

End Points, Collection, Processing, and Time: Four Key Elements to Consider When Planning for Use of Handheld Devices in a Drug Development Setting

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Digital technology is rapidly enhancing the ability of electronic data capture. In drug development, use of handheld devices in clinical trials is part of this digital revolution. When implementing these new technologies, it is imperative that the data quality remains uncompromised. Therefore, attention to data collection details, including setting appropriate hierarchical relationships, standardization of data collection procedures, and appropriate data processing for quality control, should be rigorously planned.

The line between drug development and emerging technology is merging more and more, with handheld devices becoming commonplace in clinical trials.¹ These devices not only enable convenient, real-time electronic data capture but also reduce data errors with direct transmission to clinical trial databases.² Handheld devices are a subset of digital sensors/devices being used in trials and vary from a bring-your-own-device (such as a cell phone) to a trial-mandated device or application.²

Trials using handheld devices range between comparison to standard eye care devices for visual acuity (NCT03929588),³

accuracy of handheld breast scanner (NCT02597452),³ handheld imaging platform providing real time, diagnostically relevant biological and molecular information of a wound (NCT01651845),³ improving behavioral weight loss via handheld device (NCT01241578),³ handheld device to assess spousal relationship and pain in metastatic breast cancer (NCT00386620),³ to measuring bowel urgency, and abdominal pain electronically following therapeutic intervention in patients with ulcerative colitis (NCT03653026).³ This broad application of handheld devices creates unique opportunities and challenges for

clinical trialists. Regulatory authorities are staying abreast of digital innovation and providing guidance to industry on how they will regulate specific uses.⁴

This data collection method seems, initially, to remedy many pitfalls of more traditional methods (such as written diary); however, for the whole data collection process to be ideal and meet quality standards, several different factors need to be considered during the planning stages. These include consideration of end-point type, user interface flexibility, data collection and edit-check in place, storage, and quality control. The entire process of data collection, transfer, and storage is not a simple linear process and could have several pitfalls. There are specific guidances on appropriate data processing,⁵ policies,⁴ as well as initiatives to improve input of real-world data.⁶

Using examples from the immunology therapeutic area, the authors highlight some of these important aspects to be considered while designing the data capture specifications of handheld devices in a drug development setting.

SETTING APPROPRIATE HIERARCHICAL RELATIONSHIPS

In many clinical trials, the value of an end point is preconditioned on a prior value; this scenario is also prevalent in composite end points, which are mandated by regulatory authorities in several diseases. For example, in immunology, composite end points are generally the registration end point for rheumatoid arthritis (American College of Rheumatism (ACR) score), psoriasis (Psoriasis Area and Severity Index (PASI)), systemic erythematosus lupus (Systemic Erythematosus Lupus Responder Index), and ulcerative colitis (Mayo score). In pediatric diseases, there

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has been better success in using composite scores.⁷ Similarly, in rare diseases where the sample size in registration trials may be much smaller, composite end points (e.g., North Star Ambulatory Assessment in Duchenne Muscular Dystrophy)⁸ could be envisioned to improve the quality of information without impacting multiplicity.

To implement data capture for a composite end point using a handheld device, it is crucial to understand the inter-relationships and correlations between the subscores that make up a composite end point. As an example, the PASI score is computed using scores from four different body regions—head/neck, upper limbs, trunk, and lower limbs (Figure 1).⁹ The affected percentage of body surface area (%BSA) for each region is collected as the first step; then, the severity of each body region is scored. However, the severity score for any given region is highly correlated with the %BSA⁹ so, once the hierarchical structure is defined (by selecting a numerical value for %BSA), the related subscore should have a limited number of options. Lack of such considerations in the data collection structure will erroneously inflate the uncertainty around the end points leading to false-positive results and/or false-negative

results. Hence, when a handheld device is implemented to collect such data, it is imperative that the algorithm captures the directional relationships and correlations between the composite end-point subscores to ensure clinical meaningfulness.

STANDARDIZATION OF DATA COLLECTION PROCEDURES

To implement accurate data collection for a given end point, it is imperative that the collection procedure be well understood; failure to understand and standardize the detailed process for collection could lead to data errors or incompatibility with data collected by more traditional methods. For example, traditionally in psoriasis, disease severity scores (such as erythema, induration, and scaling) are measured as the percentage of the affected body regions relative to an individual’s handprint size.⁹ When the same information (i.e., percentage of body affected) is captured on a handheld device, the numerical input is defined simply by the physician’s or patient’s estimation of how much of the body was affected (without reference to a “standardization” tool, such as handprint). Therefore, the end points captured by the two methods may not be directly comparable. This

discrepancy has the potential to introduce between-assessor variability (as there is no standard against which to compare) but also limits the ability to compare the “new” data to past clinical trials. Indeed, the different collection methods could limit the use of prior data to guide sample size in new studies. As with keys aspects of the protocol (study design, doses, population, duration, inclusion/exclusion criteria, and analysis type) collection tools have the potential to introduce bias. For such comparisons, attention should be paid to the data collection tools (i.e., whether it was standard procedure or a digital method). Similarly, for estimands it should not be assumed that if a handheld device is being used to capture a related end point it will also capture the information required for a specific estimand.

Like any other information collection tool, software implementation and the corresponding ease of user interface use are crucial for handheld devices. In clinical trials, patients are instructed on trial compliance but may not always be informed about potential factors that impact data quality. For example, in collecting the PASI score of the head/neck, if a patient is presented with a series of

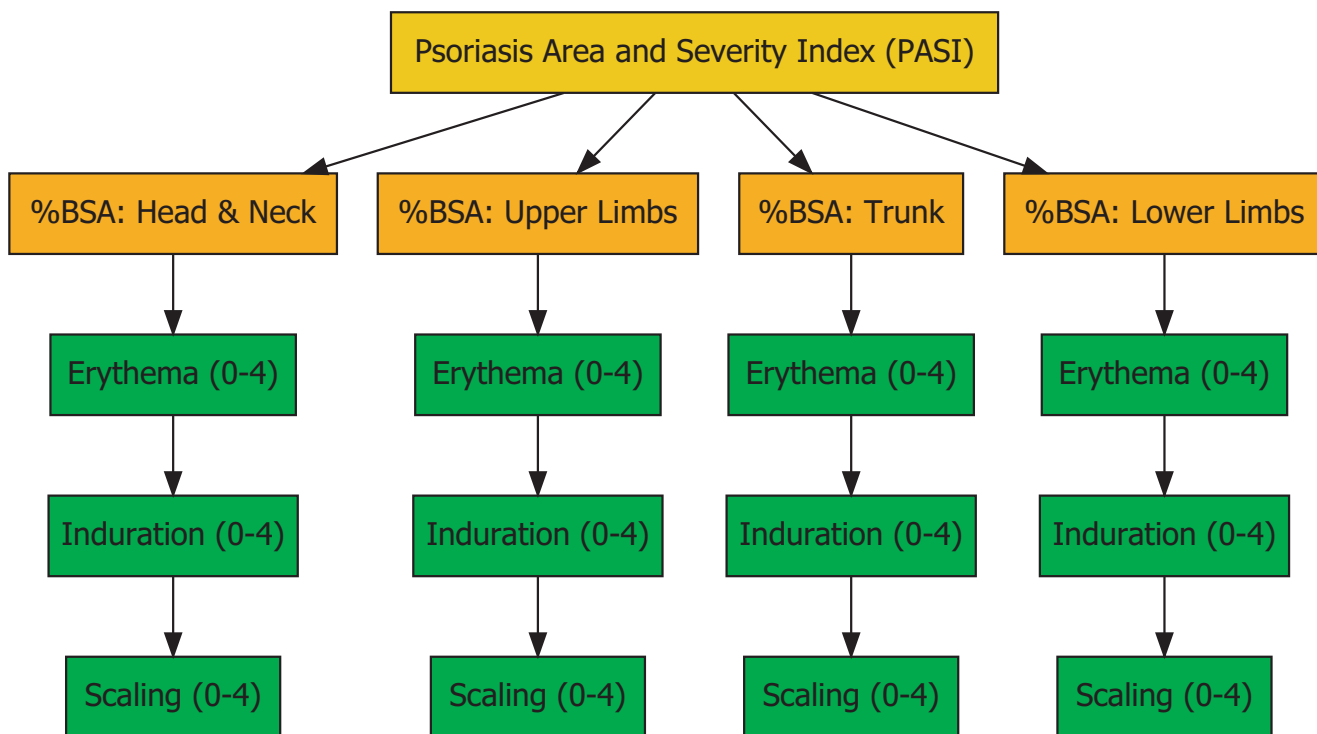


Figure 1 Example of a composite end point – Psoriasis Area and Severity Index (PASI) score. %BSA, percentage of body surface area.

screens without any review options of earlier inputs, then the patient due to pain and irritation could tend to input random numbers, which could be completely independent of the disease severity. One may enter a value for %BSA as 0% for the head/neck yet could enter the highest scores for disease severity. Therefore, if the user interface is complicated, the data collection and data quality could be negatively impacted depending on the user's sociopsychological status.

APPROPRIATE DATA PROCESSING

The data flow for digital devices differs from traditional methods in two key ways—lack of a paper trail (or source documentation) and the extent of preprocessing prior to upload to a clinical trial database. In simple terms, digital data flow for handheld devices in clinical trials involves data collection on the device, data transfer to the cloud or vendor database, data check and/or edit, preprocessing of data, then upload to the sponsor's database. At this point, standard data-management processes of reconciliation, etc., are applied. Clinical trialists should be aware of the principles and structure of the algorithms used for preprocessing of the data to enable appropriate interpretation of the final data. Issues to be resolved include definition of “irregular or missing digital data,” establishing acceptance/rejection criteria for irregular data, and establishing “source” data to aid reconciliation in the absence of a paper trail. Ideally, a decision tree should be implemented *a priori* in order to guide handling of these irregularities, which may arise from a range of sources (e.g., calibration, charging of device, lack of internet access, or nonadherence).

Once a “clean,” preprocessed dataset is available for transfer to the sponsor's database, issues with data transfer may still occur resulting in compromised data quality. Clear synchronization of the databases, using prespecified carefully crafted processes (usually known as Data Transfer Specifications), is strongly recommended to avoid data transfer issues. The lack of a paper trail, and potentially nonadherence to Clinical Data Interchange Standards Consortium standards, may compound this issue.

As noted above, clinical data management usually only gets involved when the preprocessed data are available in the clinical trial database when they start reconciling these data with other data types within the database. Because the data collected through handheld devices do not have any paper trail, data reconciliation may be difficult; hence, it is recommended that data management should be involved with the digital data from the start of the clinical trial. As part of the early involvement, discussion should ensue regarding frequency of data synchronization between databases and relevant appropriate data reconciliation procedures.

SETUP OF A HANDHELD DEVICE

Although using a handheld device seems like an “easy” solution to capturing data, teams should be aware of the substantial lead time required to implement such a device in a clinical trial. Steps involved include selecting an appropriate vendor, determining the data/end points to be collected, reviewing interface for implementation of end points in the device, validating interface, establishing user instructions, and conducting user acceptance testing. Additionally, depending on the data being collected, review and agreement with regulators may be required. Specifically, estimand(s) of a clinical trial are driven by specific question(s) ranging among study population, end-point measure, and treatment effect. Decision on the specific estimand may require regulatory interaction and input. If a handheld device is to be implemented to capture key end-points, careful assessment is required in a timely fashion to evaluate if the data collected by the handheld device will be adequate to inform the estimand in question. In such a situation, it would be advisable to plan for a 1-year process for clinical trial implementation of a handheld device.

These are exciting times, considering the advent of technology and its application in the healthcare space. Handheld devices can provide significant value. Data do not necessarily equate to evidence,¹⁰ therefore, clinical trialists in drug development need to play their part and ensure well-characterized methods of data generation assuring data quality are considered early. In addition, before implementing such a device in a clinical trial, understanding the

advantages and shortcomings of a specific device and managing expectations of the patient, the sponsor, and the regulatory agencies is crucial. As such, early careful planning is required with key stakeholders who will manage and analyze the generated data.

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CONFLICT OF INTEREST

Vivek Pradhan is an employee of Pfizer. Anne Heatherington and Indranil Bhattacharya are employees of Takeda Pharmaceuticals International Co.

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