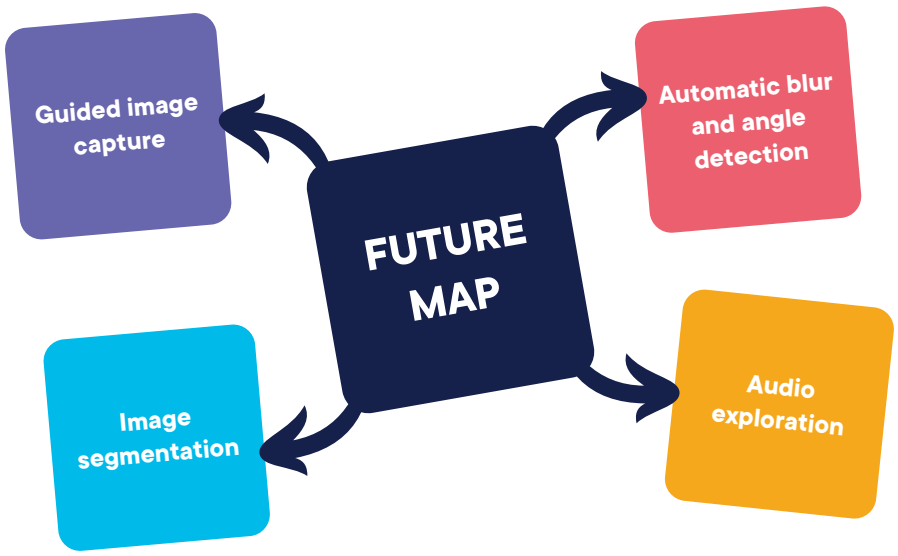
Furthermore, patients' difficulty using electronic devices and other technical issues, such as login, etc., have been reported in another survey 4 conducted by BMC. However, these were easily overcome by providing adequate training and assigning a trainer / POC for subjects.

This blog's author has experience receiving specific requirements from the sponsor, saying that all the options for the given question should be covered on a single page so that the subject doesn't have to scroll. These kinds of measures certainly aid in helping trial subjects, especially the elderly, to fill out data in less time without technical difficulties and bias.

Future Scope

From a clinical trial participant's point of view, ePRO usage and comfort level with technology are entirely dependent on the subject. But the credibility of the data is crucial.

For example, blurry images or audio recordings with ambient background noise are often unusable by the trial sponsor. This can put the participant in a stressful state where they must recapture the data to meet quality benchmarks. Still, we see AI helping subjects resolve these problems in real-time – meaning fewer data issues and better trial compliance.



Guided image capture: This can help the subjects on how to focus the camera and where to focus. For instance, the application can detect whether the patient's face is in the right place and correct it if not. This will eliminate the manual errors in the images and help the participant to get a better image.

Automatic blur and angle detection: Help the subjects determine whether the image is clear to use for further examinations. Participants will clearly understand whether the image is straightforward to use for other examinations.

Image segmentation: Can identify and eliminate unwanted visual elements such as PHI [Protected Health Information]. As said, any information other than required is unnecessary and should be eliminated from the image.

Audio exploration: AI can help eliminate unwanted noises from the audio data, such as Coughs, infant cries, hoarseness, etc. AI will help eliminate false negatives and positives and ensure data collection accuracy. In this way, participants can generate a valuable outcome for the site.

Conclusion

Even though several challenges and hurdles exist, ePRO makes clinical trials more patient-centric. Moreover, it makes the subject participation simpler and less complicated. The rapidly growing tech industry is delivering services and tools that are highly valuable to the ePRO industry. Modern trends such as 'Decentralized clinical trials' certainly demand the service of ePRO- which makes ePROs more of a need than not a choice. However, the ePRO industry is expected to grow by 15 % between now and 2025[1]. We hope to see that the use of ePROs becomes more common in the future, which, in turn, will make clinical studies more patient-centric.

References

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