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# ePRO and Agile Methodology: A Winning End-to-End Solution for Oncology Studies

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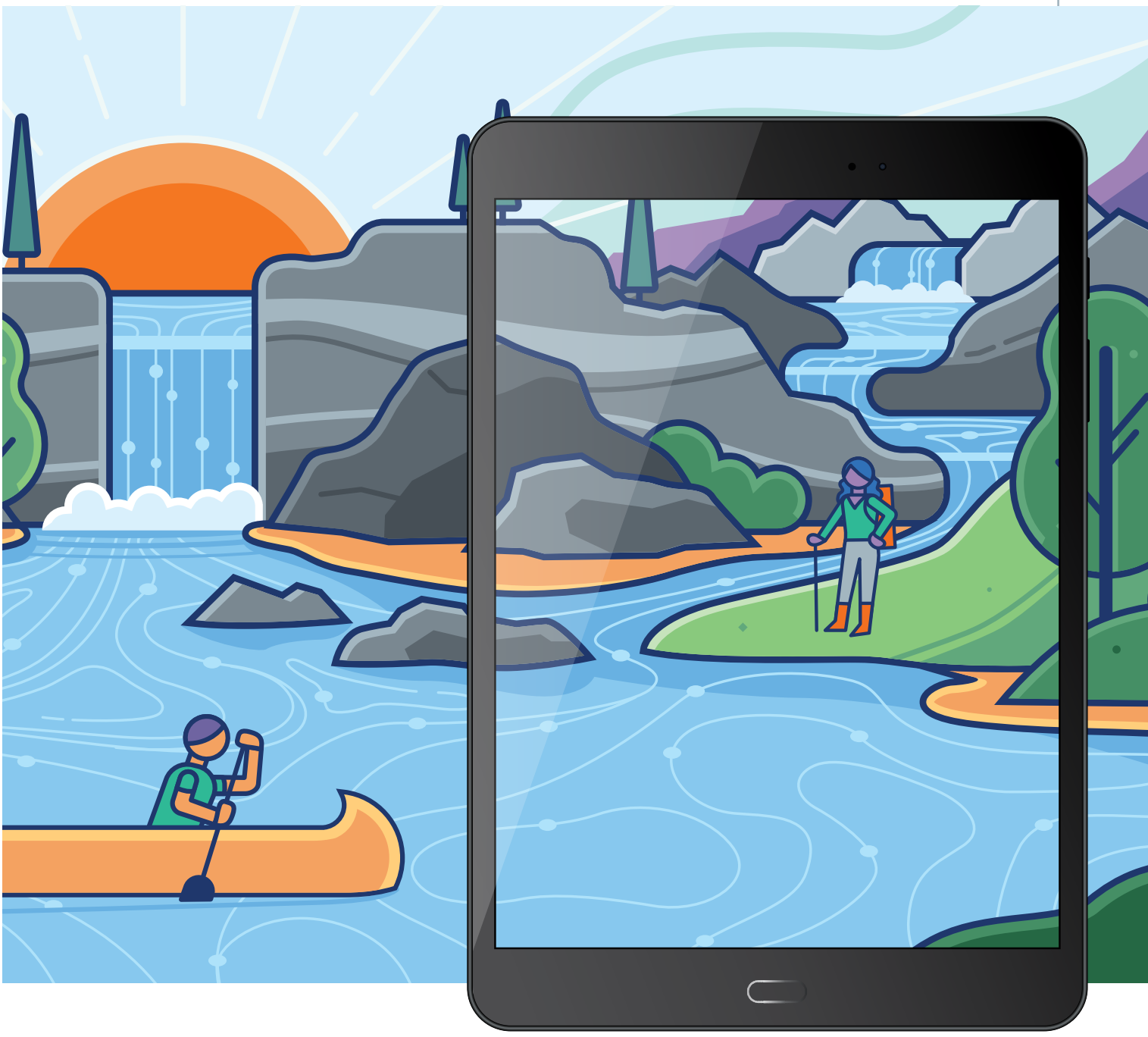


# Introduction

In oncology clinical research, patient reported outcomes (PRO) have historically been collected on paper. The FDA describes PRO as measurements "based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without interpretation of the patient's response by a clinician or anyone else."[1] Today, PRO is leveraged as a broad term that may include patient-reported information about symptoms, treatment side effects, functional outcomes, emotional or cognitive functioning, and health-related quality of life (HRQOL).

Along with the growth in all clinical research digital technologies, electronic PRO (ePRO) deployment has increased due to improving ease of use, better data quality, and real-time access to site and patient data for remote monitors and sponsors. As the technology continues to improve and costs decrease, ePRO is expected to become an even more standard practice across the clinical research industry.

This white paper describes a unique, agile ePRO deployment methodology used by Clinical Ink, a global clinical trial technology company, discusses the benefits of using ePRO in oncology trials, and explains why this agile process is beneficial for oncology trials.

# ePRO in Oncology: An Overview

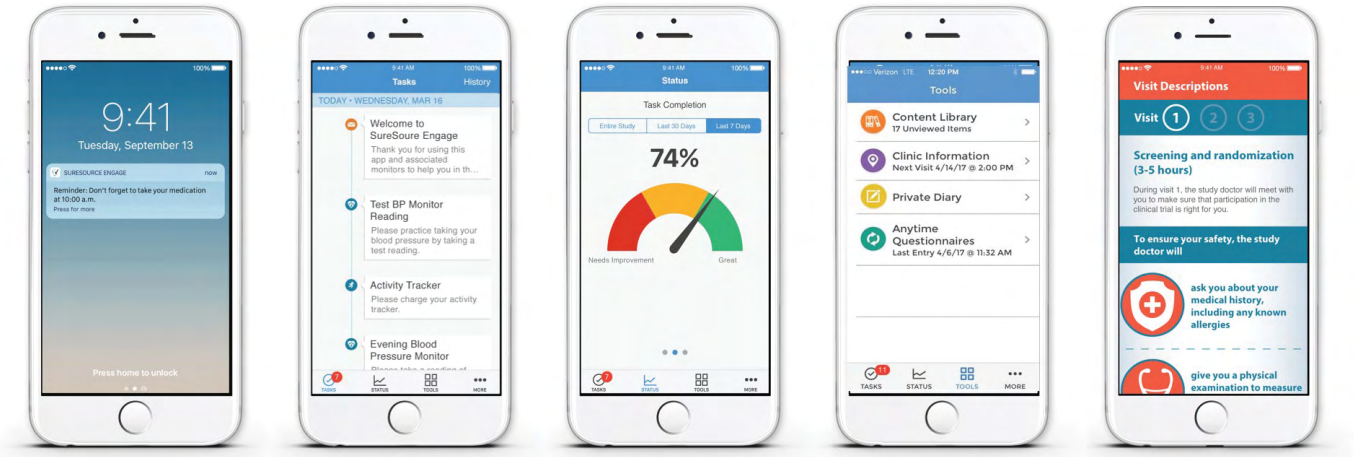
ePRO is especially valuable in the area of oncology.[2] The most frequently administered treatments, such as surgery, chemotherapy, radiation, and hormonal therapy, are generally accompanied by side effects. Patients may also experience follow-on conditions that result from the disease or treatment, and both can affect the patient's subjective experience and functioning.

While survival remains the most important measure of clinical benefit for most cancer treatments, PRO measures — including measures of HRQOL — can convey important information about the overall patient burden and the effectiveness of the treatments.

Regulatory agencies support bringing the patient's perspective into cancer decision-making. As far back as 2015, and under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), the FDA conducted 24 disease-specific Patient-Focused Drug Development (PFDD) meetings to gather patients' perspectives — including those from oncology patients. Since then, the agency has continued to promote efforts to gather patient information, especially through cost-effective and efficient means such as those offered by ePRO.

# A Better Experience for Oncology Patients

Unlike paper-based PRO measurements, ePRO offers a more patient-centric experience. One of its key benefits is that it facilitates more quality time with health care professionals because HRQOL questionnaires can be completed by the patient. Moreover, the technology eases both site and patient burden with easy-to-use apps, enabling patients to enter their information easily while in the clinic (without cumbersome selections and workflows) or at home. This is especially beneficial for oncology patients who are already facing a high patient burden of disease and the associated treatment regimens and also for site staff trying to focus on patient care rather than on the tools for data collection.




## Greater Patient Engagement

The ePRO solution offered by Clinical Ink provides a mobile app that serves as a centralized resource for all patient activities required for the clinical study, including conditional reminders and alerts, questionnaires, daily schedules, a completed task tracker, and resources like content libraries, clinic information, a private diary, anytime questionnaires, and visit-by-visit descriptions with the related preparation needed. And, with approximately 77% of the U.S. population owning a smartphone,[3] there are already high acceptance levels of these apps.

### Broader Access

Traditionally, oncology clinical trials have been conducted predominantly at major academic medical centers, making participation in these studies both cumbersome and expensive for many patients. With ePRO technology — which may reduce the number of required in-clinic visits — it may make it possible to reach more oncology patients and a more diverse population in rural, remote, or international locations.

### Improved Patient Outcomes

While paper-based patient outcome measurements are necessarily static, ePRO tools enable real-time monitoring, allowing physicians to better monitor oncology patients' symptoms and thus provide better care. Research evidence suggests some oncology patient outcomes may improve due to the timeliness of site notifications of worsening symptoms, allowing physicians to take appropriate action.

## A More Efficient Experience for Sites

There are numerous benefits that ePRO offers to sites that paper-based patient outcome measurements simply don't have. While ePRO reduces the site burden for all sites regardless of therapeutic area, this benefit may be particularly appreciated by oncology sites working with especially complex protocols. ePRO streamlines electronic data capture for oncology questionnaires and test results which, along with other inherent efficiencies, allows site personnel to spend more time with patients. Additionally, unlike paper-based measurements, ePRO enables automated reminders and notifications, which improves patient adherence while simultaneously saving the research assistant's time.

### In a recent study, ePRO use improved outcomes for oncology patients:

"For adults receiving outpatient chemotherapy for advanced cancer at a large specialty cancer center, web-based symptom reporting with automated clinician email alerts resulted in better HRQOL, fewer ER visits, fewer hospitalizations, a longer duration of palliative chemotherapy, and superior quality-adjusted survival.

Although the vast majority of patient-reported symptoms were grade 1 or 2 (mild to moderate), more than 1,400 were grade 3 or 4 (severe to disabling). In response to email alerts for severe or worsening symptoms, nurses performed direct interventions primarily composed of telephone counseling, medication changes, and ER or hospital referral. Clinical actions may also have been taken in response to symptom reports delivered to clinicians at each office visit including responses to mild/moderate symptoms, although these were not systematically tracked and may be a useful focus of future research."[4]

### Patient-Centric ePRO at Site Visits

For oncology studies today, ePRO is typically collected during site visits, enabling patients to use tablets kept at the site — all while lessening site burden and increasing patient-centricity. Clinical Ink's approach allows patients to simply log in to answer the patient questionnaire assigned to that visit. With a simple workflow and interface, this occurs without any intervention from site staff. All data collected are immediately available through the portal for monitoring and reporting.

## Improved Data Quality

The quality of the data collected through paper-based collection methods can be uncertain. A paper PRO document requires someone to enter the data, generally by scanning, adding cost, time, and inefficiencies to the process. Then, the document must frequently be stored in two formats — paper and digital (scan). Additionally, data collected on paper are nearly impossible to validate for timelines related to completion, are often incomplete due to skipped questions, and do not support any audit trails for attribution.

In contrast, ePRO:

- Eliminates the need for data transcription and potential risk of error
- Streamlines and automates data entry and checking processes
- Ensures timely and complete data entry with full attribution
- Enables health care professionals to focus on analyzing responses rather than entering them

## Real-Time Assessment of Patient Burden

Tracking quantitative changes in symptoms over time, rather than simply recording symptoms, can improve the understanding of the patient burden and side effects and allow for more rapid response. This real-time monitoring offered by Clinical Ink can be especially critical with oncology patients when quick medical response is warranted. And, when patients can avoid the burden of having to mail completed, paper-based assessments back to the clinic, response rates may increase.

## Improved Study Management

ePRO allows complete visibility of patient status. Not only can this activity be tracked at the study, patient, and task level, but it is available in real time.

## A Faster Experience for Sponsors and CROs

Today there are more than 10,000 oncology trials underway at sites in the United States[5] — far more than any other condition. Because the demand for better cancer treatments is so strong and continuous, sponsors and CROs seeking ways to speed study startup can benefit by adding ePRO technology. Not only is development and deployment faster than paper-based processes, ePRO allows sponsors and CROs to monitor for compliance and HRQOL in real time.

## Better Data

Digital formats can bring together at-home and site data from the PRO-CTCAE™ (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events), the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire), and FACT (Functional Assessment of Cancer Therapy).

Additionally, in digital surveys, branching logic and embedded history reviews can reduce patient burden and increase precision. Automation of data entry and checking processes also ensures no items are missed.

## Real-Time Data

Besides these benefits, Clinical Ink's ePRO tool allows for a complete real-time view of study data, including:

- Questionnaire compliance
- Anytime diaries submission
- Engagement compliance
- Patient status tracking
- Task data listings
- Site- and sponsor-based conditional email alerts for questionnaire compliance conditions and single-item patient responses

## Agile Deployment of ePRO

Traditional approaches for building ePRO tools require a highly iterative process — a waterfall approach that not only wastes time but that is focused on functional requirements rather than the patient experience.

Instead, Clinical Ink uses an agile approach focused on improving user experiences for patients, sites, and sponsors/CROs. It provides a more direct pathway to prototype evaluation, reduces testing burden, and moves scoring and coding earlier in the process to accelerate the deployment process for sponsors and CROs.

**Define:** In this agile deployment approach, Clinical Ink collaborates with sponsor partner(s) to define requirements based on the protocol. Simultaneously, in the definition process itself, prototypes are advanced for design confirmation and patient experience feedback.

**Configure:** With the requirements in place and through the initial design feedback, the prototype is rapidly iterated, leveraging a fully configurable "wizard-like" authoring tool. Sponsor partners provide rapid and regular feedback as they experience the application themselves in the same way their patients will when in an active study. This feedback loop makes it possible for decisions and improvements to be made quickly and the changes reviewed again.

Additionally, templates offer options for questionnaire controls and are flexible enough to allow for adaptability in implementation. Furthermore, library options ensure that, whenever possible, efficiencies are offered for both existing and future configurations; a configurable scoring and coding function enables input from data management and biostatistician teams sooner.

Also during the configuration phase, ePRO controls and parameters are selected and activated for question types based on collection requirements — multiple choice, yes-no, VAS, NRS, etc., and scheduled (daily, weekly, etc.) or episodic (time bound to specific points in the study or for the full duration of the study).

Clinical Ink's efficient process for prototyping allows sponsor partner(s) to trace the patient's steps through actions rather than concepts to better evaluate patient experience. CROs and sponsors experience firsthand how an oncology patient would navigate the app.

**Release:** Once approved, the technology automatically generates the exact specification of the approved design, eliminating the risk of human error. User acceptance testing then begins, allowing sponsor and CRO partners to review the approved prototype design through either a BYOD or provisioned device model. With this approach, sponsor and CRO partners are not experiencing the design for the first time but are simply confirming the approved prototype. In this way, the process becomes more efficient while also enabling these partners to focus on the patient experience rather than simply on the functional requirements.

## The Role of Oncology Libraries

When a configurable questionnaire library is available for oncology trials, the approved questionnaires can be easily checked out using Clinical Ink's robust and configurable ePRO tool — saving time and improving quality. To ease sponsor and CRO partner burden, this tool tracks electronic use rights of the most commonly used questionnaires based on master license agreements and individual copyright holder requirements. HRQOL questionnaires approved for electronic use then rapidly generate any approval material necessary for the copyright holder review process on future studies, drastically improving efficiency.

Clinical Ink manages the electronic use review and verification process for the most commonly used oncology-related questionnaires, including but not limited to:

- EORTC-QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire)
- EQ-5D-5L (EuroQol Group's 5-level EQ-5D version measures five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression)
- PROMIS®-Fatigue (Patient-Reported Outcomes Measurement Information System-Fatigue is a measure to assess levels of fatigue in adults and children)
- FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue Scale questionnaire assesses self-reported fatigue and its impact upon daily activities and function in relation to fatigue associated with anemia in cancer patients)
- PRO-CTCAE™ (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events)
- PGI-S (Patient Global Impression of Severity is a global index used to rate the severity of a specific condition)
- PGI-C (The Patient Global Impression of Change is the PRO counterpart to the Clinical Global Impressions scale; it evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status)
- Disease-specific measures of HRQOL, including:
  - C-Path's NSCLC-SAQ for patients with non-small-cell lung cancer
  - EORTC QLQ-BIL21 for patients with cholangiocarcinoma and gallbladder cancer
  - EORTC QLQ-HCC18 for patients with hepatocellular carcinoma
  - EORTC QLQ-OV28 for patients with ovarian cancer
  - EORTC QLQ-CR29 for patients with colorectal cancer
  - EORTC QLQ-NMIBC24 for patients with bladder cancer
  - EORTC QLQ-LC29 (update of EORTC QLQ-LC13) for patients with lung cancer
  - EORTC QLQ-BR45 (update of EORTC QLQ-BR23) for patients with breast cancer
  - EORTC RCC for patients with renal cell carcinoma

Clinical Ink also accommodates customized company-specific questionnaires in specific and/or shared libraries whereby users can configure and test a questionnaire once rather than configuring the same questionnaire across multiple studies. This approach helps avoid repeat verifications for the same screens and reduces the chances for error. Furthermore, Clinical Ink offers version control for the questionnaires in the library and facilitates processes for delivering both locked (tested, approved, and uneditable) and unlocked (available for editing) versions to ensure both flexibility and quality control as needed.

## Why Agile Deployment and a Configurable ePRO Is Important for Oncology Trials

By enabling an agile ePRO study design, Clinical Ink facilitates a collaborative partnership with CROs and sponsors, which then leads to a better site and patient experience and an improved end-to-end design, deployment, and monitoring process for the oncology trial. Rather than focusing on only conceptual functional requirements, oncology project teams work with real-world ePRO prototypes, testing questionnaires and workflows just as their patients would experience them.

Enabled by the configurable authoring tool, study teams advance through requirements definition and prototype review in a more parallel process with a cycle of feedback through iterative experiences. Baseline comparators, screening and eligibility criteria, and standard HRQOL questionnaires are controlled electronically, efficiently, and at quality. Similarly, determining question type, whether questionnaires are scheduled or episodic, or whether they are deployed in the home or in the clinic are all issues made simpler with Clinical Ink's ePRO tool. And, most importantly, the agile ePRO design means that oncology studies can start faster while lessening the burden faced by sites and, especially, the patients.

**To BYOD or not BYOD?**

**Recent research supports bring-your-own-device trials, indicating both measurement equivalence and high patient acceptance. Read our BYOD white paper.**

[1] U.S. Food and Drug Administration. Patient-Focused Drug Development Glossary. https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary. Accessed May 17, 2019.

[2] Lipscomb J, Gotay C, Snyder C. Patient-Reported Outcomes in Cancer: A Review of Recent Research and Policy Initiatives. American Cancer Society. 31 December 2008. doi: 10.3322/CA.57.5.278. Accessed May 17, 2019.

[3] Pew Research Center. Mobile Fact Sheet. https://www.pewinternet.org/fact-sheet/mobile/. Accessed May 17, 2019.

[4] Basch E, Deal A, Kris M, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol. 2016 Feb 20;34(6): 557-565. doi: 10.1200/JCO.2015.63.0830.

[5] BioPharm Insight, Active Oncology Studies at Sites in the United States. http://www.biopharminsight.com/. Accessed May 19, 2019.

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## Direct Data Capture | eCOA | ePRO | eConsent

Clinical Ink, a global clinical technology company, offers data certainty from source to submission. Our eSource clinical technology and configurable ePRO and eCOA modules — a suite of solutions for capturing and integrating electronic data from sites, clinicians, and patients at its source — naturally enhance your clinical trial workflow by reducing manual labor, providing anytime, anywhere data access, and saving resources as your trials progress. Accelerate the completion of key clinical development milestones in your study and confidently manage your trial's critical decisions with our flexible menu of collaborative services, remote monitoring support, and a complete, real-time view of your trial.


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