

Collecting Electronic Patient-Reported Outcomes (ePROs):

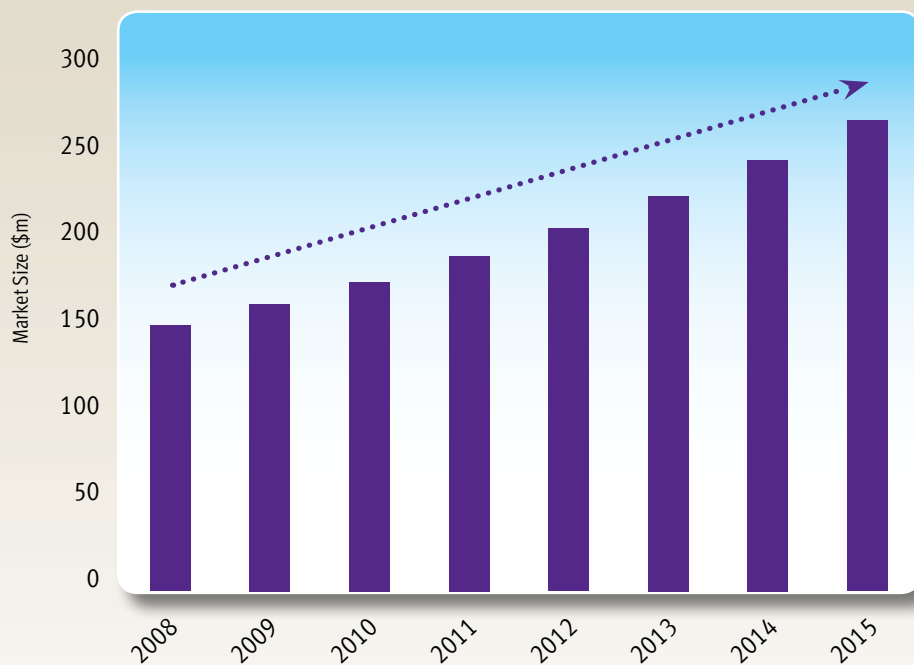
Comparing the 5 Proven Ways to Acquire Attributed Patient-Reported Data

The specialized industry of collecting electronic patient-reported outcomes is increasing linearly, in part because global government regulators want to hear directly from the patient, and because the acceleration and availability of electronic collection (vs. paper collection) improves data quality and efficiencies for data analysis and trial management. This document will review the ePRO market, and outline the five ePRO methods that successfully support the collection of patient-reported data.

I. The Growing ePRO Industry

In 2010 it is estimated that 30% of new global trials will require subjective patient data, ie they will collect patient-reported outcomes as an endpoint. While paper diary collection is the default method for many latent-adopters of new technologies, electronic capture of patient-reported outcomes is growing steadily as sponsors realize the revenue advantages of more accurate, attributable patient-reported data.

ePRO Market, 2009–2015



The ePRO market was valued at \$150m in 2008 and is expected to reach \$265m in the year 2015. The market will grow at a CAGR of 8.5% between 2008 and 2015. Increasing penetration of these solutions is the main factor responsible for the growth¹.

PHT Corporation was one of the first organizations to specialize in collecting and reporting patient-reported outcomes electronically. Since 1994 the PHT ePRO System has become the market's ePRO system of choice, used in 400+ clinical trials. Unlike other ePRO providers, PHT is dedicated to ePRO as its core competency.

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II. The Process of Collecting Electronic Patient-Reported Outcomes

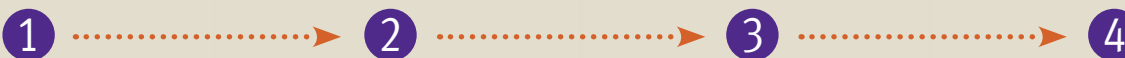
Recommendations for collecting PRO measures have been set forth by the *Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*², the *Reflection Paper on the Regulatory Guidance for the Use of Health Related Quality of Life Measures in the Evaluation of Medicinal Products*³, and guidelines from other regulatory agencies⁴.

Clinical trials using PRO measures should be designed so that:

- Endpoint models are clearly associated with the intended claims
- PRO measures are valid, reliable and sensitive to change
- The conceptual framework of PRO instruments is well defined
- Evidence is compelling that PRO data collection was completed at times specified in the protocol

As a result of these guidances, the process of collecting electronic patient-reported outcomes requires much more than a collection device, database, and a diary or questionnaire! Since 1994, the PHT ePRO System has included all the distinct yet interoperating functions as shown below. PHT's quality management system is certified to ISO 9001:2008.

Functional Overview of the PHT ePRO System

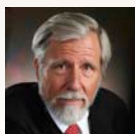


1 Consulting/PROvision

1.1 Provide developing (or final) protocol.

1.2 Science Team Protocol Consultation (complimentary) on required endpoint data points, FDA & EMA expectations, eDiary designs and ePRO symptom scales. Define project requirements including risk analysis and mitigation plan.

PROvision™ Science Team



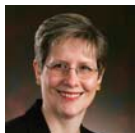
Steve Raymond, Ph.D.
Founder, Chief Scientific and Quality Officer



Valdo Arnera, MD
General Manager of PHT's European Operations



Barbara Marino, Ph.D., RN
Senior Scientist, Director of Outcomes and Study Design



Jill Platko, Ph.D.
Scientific Advisor

2 Preparation/Testing

2.1 Secure permissions to use copyrighted eDiaries and/or questionnaires. Translate and Localize each eDiary and Questionnaire to ensure global consistency.

2.2 Selection of Devices and Design of Applications, using a design tool that formats PRO measures for eDiary use.



2.3 Design, Test and Verify the ePRO Database and ePRO System to support the scientific objectives of the protocol.

2.4 PHT provides ePRO documentation for sponsors to submit with their protocol to EC's and IRB's.

2.5 Prepare ePRO system for User Acceptance.

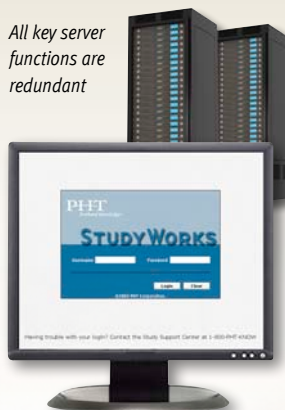
2.6 PHT supports sponsor training of sites by providing expert presenters who know the details of each trial and are equipped with hands-on devices and trial-specific training materials.

2.7 Train PHT's ePRO Study Support Group.

3 Go Live/Data Collection

3.1 Oversee PHT's Data Collection System and Project Reporting (GO LIVE!)

All key server functions are redundant



3.2 Secure, controlled and documented, role-specific access for study staff to PRO data online for trial management and patient monitoring.

4 Data Distribution/Archive

4.1 Final transmission of selected PRO data to sponsor for analysis. Preparation of archival records of all eSource and study documentation for sites to retain and for regulatory inspectors to use in reconstructing the trial.



Key: While PHT works collaboratively with study teams, some steps are taken primarily by the sponsor/CRO and are highlighted in orange type.

III. The Five Reliable Collection Methods and Devices Used to Collect ePRO

...using the patient's own technologies to capture ePRO can be risky for many reasons...

The second function within the PHT ePRO System – Selection of Devices and Design of PRO Applications – is the subject of this issue. While the flurry of new patient-owned mobile devices may seem adaptive to ePRO collection and perhaps practical, using the patient's own technologies to capture ePRO can be risky for many reasons including:

- Alterations to a PRO measure validated for one device when it is displayed and used on other devices, and
- Data security and compliance with regulatory guidelines.

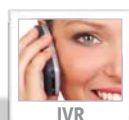
Each ePRO collection method and device must be thoroughly vetted in order to comply with various FDA, EMA and country regulations and requirements for trustworthy data. As a result, there are currently five proven and tested ePRO technologies used by sponsors today (listed alphabetically):



Hand Held

1. Hand Held Device: Electronic data capture on a mobile device

with a central system that allows for web review;



IVR

2. IVR (Interactive Voice Response): Keypad or voice data capture

with a central system that allows for web review by site and sponsor;



Internet

3. Internet Web data capture with a central system that allows for web

review by site and sponsor;



Pen

4. Pen: Digital pen that captures data and uploads to a central system

that allows for web review; and



Tablet

5. Tablet: Electronic data capture on a tablet mobile device with a

central system that allows for web review.

Following is a review of each collection option, recognizing that the ideal method of acquiring patient reported data is contingent on each therapeutic indication, size, complexity, length, locations, survey elements, patient population, budget and critical success factors. Further, each may be used by itself, or in a combination with others, depending on how the study protocol prioritizes the preceding criteria. It is assumed that each collection method is an integral part of a validated ePRO System that protects and ensures data integrity, source and attribution.

1. Hand Held Device: Electronic data capture on a mobile device with a central system that allows for web review.



Hand Held

Hand Held Devices are pocket-sized computers, preferred for collecting data from patients at work, at home, or in transit. They are especially useful for protocols that require data from frequent or episodic incidents. Patients can be prompted to fill in responses according to the protocol time guidelines

via alarms and reminders, and only allowed to enter diaries within specific time windows. This provides cleaner data than paper diary collection, and makes integration with a reminder system not necessary. Hand Held Devices are well accepted throughout the world, having been used to send data directly from patients at home to a centralized server since 1995.

These smart devices collect data in complete, logical and legible formats; and use a touchscreen that can be adapted for easy use by patients challenged by hand/eye coordination, arthritis or motor disorders. Hand Held Devices are ideal for collecting data using long and/or complex diaries, as tends to be the case for protocols for Alzheimer's, arthritis, hep c, oncology and psychiatric indications. The screen size should be large enough to present an entire item (stem and response options) without scrolling that might bias against selecting hidden options. The screen size also dictates whether Visual Analog Scale (VAS) scales and images can be appropriately viewed.

Hand Held Devices can streamline mid-study changes by deploying changes seamlessly from a centralized server, at a scheduled time.

For more than 15 years, PHT has utilized Hand Held Devices for ePRO collection. As a result of employing this method for so many protocols,

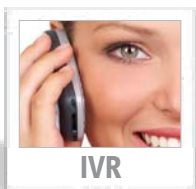
PHT has extended this modality's capacity to include

- Integration with PEF meters and glucometers, which collect objective readings on the Device;
- On-device calculations and comparisons with previous readings and medical device measurements, without transmission or uploading requirements;
- Psychometric validation of PHT Hand Held data capture elements such as the eVAS, to ensure that sponsors using PHT systems are collecting valid data; and
- Optional safety reminders triggered by on-device calculations to patients for medicine, diary and/or activity prompts; to site personnel for extreme high low patient dosages, irregular/infrequent diary entries and/or compliance management; and to sponsors and CROs for site data out-of-range.

The Hand Held Device is the most widely-used method for collecting electronic patient-reported outcomes at clinical sites, and from patients at their work, home or in transit. It can be integrated with medical devices and other technologies to combine objective measurements; and with IVR to streamline subject enrollment and randomization. Electronic capture on a Hand Held Device automatically provides patients with the logically appropriate questions/items at the correct times, simplifying diary completion and ensuring that sponsors receive reports with entirely logical response structures. When functioning within a closed-loop ePRO System, Hand Held Device data is accessible real-time, enabling sponsors and site personnel to manage compliance and monitor subject safety between visits.

III. The Five Reliable Collection Methods and Devices Used to Collect ePRO – Continued.

2. IVR (Interactive Voice Response): Keypad or voice data capture with a central system that allows for web review by site and sponsor.



IVR

The second most frequently method used to collect ePRO is IVR, due to its wide availability and common use in a wide variety of applications available on the market. IVR is familiar to use, and is favored over paper diaries for branching logic and data integrity.

IVR is primarily used for short and simple diary data collection, and integration with other ePRO modalities to streamline enrollment and randomization.

Like Hand Held Devices, IVR can streamline mid-study changes by deploying changes seamlessly from a centralized server, at a scheduled time.

IVR presents usability challenges for countries without advanced phone systems, and for surveys with lengthy or complex questions.

IVR compliance is strained when subjects lose track of, or tire waiting to hear, the entire list of response options, which can bias them to select the first options to occur. IVR also limits the ability for clinical researchers to ask all the requisite questions. Unlike the Hand Held Device, IVR systems do not have the capacity to display graphical elements and cannot utilize visual scales.

IVR is limited in capacity to collect ePRO, impeded by the public's low tolerance level for calls longer than 5 minutes. It is not typically interactive based on real-time subject responses, and unable to trigger safety reminders for subject safety and compliance rates. As a result, IVR technologies are employed for short and simple diaries or (more commonly) integrated with Hand Held Devices to streamline subject enrollment and randomization.

3. Internet Web data capture with a central system that allows for web review by site and sponsor



Internet

The Internet is gaining popularity as an ePRO collection modality, as global population gains access to the Internet on a reliable basis.

Like the Hand Held Device, the Internet can execute complex and lengthy diaries and questionnaires with images and visual scales,

and streamline mid-study changes by deploying changes seamlessly from a centralized server, at a scheduled time.

The Internet can be employed at the clinician site or at the patient's home, office or school; but must be located in a private setting with a

reliable Internet connection. If used outside the clinical setting, the patient must be near the computer for episodic or frequent diary collection.

The Internet has been used successfully for ePRO data collection using desktop computers; Internet Web data capture via Hand Held is being explored at this writing. For acceptance by regulatory authorities, this new instrument must be validated and proven to display consistent diaries and questionnaires on screen, regardless of the Hand Held device or Web browser.

4. Pen: Digital pen that captures data and uploads to a central system that allows for web review.



Pen

The Pen relies on the patient using a unique writing instrument on special paper printed with the diary or questionnaire. Some Pen systems cannot prevent patients from skipping answers, entering illogical data and entering data outside of protocol specified time

windows. Since sites and patients must use assigned papers and a Pen, the cost for Pen ePRO collection includes all the duplication, transportation and redundant data entry costs of paper diaries plus the added expenses of unique pens.

Contrary to the Hand Held Device, IVR or Internet Web data capture, the Pen requires extensive cleanup of data towards the end of the trial, and yields significantly less valuable data per patient. The Pen does not provide real time feedback in the language of patients. It must be combined with a reliable reminder system, to ensure date entry dictated by the protocol.

5. Tablet: Electronic data capture on a tablet mobile device with a central system that allows for web review.



Tablets are popular for site-based data, where they are often used to collect patient-reported, clinician-reported outcomes and/or questionnaires. Tablets are used by patients and clinicians at the site, and are often integrated with Hand Held Devices which

are used by the patient at work, at home, and in transit. They can update drug inventories and other calculations to streamline clinical administration, which can be burdensome as with some oncology trials where treatment is especially costly. Tablets are impractical for mobile patient data collection.

Like the Hand Held Devices, Tablets collect data in complete, logical and legible formats. Some are touchscreen; others use a stylus which is attractive for patients with challenging hand/eye coordination, arthritis, or tremors. Tablets are ideal for collecting data using long and/or complex questionnaires, as within protocols with Alzheimer's, Arthritis, Hep C, Oncology and Psychiatric indications. The larger Tablet screen is ideal to view VAS scales and images. Tablets can streamline mid-study changes by deploying changes seamlessly from a centralized server, at a scheduled time.

For more than 5 years, PHT has utilized Tablets for ePRO collection. As a result of employing this method for many protocols, PHT has extended this modality's capacity to include

- On-device calculations and comparisons with previous readings and medical device measurements, without transmission or uploading requirements;
- Psychometric validation of PHT Tablet data capture elements such as the eVAS, to ensure that sponsors using PHT systems are collecting valid data; and
- Optional safety reminders triggered by on-device calculations to patients for medicine, questionnaire and/or activity prompts; to site personnel for extreme high/low patient dosages, irregular/infrequent diary entries and/or compliance management; and to sponsors and CROs for site data out-of-range.

Tablet ePRO collection at clinical sites will continue to increase with the proliferation of new Tablet technologies and Internet access.

Conclusion:

Each of the five distinct ePRO collection methods has been used for successful data submission to regulatory agencies; and each has specific utility for protocol requirements.

As technologies broaden and data collection devices become more of a commodity, it will become more apparent that the ePRO '**System**' bears the burden of delivering high-quality ePRO data. ***By the end of 2011, Sponsors and CROs will choose an ePRO System for their protocol—not just the devices.***

PHT has a closed-loop controlled ePRO System that continues to mature with quality management systems certified ISO 9001:2008. This System integrates independent testing teams, an internal, global Study Support Center, certified Project Management and a Science Team known for its PRO expertise. PHT continues to lead

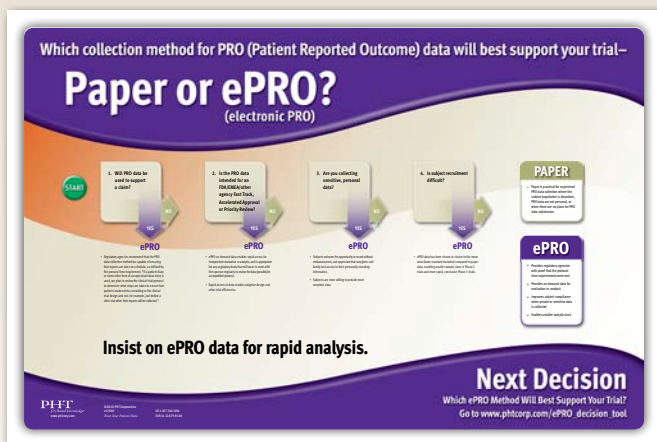
the ePRO industry with its ePRO System, actively building its scientific and technological infrastructure to meet increasingly rigorous demands of the market.



Call PHT for these FREE ePRO decision tools:

PRO Selection Tool:

- Which collection method for PRO data will best support your trial—Paper or ePRO?



Online ePRO Decision Tool:

- Which ePRO collection method will best support your protocol?

Which ePRO Method will Best Support Your Trial?

Introduction

Welcome! This tool will help you determine which of the 5 proven methods is most effective for collecting ePRO data. In the time it takes for you to answer 3 questions about your trial, you'll discover which collection method or methods are practical, and why.

How to use: As you answer each question, you'll notice that certain collection methods may be eliminated. Use your pointer to rollover the to read why this method is not suitable under your stated conditions; or the to understand the caveat about using this collection method.

Please Note: The terms modality and collection method are used interchangeably. Also, it is assumed that each collection method will be properly implemented and used to its correct, full and appropriate advantage. Certain modalities are technically limited.

5 Proven ePRO Methods [Click here for definitions of ePRO Methods](#) **Icon Key**

Hand held, IVR, SMS, PDA, Tablet

ePRO Method Not Suitable
 ePRO Method Caveat

NEXT

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¹ GBI Research, 'The Future of eClinical Trial Solutions – Market Forecasts to 2015, Competitive Benchmarking and Case Studies, pp53-54, December 2009. ² U.S. Department of Health and Human Services, Food and Drug Administration, December 2009. ³ European Medicines Agency, July 2005. ⁴ Other global regulatory agencies include the Pharmaceuticals and Medical Devices Agency, Japan; European Union, the International Conference on Harmonization; and other country-specific government agencies.



Electronic Patient-Reported Outcome (ePRO) System Components

- LogPad System
- SitePad Tablet
- StudyWorks
- eSense™ Family of Integrated Medical Devices
- ePRO Designer
- Study Archive
- PROvision Scientific Services
- Trial Success Program™ (TSP)
- PHT Global Study Support Center
- Scientific Review and Validation
- Site Telecommunications Assessments

US HEADQUARTERS:

PHT Corporation
500 Rutherford Avenue
Boston, MA 02129 USA
Toll-Free: US 1.877-360-2901

EUROPEAN HEADQUARTERS:

PHT Corporation Sàrl
2, chemin Louis-Hubert
1213 Petit-Lancy, Geneva, Switzerland
Phone: 41.22.879.91.00

www.phtcorp.com

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