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Industry Report

Electronic Patient Reported Outcome (ePRO) – Adoption State in China Clinical Trials

2019 // By Le Song, Kevin Lin
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The incorporation of the patient perspective in the evaluation of medical products (i.e. drugs, biological, and devices) is increasingly important and considered essential in many cases. Medical products aimed at relieving patients' symptoms and/or improving levels of self-reported functioning will require measures of patient reported outcomes (PROs) as end points in clinical trials. A PRO instrument systematically collects treatment benefit data directly from patients, without interpretation by clinicians or others[1]. In addition to the FDA's increased focus on well-defined and reliable assessment of clinical trial end points, one of the most important developments in the field of PRO measurement has been the emergence of technologies that enable the collection of data electronically. Advantages of using electronic data collection include less subject burden, avoidance of secondary data entry errors, easier implementation of skip patterns, date and time stamping, reminders/alerts, edit checks, and more accurate and complete data [2-9].

An electronic patient-reported outcome (ePRO) is a PRO that is collected by electronic methods. ePRO methods are most commonly used in clinical trials, but they are also used elsewhere in healthcare. As a function of the regulatory process, a majority of ePRO questionnaires undergo the linguistic validation process. The two main methods currently used for ePRO are computers/smartphones and telephone systems and research has shown more people prefer device-based ePRO applications to non-device-based applications[10]. As time develops, the newly evolved BYOD mode creates infinite imagination space towards heath outcome collections in all possible directions such as real world evidence exploration and virtual trial set up. The recent conducted survey reveals the adoption state of ePRO in China clinical trials and voices from the local trial community upon e-clinical use.

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Foreign Regulatory Voice

Regulatory bodies such as FDA and EMA has made vital efforts in helping with the transition from paper based PRO to ePRO. This transition, along with FDA's release of the PRO Guidance, has elevated the science of PRO measurement. Among the regulatory bodies of the world, the FDA has taken a leadership role in advancing sound COA endpoint assessment. For example, the following quote from the PRO Guidance explicitly endorses the functionality of electronic data collection platforms and, hence, implicitly endorses the shift to ePRO: ''If a patient diary or some other form of unsupervised data entry is used, we plan to review the clinical trial protocol to determine what steps are taken to ensure that patients make entries according to the clinical trial design and not, for example, just before a clinic visit when their reports will be collected'' .[1]

Overseas Adoption

ePRO has been utilized in global clinical trials for decades and recent survey report has shown that over 60% of clinical trials conducted in US and Europe has included ePRO solutions as a standard data capture tool, that percentage is expected to increase to 74% two years from now.

Specifically, overseas research figure has shown 56% of Phase I, 63% of Phase II, 68% of Phase III and 67% of Phase IV trials will have an eCOA/ePRO component. By the year 2018, each sponsor/CRO is using an average of 3.2 eCOA/ePRO systems providers, it's also anticipated that an average of one additional system provider will be utilized in three years' time.[10]

Percent of clinical trials using eCOA/eRO: 2016–2020[10]

39% >> 56%	46% >> 63%	52% >> 68%	49% >> 67%
Phase I	Phase II	Phase III	Phase IV

Average number of eCOA/ePRO system providers used by each Sponsor/CRO[10]

3.2	4.2	1.9	2.6
Average number of eCOA/ePRO systems organizations are currently using	Average number of eCOA/ePRO systems that will be used in three years	Average number of official preferred eCOA/ePRO providers per organization	Average number of official preferred eCOA/ePRO providers per organization in three years

Survey Methods

The design of the study is in the form of an electronic survey which was distributed through new media platform (i.e. wechat) and large clinical trial forum exhibition center. And volunteered participants' general demographics such as type of company they work for and their roles and responsibilities were collected at the beginning of the survey questionnaires. Afterwards, participants were asked to answer 9 questions regarding ePRO and 2 other questions on the general e-clinical field. Data collection and statistical reports were performed and generated automatically by electronic system.

Demographics

There are altogether 90 participants joined the survey study and 71 electronic questionnaires were successfully submitted and returned for statistical analysis. 19 e-questionnaires were lost due to technical issues mainly with the net connection.

As shown in Figure 1 and Figure 2, most participants came from pharmaceutical and CRO companies and they mainly take responsibilities in different parts of the clinical trials including portfolio management, project management, data management, inspection as well as service outsourcing.

Figure 1 Type of company participants work for

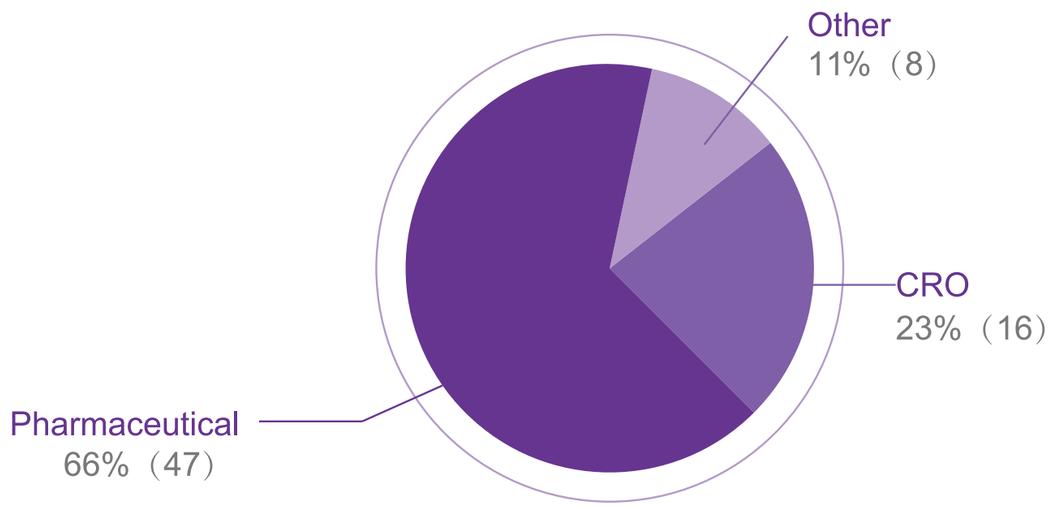
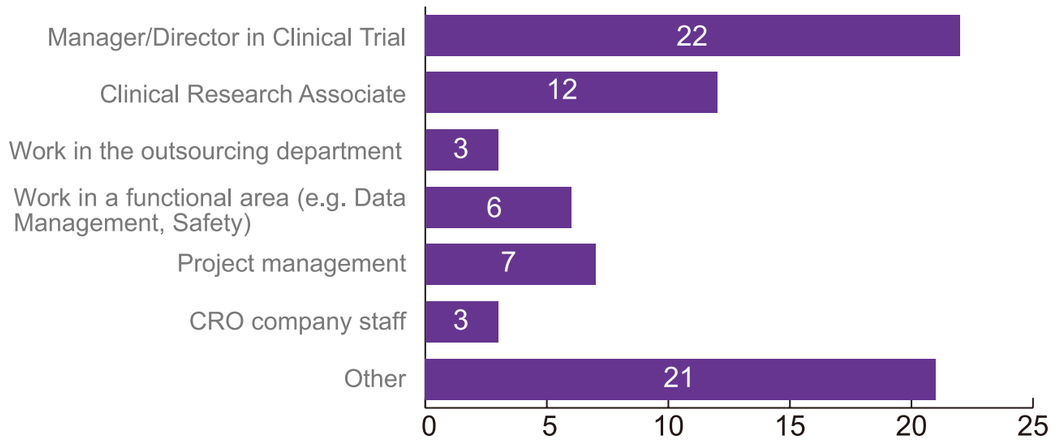


Figure 2 Participants' roles and responsibilities for



Status of PRO and ePRO in China Trials

Eventhough the concept of PRO has been raised a lot more often these years especially in western and developed countries, it's still quite underused in China trials as shown in Figure 3. The majority people had very limited PRO use experience in their trials. There are 12 people claimed that PRO was included in only 10% of their trials and only 10 people had PROs in over 80% of their conducted trials.

However, interestingly 63% of participants had some experience in using ePRO before whereas 37% of people have not yet used in the past trials (Figure 4). This figure was further analyzed by the sub-group of company attributes which divide multinational pharmaceutical and CROs from local ones. It was found that the 42 out of 45 people who answered positively all came from cross-border companies which may be due to the larger possibility for conducting international multi-centered projects where ePRO was prevalently adopted.

Figure 3 Percentage of participants' managed trials involved PRO

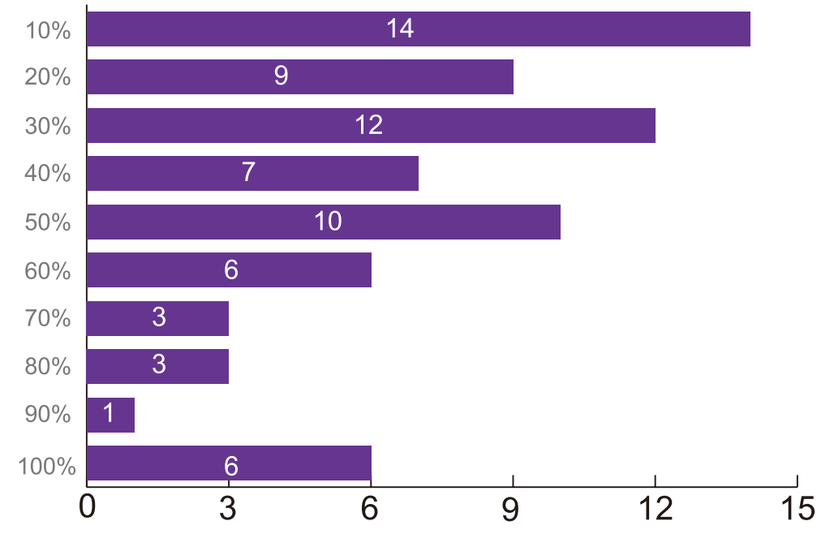
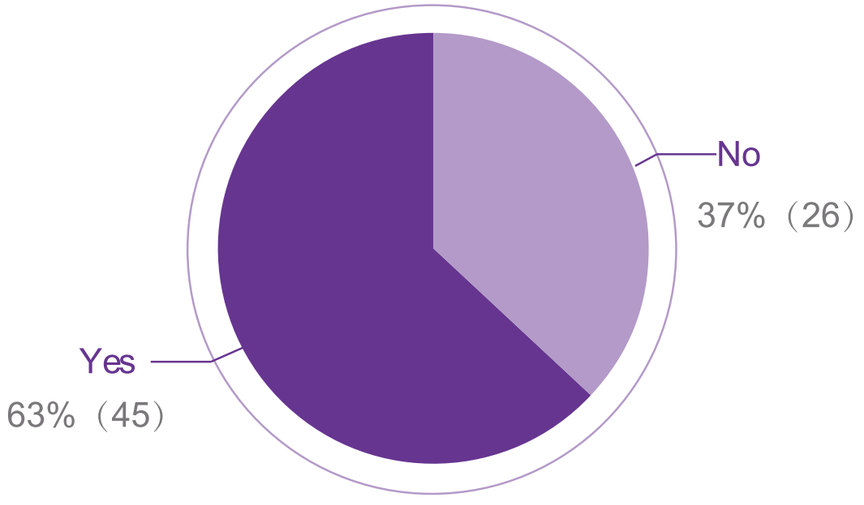


Figure 4 Percentage of participants has used ePRO



Paper Diaries VS Electronic Diaries

While collecting opinions on the preference between ePRO and traditional paper diaries, 82% of people admittedly favored ePRO and 18% supported the old paper-based model (Figure 5). This is compliant with other industry reports that paper-based model is ought to be transformed into e-model, and there have been study reveals that mobile electronic data captures have become the new state of the art methods[10].

As for the benefits of ePRO utilization in clinical trials, data accuracy optimization was chosen to be the top benefit among all and real time monitoring of trial progress came as the second advantage. About 25% of people agreed on the other benefits including cost containment, reducing site inspection issues and other trial software integrations (Figure 6).

The questionnaire also covered people's thoughts on the disadvantage of using ePRO, as shown in Figure 7, nearly half of participants worry that trials subjects may have difficulty reporting through e-version. This result double confirms that ePRO is still in its early phase adoption in China and the number of subjects have experienced an ePRO contained trial is still too small to either show firm evidence in its difficulty using or to dispel the general worry of people towards new methodologies. There have been overseas' studies showing that patients actually preferred the e-reporting way to paper-based reporting and of course this needs to be validated for the Chinese group[11].

Figure 5 Participant's preference between paper PRO and ePRO

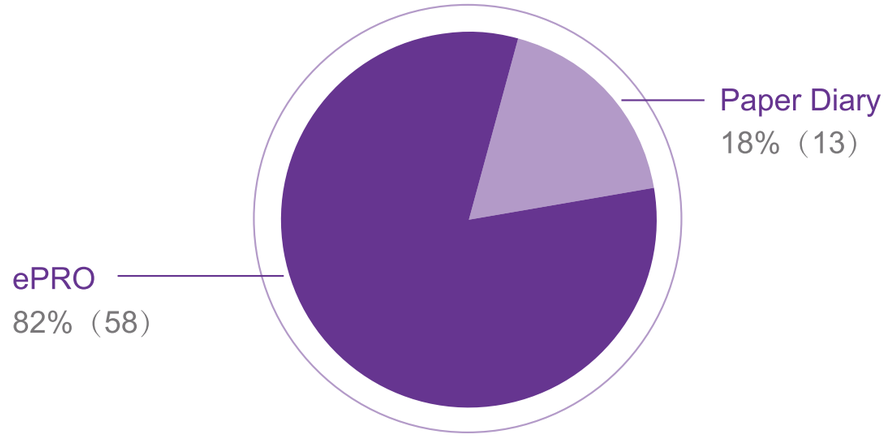
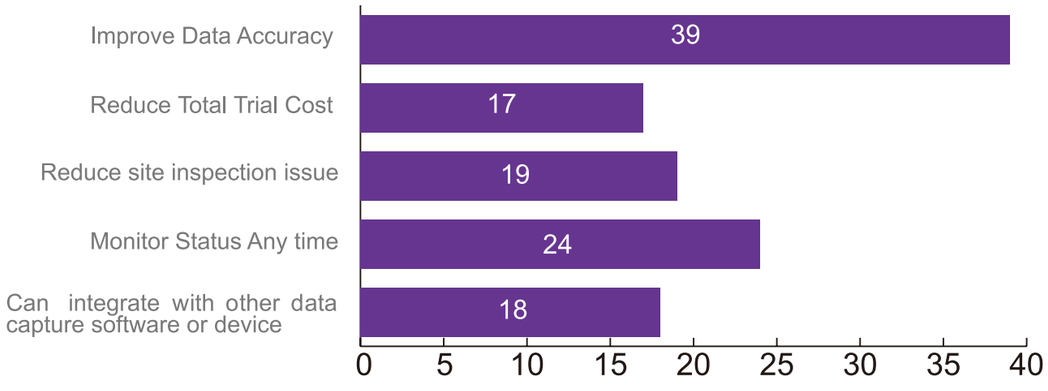
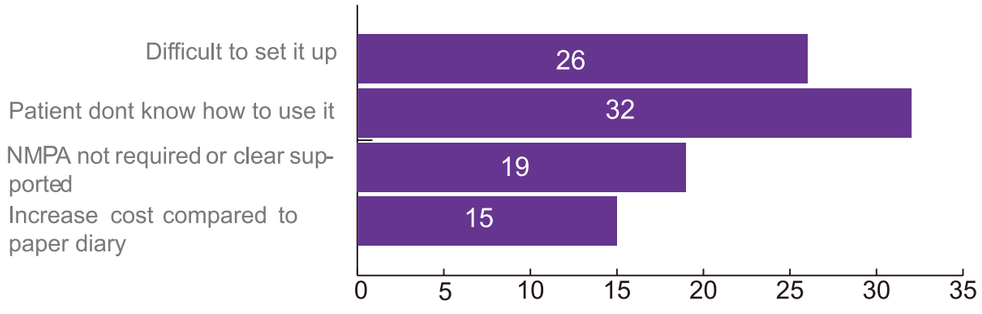


Figure 6 Participants' view on ePRO benefits



Another important factor for this concern is the lack of training in China while adopting ePRO as clinical staff is too busy to provide instant assistance and repetitive trainings to trial subjects. Therefore, ePRO vendors would have to take on more responsibilities and try to engage as much as possible with more alternative service options for all parties in the trial. About 37% of people have chosen “difficult to set up” as a disadvantage. This was reasonable as research has shown that the main challenge for ePRO is the migration validation process[12]. However, as more and more widely used PRO instruments are migrated into electronic version, those end-products have enabled simpler and faster future trials adoptions. With the addition of modern IT technology, the ePRO set up time frame has been significantly reduced. 19 people had concerns with NMPA’ vague attitude and 15 people thought that ePRO increases cost compared to paper PRO. The national governing bodies do play extremely important role in not only supporting new transitions but also leading with guidance. In the past 2 years, we have witnessed how NMPA has transformed and opened to connect more closely with international organizations. We believe that time is only consumption for the local trial community to become more confident in adopting new methodologies. Last but not least, global ePRO vendors have done a statistical cost analysis compare ePRO and PRO in a large phase III trial. Results have shown that there has been a substantial reduction by using ePRO[13]. For the cost increase opinions, it would be interesting to conduct a study to gather more evidence on the cost data in the local trials.

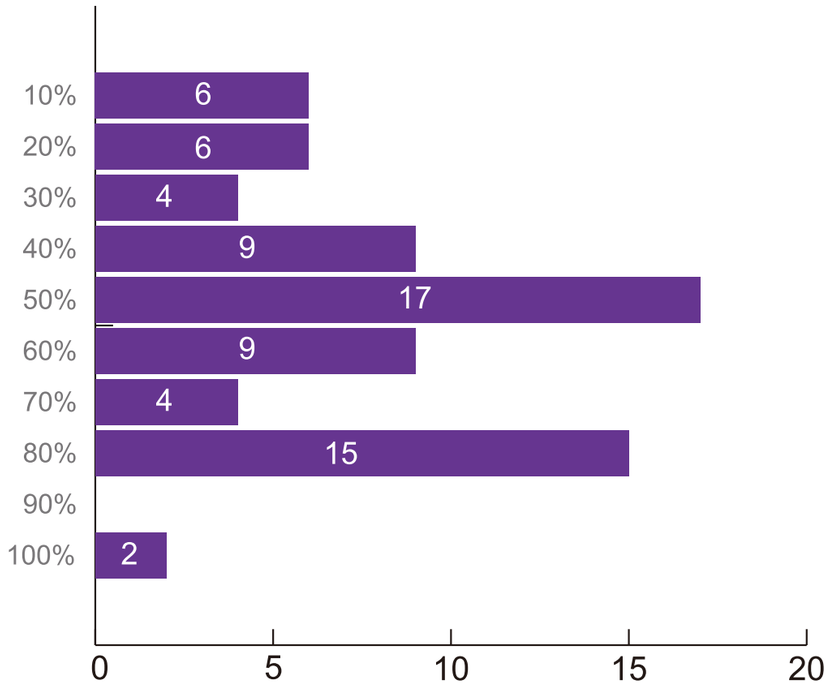
Figure 7 Participant’s view on ePRO disadvantage



The future Market Prediction of ePRO

The survey also investigated the people's views on the 5 year prediction of ePRO adoptions. Over 66% of people believe that 50–80% of all trials contained PRO will be using electronic version instead of paper version in 5 years time (Figure 8). There was a similar survey question taken place in the global market and its result has shown that the percentage of ePRO use through different trial phase would reach 56–67% within 2 years[2]. Both results have shown promising trend for the e–transformation.

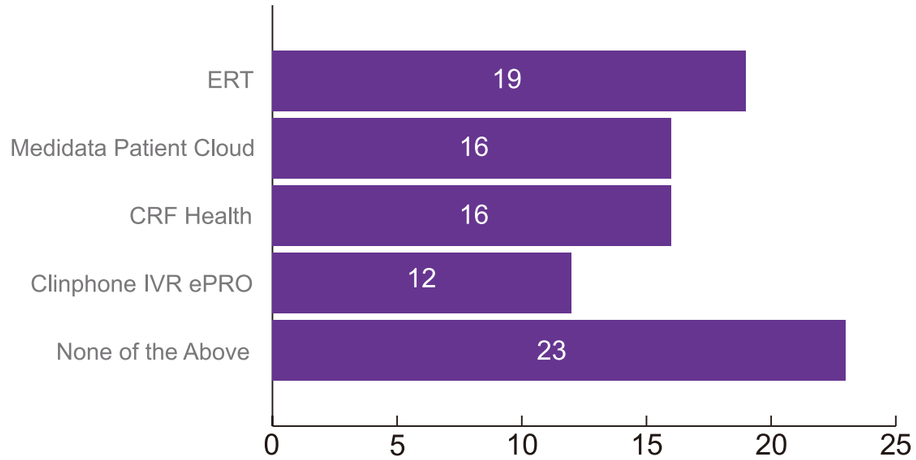
Figure 8 Participants forcast for percentage of ePRO use over total PRO in 5 years



User Preference Over ePRO Providers

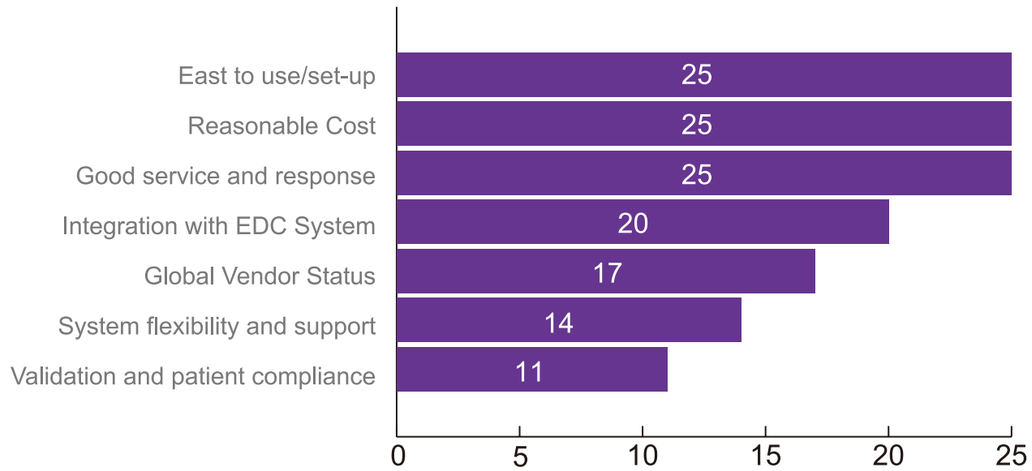
Currently, all market recognized ePRO brands come from US and European regions including ERT, Medidata, CRF and clinPhone. Eventhough there have been few new local market players, the brands are not yet recognized by the China trial community such as Jsure ePData, BioKnown ePRO. Over 32% of people have never heard of any listed ePRO vendors, this objectively reveals the lack of marketing activities of ePRO providers in China. (Figure 9)

Figure 9 Participants known ePRO vendors



Three factors came on top of the consideration points for vendor selection which are easy to set up/use, cost reasonable with good service and response. Those feedbacks fell into expectations while there are still lots of improvements to be done for the current ePRO utilization status and user experiences. Multi-platform integration is a future trend as more electronic data capture tools and methods are adopted and for vendors who are capable of providing seamless integration service among all are definitely a plus in the selection process[14]. In addition, since China has joined ICH with many open policies being taken effective, having had experience in global trial and get qualified as a global vendor is a firm way of showing vendor capabilities, so 24% of people have included it in their selection. Surprisingly, only 11 people chose validation and patient compliance while in the previous question, patient not knowing how to use it was marked as the most concern of ePRO (Figure 7&10). This could due to the fact that most data on patient compliance came from foreign countries and the local trial staff is still reserved to the foreign data as for different races and culture.

Figure 10 Participants' considerations towards ePRO vendor selection



More About e-Clinical Solutions

In the end of the questionnaire, 3 questions were included to investigate participants' views on the other e-clinical status such as e-consent and greater integration with HIS, LIS and smart devices for phase II/III trials. As expected, the majority of people has already heard of e-consent and believes in its gradual adoption for trials in 5 years time. Most people also think positively on the integration of data capture platforms and admit to the unstoppable electronic trends as already happening and affecting our daily life. (Figure 11-13)

Figure 11 Percentage of participants heard of e-consent

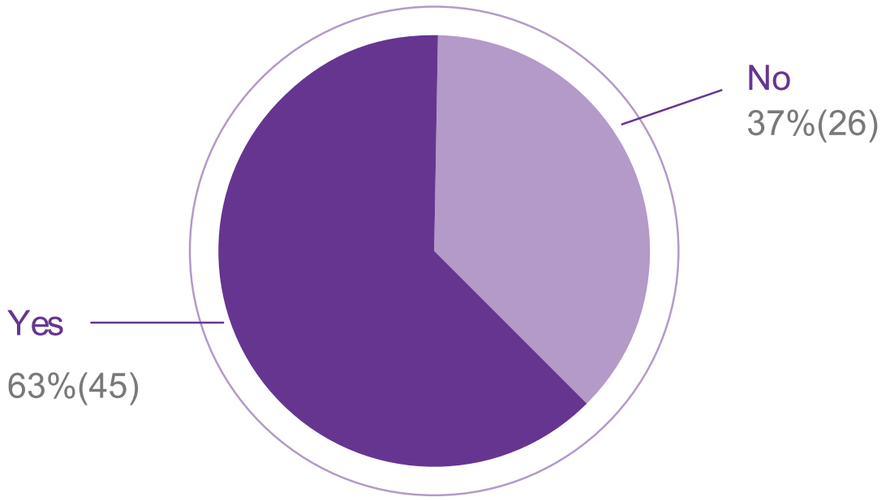


Figure 12 Participants' forecast for percentage of e-consent use in clinical trials in 5 years

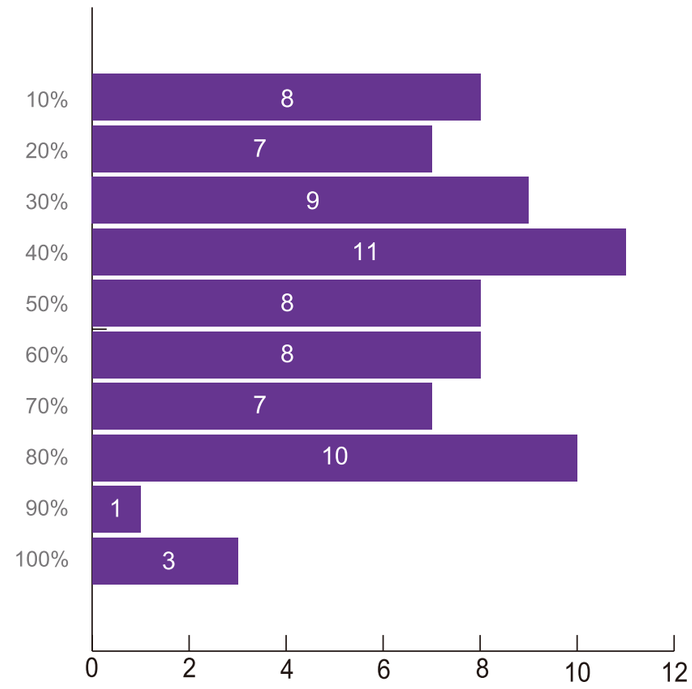
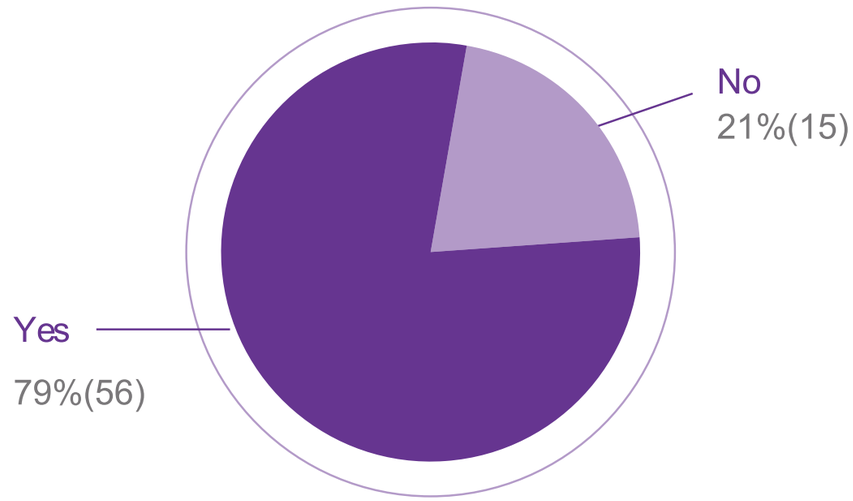


Figure 13 Percentage of participants who believe in HIS, LIS and smart devices integrations for phase II/III trial



The ePRO Way to Clinical Success

The movement toward ePRO data collection has been one of the most significant advances in PRO measurement. Its numerous advantages over paper-based data collection result in more complete and accurate PRO datasets, which could be the difference between a failed and successful clinical trial. The significance of this has not been lost on the regulatory and scientific community. The FDA has asserted its support and expectations for electronic capture of clinical trial source data, including PRO endpoints[1, 15]. ISPOR has established three task forces that have issued ePRO related good research practice recommendations[16-18].

Although ePRO adoption in China is still at the beginning phase, as the local governing bodies and trial community become more globally recognized towards closer international collaborations, it is no doubt that China market would move fast to enhance all aspects of trial qualities. And this industry survey study has not only provided us with the current status of ePRO adoption, but also valuable suggestions and wishes for the e-clinical field for the next 5 years. From here, we could conclude that the future of ePRO data collection in clinical trials is bright and, although there remain a number of issues to be resolved for better user experience.

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