

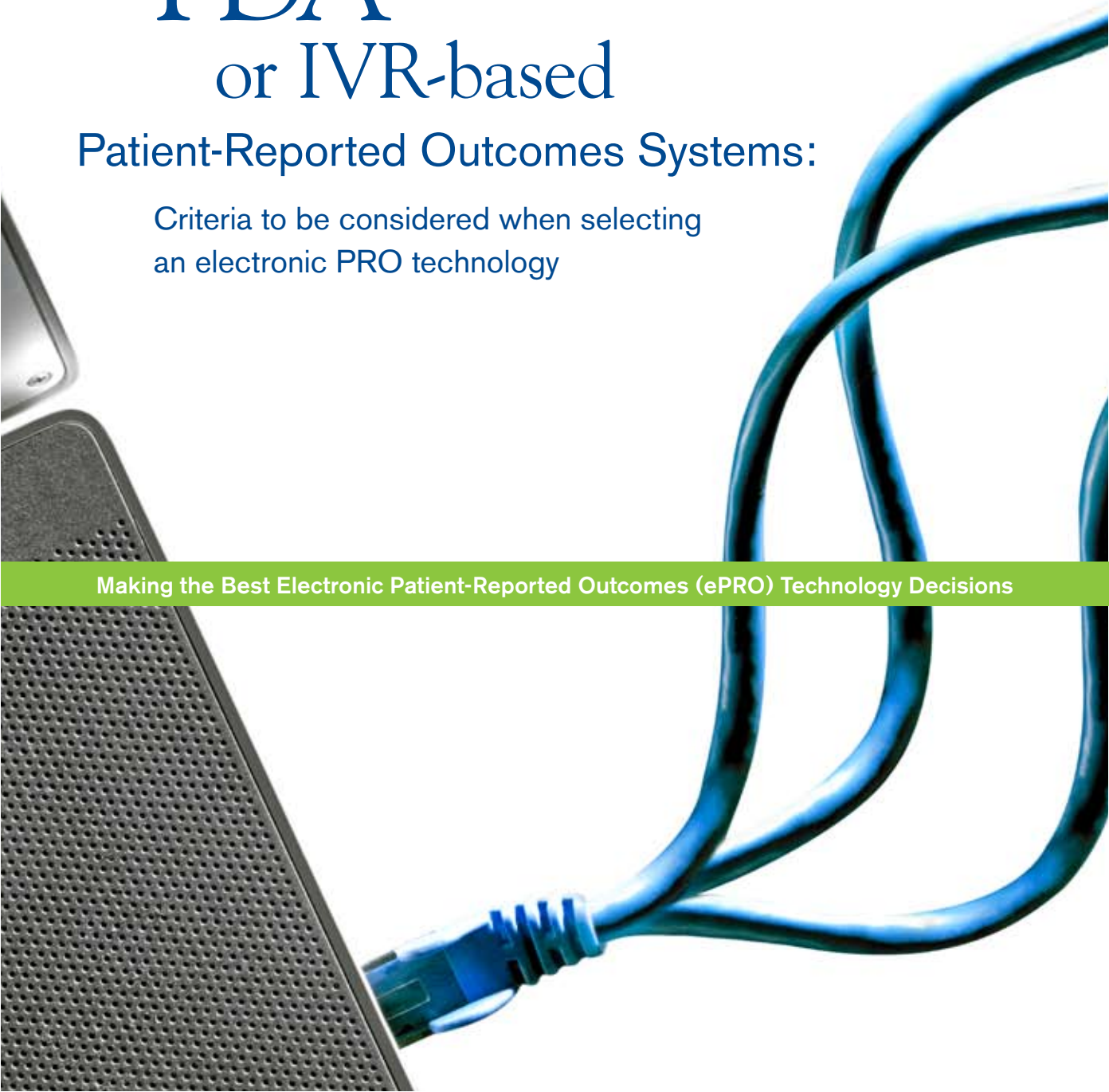


PDA or IVR-based

Patient-Reported Outcomes Systems:

Criteria to be considered when selecting
an electronic PRO technology

Making the Best Electronic Patient-Reported Outcomes (ePRO) Technology Decisions



Overview

This paper describes an electronic patient-reported outcomes (ePRO) modality decision tool that provides a systematic, standardized framework for assessing the utility and feasibility of the two main electronic patient-reported outcomes modalities: handheld device and interactive voice response (IVR) systems. The components of this tool are based on published and unpublished research as well as the substantial experience of two ePRO market leaders. These elements have also been further validated by market research with clinical trial sponsors. The use of a more informed process for selecting a mode on the basis of the user's needs and study requirements will result in more effective clinical trial planning and greater study efficiency.

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Introduction

Based on current scientific knowledge and collective practical experience, the modality decision tool applies an objective score for numerous study-specific factors. Thus, it provides a basis for determining which modality is preferred.

As far as we are aware, this is the first ePRO modality tool made available to multiple sponsors to aid in identifying the ideal solution based on individual study requirements. The tool is proprietary, so we do not provide the precise scoring algorithms and methodologies in this paper, but instead detail the logic behind a variety of important study-specific factors.

The migration from paper to electronic is perhaps one of the most significant recent advances for patient-reported outcomes (PROs). Although there are major advantages to collecting data electronically, it is not always clear whether sponsors view these technology systems from the perspective of what is best for patients who will be enrolled in clinical trials. The US Food and Drug Administration guidance states that sponsors must demonstrate evidence of mode equivalence and conduct end-user testing when using an electronic version of an existing PRO instrument that has been validated in paper format or originally developed as a clinician interview.

There is little peer-reviewed or publicly presented information addressing the important principles to consider when selecting an ePRO system. Accordingly, the goal of this white paper is to describe the important factors sponsors should consider when selecting an electronic PRO modality. To achieve this goal, this white paper will:

- Discuss the pros and cons of the various ePRO modalities;
- Explain the important study-specific differences between device- and IVRS-based ePRO;
- Describe the modality-specific validation or documentation required when using an IVRS- or device-based ePRO system; and
- Demonstrate that there are circumstances in which one modality is clearly preferred over the other.

It is our contention that general sponsor preferences (e.g., this solution “works for us”) should not serve as the basis for an ePRO modality decision. Instead, modality decisions should be based on a comprehensive consideration of scientific and economic factors relevant to a specific project or study.



What factors are important when selecting a PRO technology?

Typically, there is no single deciding factor when choosing between modes for administering ePRO. Preferably, the appropriate modality should be determined by careful consideration of multiple study-specific parameters. These include: the nature of the outcome measures used, the patient population that will be studied, and required PRO assessment schedules. Not surprising, many of the aforementioned study-specific factors will have an impact on study support requirements and associated costs.

Instrument/Study Measure Characteristics

Characteristics of the instruments or measures to be used in a study are important factors to consider when deciding on an ePRO modality. Since there is the potential for instrument-related factors to influence patient responses, it is essential for sponsors to think through the following:

1. How many questions are the subjects asked?
2. Are the questions and/or response options in the instrument lengthy or complex?
3. What if the instrument uses a visual analog scale or other graphic type of presentation?
4. Can clinician-administered instruments be modified for use as self-report ePRO measures?






Length or Complexity of Instrument Measure

PRO measures vary substantially in length and complexity, and care is needed to avoid an excessive burden to subjects. Careful attention is needed for instruments that are lengthy or require administration over an extended duration of time. Based on our experience, the more frequently an assessment must be completed, the shorter it must be to maintain satisfactory compliance. Depending on the circumstances, lengthy measures are more appropriate for device-based measures because completion of IVR questions can take longer and in some cases more information must be remembered by the subject. IVR systems can be complemented by providing convenient, written versions of the questionnaires to reduce memory load. However, it is still important to realize that, as the number of questions and duration of the telephone-based administration increase, so too will the patient workload.

Screen layout needs to be considered for implementation on devices, particularly smaller ones. Splitting questions, responses or instructions across two or more screens may help to fit material onto a palm-sized device, but can also increase memory load because material presented on one screen must be remembered when a response is made on the next screen. This is generally not an issue with larger devices.

It is essential to consider how much effort is required by the subject to complete a particular instrument before deciding on an electronic PRO modality. If subject burden is increased by an electronic implementation, it will be necessary

to provide evidence that this increase has not affected patient responses. Issues of equivalence and validation are discussed in more detail in a later section of this paper.

Device	Length & Complexity	IVRS
<p style="text-align: center;">  Either option will work well when questions are straightforward and responses do not require detailed description or explanation.  </p>		
<p>  Questionnaire length is no more of a problem for patients using ePRO than for paper. </p>	<p>Does your application include a lot of questions, or long responses or instructions?</p>	<p>  For complex or lengthy measures, it is important to think through patient burden and user acceptability. It may be prudent to provide subjects with written versions of instruments to reduce memory load. </p>
<p>  If questions or instructions need to be split across screens, you may need more work to show equivalence. Or you could use a larger device. </p>		

Visual Analog Scales (VAS) or Graphical Scales

In determining which mode is most appropriate, the first question to address is what kind of scale is to be used. The classical VAS consists of a line with the ends marked with anchors, but with no subdivisions or numbers along the line

(Zealley and Aitken, 1969). In contrast, for numeric rating scales (NRS) subjects enter a specific number to describe a threshold range for a given health outcome (i.e., an 11-point scale with 0 = no pain and 10 = worst possible pain (Jensen et al., 1986). These two types of scales are shown below.

Classic Visual Analog Scale:

Make a mark on the line to indicate your level of pain now

No Pain
Pain as bad as it could be

Numeric Rating Scale:

If a zero (0) means “no pain” and a ten (10) means “pain as bad as it could be”, on this scale of 0 to 10, what is your level of pain now. Put an “X” through that number.

0	1	2	3	4	5	6	7	8	9	10
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There is some confusion in the literature because the term VAS may sometimes be applied to either type of scale.

Increasingly numeric rating scales are being preferred to classical VAS for PROs in general (not just ePRO). Thus, the current IMMPACT paper (Dworkin et al., 2006), referring to pain measurement, states “VRS (verbal rating scales) and NRS measures tend to be preferred over VAS measures by patients. Furthermore, VAS measures usually demonstrate greater amounts of missing and incomplete data than NRS measures, presumably because NRS measures are less abstract and easier to understand.”







Numeric rating scales present few problems for migration to either a device or to IVRS and this may be an additional reason for preferring them to VAS.

If, however, a classical VAS containing a descriptive anchor and straight line is required, you should first consider using a device-based system because less modification is required to the scoring scheme. With smaller devices the

scale may need to be shorter than with paper and this will need supporting documentation. There is data to support scale equivalence in this situation (see Jamison et al., 2002).

Recent evidence also suggests that the health state rating in the EQ-5D, an instrument that has elements of both a VAS and an NRS, can be administered validly in IVR- and device-based formats (Lundy and Coons, ISPOR 2008; Ramachandran et al., 2008).

There are also other uses for graphical displays. An example of this could involve displaying body diagrams for identification of a pain location. A device-based ePRO system provides the simplest approach and is the recommended modality for this specific type of measure if it is converted with minimal changes. However, if supportive paper-based materials are provided to subjects, there is no reason to believe patients could not validly and reliably enter this information accurately via IVR. For such an IVR circumstance, evidence of equivalence and patient use of supportive material may be required.





Device	Graphics	IVRS
<p style="text-align: center;">  Both IVRS- and device-based systems will work well for a numeric rating scale (e.g., an 11-point scale with 0 = no pain and 10 = worst possible pain). This type of scale is equally suitable for use with either modality and is increasingly being preferred to the VAS.  </p>		
<p> Device-based ePRO readily supports graphics.</p>	<p>Does your application require graphics, such as body diagrams or visual analog scales?</p>	<p> Recent evidence supports visual analog scales can be converted to numeric rating scales via IVRS. In many instances, this requires a small scale equivalence study.</p>
<p> Visual analog scales may need to be reduced in size to fit. This will need to be documented – there is evidence to support this.</p>		<p> IVR-based ePRO cannot support graphics directly but graphical material can be supplied as supplementary material.</p>

Clinician-Administered Instruments

Clinician rated outcomes are distinct from PROs, but many offer a useful framework for assessment that can be adapted for use as a PRO. A substantial amount of work on implementation of such instruments as IVR-based PRO has been reported (Mundt et al., 1998; Mundt et al., 2006).

If a clinician-administered instrument has not been previously validated for use in an IVR- or device-based ePRO format, it will require full validation and testing. For device-based ePRO, it is important to keep in mind that conversion

from a verbal to visual assessment will potentially require more development and validation work to administer. There are clinician-based instruments from the field of psychiatry and related disorders that have been validated in an IVR format, and consequently, there is a longer history of migration of clinician-based instruments into this format. Because the assessments are spoken or verbal, fewer changes are normally required in migrating them to IVR and it is widely believed that IVR-based ePRO is the preferred modality for clinician-based instruments being converted to a self-report format.

Device	Clinician Interview	IVRS
 Device-based ePRO can support conversion from a clinician-administered instrument to patient self-report, but additional modification is required.	What should I use if I want to convert a clinician-administered instrument into a patient self-reported measure and implement in an ePRO format?	 IVR-based ePRO is the preferred modality for clinician-based instruments because the task is similar and assessments are spoken thus requiring fewer changes.
 Clinician-based instruments would require more development in a device-based format. The task will change from auditory to visual and one will need to document validity.		 There is a much longer history of migration and numerous examples in the field of psychiatry to support the use of telephone-based systems.



Patient Population



It is sometimes believed that older patients may have difficulty with ePRO either because they are less likely to be familiar with computer technology or because of cognitive limitations associated with aging. This is not the case, at least for normal aging. Our experience and published research show that age itself is not associated with either compliance issues or user acceptance of device- or IVR-based systems (McKenzie et al., 2004; Piette and Mah 1997; Tiplady et al., 1997). Older patients, including those who are unfamiliar with computer systems, are comfortable using either type of ePRO system and generally prefer them to paper. In fact, we have data to suggest that older patients are more compliant than younger ones (Meacham, 2008 ISPOR Poster).

Patients with substantial cognitive or memory impairment, such as that due to Alzheimer’s disease, are another matter. Patients with cognitive difficulties may be better assessed with device-based ePRO as less material has to be held in memory. Clearly, there is a degree of cognitive impairment that will render a patient incapable of completing any kind of PRO measure



adequately and, in these cases, proxy assessment by a caregiver might be considered. However, outbound calling adds some logistical challenges; thus, if assessments are very frequent on a daily basis or if convenient reminders are required, device-based ePRO is our recommendation.

Literacy is another important factor to consider. There is some research suggesting that having questions and responses read to patients is the preferred method when dealing with functional illiterate patient populations (Crow, 1986; Henriksen B, 1999). Accordingly, IVRS-based ePRO is not a constraint in this situation. Alternatively, device-based ePRO requires that patients are literate and this should be clearly specified in the inclusion criteria.

Language is an important issue for PRO in general and there is extensive literature on ensuring equivalence of PRO measures across different languages and cultures. However, this is not an important factor in choice of modality as both IVR and devices can handle all the languages likely to be used in a clinical trial. Issues raised by country/location are discussed in a later section.

Device	IVRS
 <p>Cognitive difficulties. Patients with cognitive difficulties may be better assessed with device-based ePRO as less material has to be held in memory.</p>	 <p>Reading difficulties. Patients who are illiterate or have poor reading skills are not suitable for device-based ePRO (or paper) but IVR may be successfully used in this group.</p>



Device	Alarms or Assessment Reminders	IVRS
 <p>These are readily implemented on a device and have been shown to help compliance.</p>	<p>Does your application require alarms or reminders?</p>	 <p>Patients can be called by the system. This is a less flexible approach than is available with a device.</p>

Assessment Frequency and Reminders

Defining how ePRO assessments will be used is a key part of the trial protocol. Aspects such as the frequency of assessment, quality of user interface, and feedback and reminders to patients will influence patient compliance, which is crucial for good data quality. Clearly, the simpler the protocol, the easier it will be to implement either an IVR- or device-based ePRO system.

If the protocol requires more than twice daily assessments, these may need to be made wherever the patient is located. In this case, device-based ePRO is likely to perform well as patients can carry the electronic device with them and have convenient access to the assessment. When entries are to be completed frequently, alarms and reminders may be used and these are readily implemented on a device. Device-based ePRO can offer flexibility by allowing the user to control alarms. Additionally,

there are alarm options available that repeat with gradually increasing intensity if the user has not responded. IVR systems can be designed to make automated outbound calls to patients and these systems have been successfully implemented. In our experience, offering assistance or encouragement to such patients can help improve compliance.

In contrast, assessments administered daily, weekly or less frequently might be more appropriate for IVR because patients would not need to have constant access to a device based e-diary and could simply complete the assessment over the telephone. Also, the use of IVR for assessments that are administered weekly or less frequently has the potential to reduce patient burden and study cost.

The study's schedule of PRO assessments also has cost implications and this is discussed in a later section.





A glucose monitor communicating with an ePRO device via Bluetooth®

Data Integration and Access

Both modes provide high levels of data security and integrity. Device-based ePRO systems generally use store and forward, which means that data collection does not depend on a network connection. Data will normally be transmitted to the central server immediately after the entry has been made, but if this is not possible it will be transmitted automatically the next time a connection is available. Data are not deleted from the device, which serves as backup data storage.



For IVRS-based ePRO, the ubiquitous nature of the telephone means that patients can readily access the system from almost anywhere at any time. The “up time” of the phone and any robust IVR system is practically 100 percent. With IVR, data are always stored immediately on the server. Further, the data are immediately available on the IVR database as soon as the patient records the entries.





For both IVR- and device-based ePRO, access to the data is an important feature. Both modes allow access to data in real time or near real

time, which allows patient compliance to be monitored on an ongoing basis, and patients who are completing data less often to be identified. In our experience, offering assistance or encouragement to such patients can help improve compliance.

Both systems can be integrated with a clinical trial randomization system. However, with device-based ePRO, a separate integration link is typically required. Since IVR-based ePRO and randomization are generally on the same platform, data can be easily shared between the systems.

Integration with other types of data collection is also possible. This generally uses device-based PRO. Examples of companion devices are glucose meters for patients with diabetes, peak flow meters for those with respiratory disorders and blood pressure monitors. Typically the ePRO device collects data from the physiological monitor via a local wireless link (e.g., Bluetooth®) and transmits the diary and physiological data to the central server. This avoids unnecessary complexity for the patient.

Device	Data/Device Integration	IVRS
 <p>Physiological measures. Devices can be readily integrated with other instruments such as glucose meters, lung function testers or blood pressure monitors.</p>	<p>Does your application include other instruments or systems?</p>	 <p>Randomization, Medication Management, Adaptive Trials, Clinical Trial Medication Services and Electronic Data Capture (EDC). IVR can be readily integrated with study randomization systems, which commonly use IVR entry.</p>

Device	Demonstrating Equivalence	IVRS
<p> If the instrument has been validated on device-based ePRO, this may be the better choice. There is more extensive published validation work on device-based ePRO.</p>	<p>Has the instrument been validated for the mode you wish to use?</p>	<p> If the instrument has been validated on IVRS-based ePRO, this may be the better choice. Several PRO and clinician-administered scales have been validated and are commonly used on IVRS-based ePRO.</p>
<p> If not, this doesn't mean that you can't use a device, just that you will have a bit more work to do.</p>		<p> If not, this doesn't mean that you can't use IVR, just that you will have a bit more work to do.</p>

Documenting Equivalence

When any instrument is migrated from a validated paper version to an electronic modality, it is necessary to document the migration process and provide evidence for the equivalence of the modified instrument. The FDA has issued draft guidance on PRO measures which includes migration to different modalities (FDA, 2006). These requirements are the same for any mode shift, but the extent of work required to demonstrate equivalence depends on the amount of change. The general framework for describing these requirements is based on the degree of change as proposed by Shields et al., (2006) and included in revised form in the ISPOR guidance document (Coons et al., 2009).

There are specific situations where requirements may differ between IVR- and device-based ePRO. For example, migrating a paper instrument may require a greater degree of equivalence work because of the shift from visual to spoken presentation with IVR, while no such shift occurs on a device if there are no additional significant changes to the original paper-based measure. Conversely, migrating a clinician-administered instrument would represent a smaller shift to IVR, as both original and electronic use spoken presentation of data, while the shift to the device screen would involve a greater degree of change.

The other situation in which requirements for establishing equivalence may be a factor in selection is where an instrument is already validated in an electronic modality. The current



Changes in Migration

Based on Shields et al. (2006) and Coons et al. (2009)

Level	Type of change	Action
Minor	No change in context or meaning	Cognitive debriefing
	Justified by existing literature	
Moderate	Changes in layout or wording that could affect interpretation	Equivalence testing
Substantial	Changes that clearly affect context or meaning	Psychometric Validation

consensus is that there is more available literature supporting equivalence between a device-based ePRO assessment and the original paper-based instrument. A meta analysis conducted by Gwaltney and colleagues have reported findings to support the claim that device-based ePRO systems have demonstrated equivalence to paper without qualification (Gwaltney et al., 2007). There is growing evidence suggesting IVR is equivalent to paper, but this is not yet on the same scale as the literature supporting device-based ePRO systems.

There is an important caveat to the aforementioned. That is, if an instrument is being used in a different population, condition (disease state) or new language, or if there are changes to content or meaning of an item/assessment and there is no existing data to support equivalence, validation work is likely required to illustrate that changes to the existing instrument did not introduce measurement error or bias. This is a requirement for both IVR- and device-based ePRO systems.

For all migration, it is widely recommended that a cognitive debrief and user acceptance testing accompany any new ePRO system. This is useful to show that patients are using the anchors and time frames as intended. When there is a delay between presentation of instructions or other relevant information and the actual questions, cognitive debriefing can show that patients' remember and understand all the material they need to consider in framing their responses. This issue is not confined to one modality.

Economic and Logistical Considerations

Obviously, cost is a factor to consider when determining which ePRO modality to use. Although we have not included cost in the model, we felt it was important to address this issue in the context of a modality decision regarding the best ePRO solution. Our experience suggests that cost should not be the primary driver for a modality decision without first considering the factors outlined above. However, cost may become a key influencer when both modes are suitable for a study's PRO data collection.

Perhaps the most straightforward costs associated with ePRO solutions include language translations and help desk support. These are standard costs for the two modes and there is no evidence that these costs vary. In contrast, the cost structures for device- and IVR-based data collection are more complex because there are no fast or hard rules about cost. For studies that utilize device-based systems, there are more front-loaded costs to procure the devices, load the software, test the devices and ship the devices to sites. These fixed costs of providing the device are often a significant component of the total cost of the ePRO solution. The opposite pattern is found for IVR, where the cost of providing a device to each patient is generally zero, as patients already have phones. IVR costs per call and call connection costs may be significant depending on the duration of the trial and number of instrument administrations. Thus, over time and especially with longer diaries and assessments, the IVR associated costs will begin to approach or even surpass the front-loaded handheld costs. Unfortunately, we cannot predict the

costs associated with a trial without having all of the study details since pricing is based on several components (e.g., size of study, number of administrations, length of instrument and volume of data, among other factors) and as a result, we cannot make general statements about which modality is more cost effective.

The location of patients in a study can also have implications on mode choice. For devices, the process for managing both the shipment of and payment for handheld devices can be significant. Device setup, deployment and support may become more complex for device-based ePRO if many countries are involved. Conversely, some countries have unreliable and sparse phone networks which could impact the conduct of an IVR study.

Despite the fact that cost considerations are not formally included in the model, we collectively have a great deal of practical experience (400+ studies) in handling international studies with both modalities from the logistical and network perspective and we can guide clients on these issues once the study details are provided.



Conclusion

While the critical parameters have been separated and discussed individually, it is essential that we underscore that the answer to which ePRO modality is most appropriate for your study may not be straightforward. Given that every study is unique, we strongly recommend sponsors evaluate ePRO modalities by weighing the importance of the parameters identified throughout this paper and then making a decision based on all of the factors, not just on one or two factors in isolation. We would not recommend that sponsors choose a single modality for all of their trials as no single modality is fit for purpose for all trial designs. Toward that end and based on our experience, we have taken an exhaustive approach to this decision tool methodology. We urge sponsors to consider all of the aforementioned factors to reach a modality decision.

Although cost was not a component of this model, it is a factor many sponsors express as a rate-limiting factor. Thus, we have tried to address cost in a transparent and honest way as there are no hard and fast rules relative to costs of ePRO solutions. With that in mind, it is best to discuss the specifics of a given study

with a trusted vendor and obtain estimates to fairly factor in cost considerations. Also, we must not forget that paper also has substantial costs associated with it in terms of data entry and cleaning. We feel strongly that sponsors should avoid thinking about cost independent from the factors discussed throughout this paper because the least expensive solution may not necessarily translate into the best solution after taking into account all of the parameters of the study and current regulatory guidance.

In summary, there are two main modes of electronic data collection available for collecting data directly from patients: telephone (IVR)- and screen (PDA)-based systems. Both systems offer major advantages over paper-based administration; however, determining which mode is best should not be based on individual preference but rather relevant study-specific factors that have implications on data quality and acceptance.

This paper describes a science-based tool that, when used properly by clinical trials sponsors, results in an objective, quantitative comparison of the relative merits of the two most commonly used ePRO modalities.

To schedule a demonstration and review of the Modality Decision Tool, please contact us:

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To submit your study characteristics for complimentary evaluation by the tool, please visit:

<http://www.invivodata.com/modality-decision-tool/>



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