Utilizing Digital Pen for ePRO

An Overview of the Technology

Dennis Salotti

Data collection in clinical research has undergone a dramatic evolution over the past two decades. Recent innovations have focused on creating a more intuitive user experience, where data collection methods have matured to integrate the efficiencies of electronic data capture with tools of everyday life. One such example is the collection of clinical data utilizing digital writing technology, an approach that combines the ease of pen and paper with the efficiencies of EDC. Digital writing technology is comprised of digital pen hardware, digital pattern-printed materials, data transmission software and a document repository system for digitally written images. In the following sections we will describe each component, its function within the digital writing platform and practical considerations for implementation as an EDC tool in clinical development - with specific focus on its application for collecting patient-reported outcomes data.

Digital Pattern Paper

The digital pattern, though visible to the naked eye as shading on the page, is an intricate arrangement of small dots in various positions. When a digital pen is used to record data on a digital pattern-printed page, the pen does not "see" anything on the printed page other than the digital pattern. The pattern of dots is unique for every digital pattern-printed page and allows the pen to immediately identify its exact location on the page and attribute the captured data to the corresponding page during data processing.

When multiple digital pattern-printed pages are associated with identifiers for a unique patient, they could be used to reflect the physical arrangement of pages in a patient case book. This many (pattern-printed pages) to one (digital case book) relationship enables many of the efficiencies and features described in the WriteResult whitepaper entitled "Digital Pen Data Management".

The Digital Pen

The digital pen has been purposefully designed to maintain the attributes of a regular ballpoint pen in both physical appearance and in the user's writing experience. Current models approximate the profile and thickness of small markers or "comfort grip" pens, and are a comfortable writing instrument for children, healthy adults and patients with conditions limiting manual dexterity and/or hand strength.

Beyond the unassuming exterior, the digital pen device consists of a rechargeable battery, a digital camera with pressure-

sensing switch, an an image microprocessor and memory. The rechargeable battery will power up to 2 hours of active writing and up to 10 hours of non-active or "stand-by" time when the pen is on but not in use[i]. The pen memory will store approximately 250 pages (Letter or A4) and, by extrapolation, a far greater number of case report form pages when designed with structured response areas. Both the battery and memory levels are communicated to the user via LED indicator lights located on the front of the digital pen.

Recording data with the digital pen is as easy as writing with a regular ballpoint pen and paper. To capture data, the user writes with the digital pen on a substrate containing digital pattern (described in the below section) in the same manner as is used with a normal ball point pen. As the pen tip is touched to the surface during writing, the pressure sensor triggers the camera to begin recording images of the pattern at a general rate of 50-100 images per second. The image microprocessor uses these images to immediately determine the precise location of the pen on the pattern-printed page and the pen strokes that are being written. Additional metadata, such as the specific pen being used and the time and date of the writing, is also recorded. All data are stored in memory and retained until a successful data transfer[ii].

The digital pen docking station offers a single, small foot-print accessory to both transmit data and recharge the pen battery using a computer and USB port. The advantage of utilizing the docking station as a means of charging the pen and transferring the data is in the universal format of USB connections. For implementation in global clinical trials, charging via USB port eliminates the requirement to account for multiple, different power source adapters to satisfy varying electrical standards. Additionally, this creates a single-step routine for sites and/or patients to recharge and transmit data from the device regularly that can further simplify training and increase compliance for routine data transmissions.

Data Transmission Software

The data transmission software for digital writing performs two main actions: 1) Retrieve data from pen memory, and 2) Transfer data via the internet to the intended data server. Software for digital writing requires a very basic computing environment and is easily installed by non-technical personnel. In practice across investigative sites worldwide, the commonly encountered challenges include minor updates to operating system software, proper configuration of proxy server internet connections and general IT security questions that must be satisfied prior to installation on institution hardware. Generally, all of these challenges are overcome rapidly through communication between vendor technical support and the investigative site local IT support staff.

Feasibility Assessment Applications

In order to be proactive in addressing pertinent digital writing software installation challenges, it is important for the Sponsor or delegates to investigate the few critical infrastructure items such as computing platform, operating system and site procedures for installation of new applications. Top-tier digital writing providers will support these efforts by providing a simple, rapid site infrastructure assessment tool.

Data Processing Software

Once transmission software is installed and data are received at the vendor data server, the digital writing system will utilize handwriting recognition software to transform the data supplied by the digital pen into meaningful information through several steps. First, the digital pen captured data must be transformed into pen strokes using a complex algorithm that recreates the handwritten strokes based on the information captured during digital writing. Second, the digitized pen strokes are merged with an electronic image of the source form file in the exact location they were written on the paper source document. Finally, for each data field created during the form digitization process, multiple handwriting recognition engines evaluate the pen strokes and provide several candidate interpretations of the digitally captured data. The interpreted data are now ready for processing by the trial data management team.

Document Repository Services

Digital writing differs from other forms of electronic data capture in that in addition to capturing data points stored in the clinical database, the digital writing system also generates an electronic image of the handwritten source document. This image of the completed form(s), often in PDF format, can be utilized in several ways. Site staff can use the digital image of the form to verify the quality and completeness of data capture by comparing the electronic image to the source document. Similarly, field monitors and Sponsor study managers may utilize the digital images to check quality of form completion; this is especially beneficial for complex study designs and for assessments with complicated administration guidelines. This feature should only be utilized as a supplementary tool to study oversight; the original document remains the source data and must be treated as such as per applicable guidelines and regulations for monitoring study conduct.

Selecting Digital Pen Technology as an EDC Tool

Selection of the appropriate EDC tool(s) is critical to realizing the anticipated benefits of moving from paper to electronic data capture. For all clinical studies, decisions regarding selection of data management tools should be supported by an assessment of "goodness of fit" for the clinical study and clinical development program requirements. This task involves careful consideration of the users, the operating environment, the study endpoints and objectives and the overall organizational strategy. Below we present an approach to determine if digital writing is a viable data collection tool through evaluation of these parameters.

The first step when evaluating use of an EDC tool is to assess how well the tool will address the needs of end-users (i.e. clinicians, study coordinators and patients) that will have direct interaction with the tool for collection, data transmission and query responses on the data. In the context of the clinical research study, this is of particular importance for the collection of patient-reported outcomes data where the patient experience with the collection device may have direct bearing on the quality of data collected. Items to consider when selecting the digital pen, or any ePRO EDC device include:

The Patient Perspective

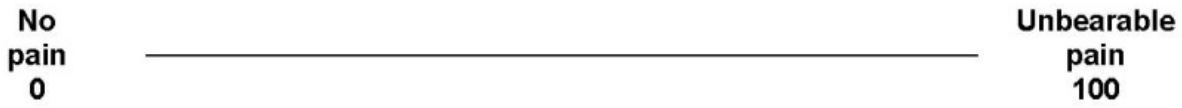
As with any patient procedure under consideration in a clinical study protocol, administration of EDC tools for use in collecting patient-reported data should be compared against the target patient profile and demographic to evaluate which, if any, electronic device is best suited. The digital writing platform provides a user-experience nearly identical to that of regular pen and paper. Thus, the training required to implement a digital writing EDC system is minimal. In this regard, the digital pen is well-suited for use in patient populations that would require additional attention for training--and subsequent retraining--on more complex EDC devices. In addition to training, the study population may, by definition, suffer from physical limitations that prohibit use of other EDC devices whose proper operation requires a certain level of manual dexterity and fine motor control. This is of particular consideration for therapy areas such as Pain, Rheumatology, Emergency Medicine and Neurology where patients may be especially compromised. The slightly thick, marker-like profile of the digital pen may be preferable in these populations with or without the use of additional adaptive devices.

Picking the Right Tool for the Job

Feasibility of data capture for the actual assessments selected for the study must be evaluated with any EDC tool to ensure proper data capture. While digital writing offers the flexibility to capture any traditionally handwritten document electronically, it holds specific opportunity and limitation in various areas.

Digital writing in the clinical research setting empowers both the creation of digitized images from handwritten documents and the movement of handwritten data points from the case report form to the clinical database without intermediary transcription. While the former feature is amenable to any writing on digital pattern paper with a

digital pen, the latter feature of automated recognition, interpretation and entry of handwritten data is greatly facilitated by limiting the range of expected values for each field. For this reason, digital writing is best suited for capture of highly structured data collection forms with limited free text entry. In the context of clinical research, patient-reported outcomes assessments (PROs) are particularly well suited for digital pen data capture. These assessments are generally structured as a series of multiple choice, true/false, checkbox and graphical response items with limited narrative information. This obviates the requirement for translation of item responses and streamlines the flow of data from initial capture with the digital writing system to a final clean dataset. Digital writing data capture is of particular utility when collecting graphical data such as visual analog scale (VAS) data. An excellent example is the common 100 millimeter pain scale measurement:



With digital writing, all responses on the 0 – 100mm line are measured systematically by the interpretation software. This increases data quality by eliminating inter-measurement variability and transcription error while greatly reducing the time between data capture and data processing. The patient response is captured to the nearest 0.1mm to give the most accurate reflection of patient pain response. The digital writing solution has been used extensively in pain studies for indications such as Rheumatoid Arthritis and Psoriasis.

---

[i] Anoto DP-201 Data Sheet

[ii] Anoto Group AB , 2012