

COLLECTING RELIABLE AND VALID REAL-TIME PATIENT EXPERIENCE DATA

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The collection of real-time, real-world patient experience data that are reliable, valid, and sensitive to drug effects presents many challenges to clinical trial sponsors and investigators. Recent developments in electronic patient experience diary (PED) systems highlight the importance of building a robust, subject-friendly system that can enhance subjects' protocol compliance and is regulatory compliant. To succeed in a clinical trial, an electronic PED system must simultaneously meet two related standards: clinical integrity and system integrity. Clinical integrity includes the elements of protocol compliance, measurement reliability, data validity, and auditable subject quality. An electronic PED system with clinical integrity produces compliance metadata that can be used to better understand and evaluate the efficacy data. System integrity includes the elements of management control, system reliability, data integrity, and auditable system quality for computerized data handling. An electronic PED system with system integrity collects data that have been authenticated by built-in logic and security checks and can be attributed to the subject. The challenges and promises of such a system are presented.

Key Words: Clinical integrity; System integrity; Validation; Compliance; Electronic diaries

INTRODUCTION

THE RELIABLE AND VALID measurement of drug effects is a cornerstone of pharmaceutical research. While the physiological measurement of drug effects has evolved considerably over the past 50 years, the measurement of patients' subjective experiences of drug effects has not kept pace with the 'harder,' physiological measures. Recent

methodological advances make it possible to capture reliable and valid data from subjects regarding their experiences with medication effects, symptoms, self-observations, and quality of life—which we collectively term *patient experience*. As will be presented below, the collection of reliable and valid patient experience data requires data collection from subjects in the real world, in real time. Increasingly, electronic methods are being used in an attempt to capture these data. The criteria for the successful capture of patient experience data include clinical and regulatory issues.

Patient Experience Measurement

Before delineating the criteria for collecting reliable and valid diary data, we will first

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distinguish among three types of patient experience data: self-observations, subjective symptoms, and quality of life. Self-observations are objective and could, in principle, be observed by others, but the subject is in a unique position to report on them as they occur in the real world. In these instances, subjects are acting as proxy research observers because they are uniquely positioned to observe symptoms over time and across a spectrum of environments and circumstances. Examples of self-observations include episodes of urinary incontinence or the use of rescue medications in the study of asthma. Subjective symptoms are those important symptoms that could not, even in principle, be observed by a third party; common examples include pain, fatigue, anxiety, or drug withdrawal symptoms. Finally, patient quality of life (QOL) refers to subjects' evaluation of their mental and physical well-being. A number of QOL domains have been proposed, including: symptom severity, social interaction, objective functioning, subjective well-being, mental health, physical health, and health-related QOL (1,2,3).

The collection of reliable and valid patient experience data is a substantial scientific challenge (4). One of the simplest ways to collect patient experience data is to ask subjects how they are feeling. Indeed, in-office interviews and global retrospective measures are frequently used methods for collecting these types of data. Interviews with subjects are labor intensive and often fail to provide sensitive data on patient experience. For interviews and retrospective questionnaires that ask subjects to recall how they have been feeling in the recent past, a host of well-established inaccuracies and biases can affect the data, producing unreliable and inaccurate results (5,6,7). Because these biases influence all subjects regardless of whether they have received active medication or placebo, they may obscure differences between subjects in the treatment and placebo groups.

Paper Diaries. Since the 1940s, paper diaries have been widely used in clinical trials as a way to avoid retrospective biases and collect

patient experience data from subjects in the field (8). Empirical data support the notion that diaries can detect variability in patient experience that can be missed if data are only collected during office visits (9,10).

In practice, poor subject compliance with paper diaries often prevents these methods from collecting reliable and valid data. For example, many subjects complete their diary entries after the fact, often just before attending a study visit where the diary is to be collected. This pattern of faked subject 'compliance' with clinical trial protocols that occurs immediately before a site visit is so common that it has its own name—'white coat compliance' (11,12).

Studies have examined compliance rates by comparing entries into paper diaries with data about the time and date collected with various instrumented devices (eg, inhalers, blood glucose monitors) (13–20). The correspondence between these data and the paper diary entries revealed a dramatic difference between subjects' reported versus actual compliance. *Actual* rates of compliance averaged 54%, compared to subjects' *reports* of 88% compliance with study procedures. In other words, at least a third of diary data are invalid.

Poor and/or faked compliance is the greatest limitation of paper diary methods. Perhaps most disturbing, there is often no way to tell which data are accurate and which are invalid when using paper diaries. Both subject data entry errors and outright falsification of data constituted the difference between actual and reported rates of compliance. Given the poor rates of compliance with paper diaries noted above, it is important to note that Goldsmith (21) calculated that a trial with 50% compliance can require four times as many subjects to have the same statistical power to detect medication effects as a trial with 100% compliance. In sum, most diary studies are dramatically underpowered to test study hypotheses because of poor compliance.

From 'Digital Paper' to Electronic Patient Experience Diaries. Technology was initially

seen as a panacea for the data quality and compliance problems associated with paper diaries. Palmtop computers are sometimes used as direct substitutes for paper diaries—essentially as ‘digital paper.’ Investigators could use ‘digital paper’ diaries to avoid data quality problems at the point of entry by structuring the input parameters, and the records could be time and date stamped to avoid faked compliance. The application of electronic diaries in clinical trials has resulted in improved data quality, significantly reduced data management effort, and reduced time to data lock (22,23). However, subjects can be just as noncompliant with ‘digital paper diaries’ as they can be with paper diaries (24,25). Importantly, many of these approaches also failed to recognize the importance of computer system validation, system reliability, and regulatory compliance when applying technology to clinical trials. In short, an electronic diary is only part of a solution that ensures that diary data are valid and collected in compliance with the protocol.

What has been missing from many diary systems is an application of principles from behavioral science that can be used to achieve and maintain high rates of diary compliance. The systematic application of principles from behavioral science allows subject noncompliance to be seen as a problem to be solved rather than a default handicap to be endured when conducting a clinical trial.

Palmtop technology has been combined with principles of behavioral science to collect patient experience data using electronic ‘patient experience’ diaries. The integration of behavioral science with the recent technological advances in hand-held computing distinguishes a new generation of electronic diaries from their paper and ‘digital paper’ counterparts. This combination of technology and behavioral science has yielded compliance rates significantly greater than those seen with paper diaries.

Humane Technology and Human Responses. All electronic diaries have limitations and challenges that must be addressed. Consider-

able time must be invested to develop an electronic diary that will survive daily use in the field. Developing and validating the software is also a considerable financial investment. Some data suggest that these costs are offset when the dramatically reduced rates of query generation are taken into account (23). A variety of technical hurdles must be addressed, including data security, battery life of portable devices, and the routine technical problems that arise when using palmtop computers. One overlooked, but critical, component of patient experience data collection is how user-friendly, or humane, and intuitive the diary interface is for the end user—subjects. User-interface issues that are not often considered when developing an electronic diary include how memory, attention span, habit formation, effortful cognitive processing, and the graphical interface all combine to affect the subject and his/her compliance with the diary protocol (26).

Summary. To succeed in a clinical trial, an electronic PED system must reliably collect real-time, real-world patient experience data that are trustworthy, valid, and sensitive to therapeutic effects. It must capture valid patient experience data from subjects in the field while ensuring its attributability to a specific subject and compliance to all other regulatory requirements. We distinguish this collection of requirements by referring to *clinical integrity* and *system integrity*. These issues, while focused on systems designed to capture real-time patient experience data, are also more broadly relevant to any type of subject-based data capture in a clinical trial.

CLINICAL INTEGRITY

A data collection system with clinical integrity captures the data of protocol interest, that is, the subject has followed the protocol and relayed his/her experience at the correct moment in time. The only way to accomplish this goal is to focus the data collection system on the needs of the subject. A PED system with clinical integrity portrays a user-friendly interface to the subject, while main-

taining scientific and regulatory integrity for the researcher.

Four key components define a data collection system with clinical integrity: protocol compliance, measurement reliability, data validity, and auditable subject quality (see Figure 1).

Protocol Compliance

As reviewed above, subject compliance with clinical protocols cannot be assumed. Falsified data resulting from noncompliance are a direct threat to diary data validity. Researchers are perhaps most aware of noncompliance issues from the extensive literature on noncompliance with medication regimens (12,27,28). Indeed, this literature informs our understanding of noncompliance with diary protocols in several important ways. From a review of the medication compliance literature, it is possible to extract several keys to engendering high rates of compliance with electronic PED protocols:

1. Protocol compliance must be part of design, execution, and write-up of a trial (27),

2. Subjects must be thoroughly trained to use the diaries (8),
3. Making diary entries should be easy for subjects (27),
4. Reminders have consistently been found to improve compliance rates in clinical trials (27,29), and
5. Subjects are more compliant with protocols if they feel a sense of accountability for the data (11). In other words, if subjects know that they will be held accountable for their data, they tend to be more vigilant with the diary protocol (17).

Collectively, these five principles form a foundation for a real-time electronic PED system that tracks and maintains protocol compliance in the field. To begin with, compliance checks should be identified *a priori* and built into the PED system so that the relevant compliance data are tracked and logged in the diary datastream. Ideally, the compliance checks used in such a system should be empirically derived from prior PED studies. Subjects must receive adequate training to use the PEDs. More generally, effective subject training is critical to the success of any electronic data collection system.

<p>Protocol Compliance</p> <p>Part of design, execution & write-up Patients must be adequately trained Making diary entries should be easy Include electronic reminders Ensure patients accountability</p>	<p>Measurement Reliability</p> <p>Repeated assessments Completed as required by the protocol Consistent assessment completion throughout study</p>
<p>Data Validity</p> <p>Ecologically valid data collection Capture data in the moment Track patient protocol compliance</p>	<p>Auditable Patient Quality</p> <p>Systematically track patients' interactions w/ PED Compliance metadata allows evaluation of efficacy data</p>



FIGURE 1. The PED clinical integrity matrix.

This is especially important in that educational and socioeconomic variability across heterogeneous groups means that each subject must be trained, assuming that he/she has never used any type of computerized device.

Importantly, the user-interface must be easy to use and help subjects succeed in completing each assessment so that they succeed more broadly in the study protocol. If a device is to be used by subjects in their daily lives, the software needs to include ‘livability’ functions, such as putting the device to sleep at night, to allow subjects to remain compliant with the protocol as they go about their daily lives.

Real-time compliance reminders and data quality checks can and should be used to enhance compliance and ensure data quality. Reminders can be programmed to respond to various compliance checks depending on the specific needs of the protocol. When specific compliance checks are tripped, the PED system can help subjects adhere to the study protocol. If a subject fails to make a scheduled entry, the PED might present a message, “You have missed a diary entry, please be careful.” Similarly, on-screen reminders can ask subjects to confirm unusual entries (eg, going to bed at 4:00 p.m.) and also praise subjects for good compliance. Moreover, by providing subjects with real-time compliance reminders, electronic PEDs encourage the type of habit-forming interactions with the device that are characteristic of effective and humane computer interfaces (26). The PED system can also give compliance feedback directly to research staff. In this way, subjects receive compliance feedback both from the device and from an individual, increasing the subject’s sense of accountability for the data.

If subjects know that their compliance with the diary protocol is being tracked, and they receive real-time feedback regarding their compliance, many report feeling very engaged in the study protocol. In other words, if subjects know that they will be held accountable for their data, they tend to be more vigilant with the diary protocol. In contrast to the paper diary studies reviewed above that had mean rates of compliance of

54%, studies using electronic PEDs to collect patient experience data have routinely achieved compliance rates between 93% and 99% even in highly demanding protocols involving 10 to 20 entries per day for weeks of monitoring (Kamarck et al., 1998 [30]; Shiffman et al., 1996 [31], 2000 [32]). These rates are also significantly higher than other electronic diary configurations that lack the compliance features that we have discussed (24,25). Empirical data support the efficacy of a protocol compliance system to achieve and maintain subject compliance with diary protocols.

Measurement Reliability

A second component of clinical integrity involves measurement reliability. When repeatedly administering assessments in the real world, it is important that they are both brief and psychometrically sound. As subjects repeatedly complete diary reports throughout the study, treatment effects can more readily emerge as the ‘signal-to-noise’ ratio of their data becomes clearer. Indeed, one of the key promises of all diary research is that repeated assessments enhance the ability to detect group differences. Only a PED system that produces high rates of compliance with the protocol can successfully increase measurement reliability.

Data Validity

The third component of clinical integrity in a patient experience data collection system is data validity. Simply put, data validity refers to the extent to which the data that are needed match the data that are captured from subjects in the field. The successful collection of patient experience data in clinical trials requires that the real-time data collection match the study objectives, that is, one key reason to collect diary data in the first place is to more sensitively measure patient experience by moving data collection to the field (increasing ecological validity) (33) and moving measurement closer in time to the phenomenon of interest (decreasing retro-

spective bias and inaccuracy) (7). Thus, for diary data to be valid, they must be completed in the subjects' natural environment as required by the protocol. Moreover, they must be collected close in time to the phenomenon of interest. By collecting verified data from subjects in real time in the real world, the validity of the diary data is remarkably enhanced relative to paper diaries.

Auditable Subject Quality

Electronic PEDs can provide a new perspective on the quality of the efficacy data gathered from subjects in the field. Traditionally, researchers have had to rely on the efficacy data themselves to judge the veracity and quality of the efficacy data. Audible subject quality means that there is a straightforward and independent means of assessing data quality. Some PED systems collect data on subject compliance with the protocol that extends beyond the efficacy data. This independent datastream, or 'compliance metadata,' allows researchers to evaluate the quality of the subject data without relying on the efficacy data.

Several types of sampling strategies are used in PED studies, each with its own corresponding compliance indicator that can be used to gauge compliance. For example, consider a study that aims to characterize subjects' average level of pain. This might be done using randomly scheduled assessments to collect a representative sample of patient experience. The rate of compliance with these randomly scheduled assessments $[(\# \text{ assessments completed} / \# \text{ random prompts presented}) \times 100]$ (21) reflects one important metric of a subject's compliance with the diary protocol. Logging data regarding whether each random prompt assessment was completed, as well as how long it took the subject to respond to the audible prompt, generates an ongoing record of compliance. Beyond that, analysis of these compliance data can also indicate underlying problems, such as the extent to which the subject was carrying the device as instructed, or whether

the patient is avoiding prompts at a particular time.

The productive reduction and management of diary data, compliance metadata in particular, presents some unique challenges to data managers and researchers alike. Just as indices of protocol compliance must be identified *a priori* and built into the study protocol, so too must compliance algorithms be used that allow researchers to sensitively test for subject compliance with the protocol. Ideally, these compliance algorithms should be based on empirical data so that an audit trail is produced and decisions regarding the evaluability of subjects' data can be scrutinized and defended.

Summary

Clinical integrity ensures that the electronic data collection system captures reliable and valid patient experience data in real time, in the real world. The four components of clinical integrity—protocol compliance, measurement reliability, data validity, and auditable subject quality—require a system specifically designed to help subjects succeed while at the same time providing the right clinical data captured at the right time. These solutions exist today for implementation in clinical trials.

SYSTEM INTEGRITY

Even if the electronic data collection system meets all of the requirements for clinical integrity, the system also must meet regulatory requirements. It must operate reliably and protect the integrity of the data it gathers. Regulatory authorities expect computerized systems used in clinical trials to provide data that are at least equally as reliable as data provided by paper-based methods (see Table 1). In order to have confidence that data from PED systems are reliable, the PED systems must be controlled, tested, and validated to 21 CFR Part 11 standards for every clinical study they support. A computerized system validation effort is needed on three levels to ensure the system integrity of any Good

TABLE 1
The Basic GCP Concern

FDA Guidance for Industry: Computerized Systems Used in Clinical Trials (April 1999)

- Introduction:
Persons using the data from computerized systems should have confidence that the data are no less reliable than data in paper form.

Clinical Practice-regulated system (34,35,36), including PEDs:

- Computerized system validation by the developer of PED platform technology (PED device plus PED software),
- Computerized system validation by the clinical information technology/information systems department for installation of a PED platform in-house and deployment of trial-configured PEDs to clinical sites, and
- Computerized system validation by the clinical project team for the specific configuration of PED software used in support of a given clinical trial protocol.

System integrity for any computerized system is built on the elements of management control, system reliability, data integrity, and auditable quality. When applied to PEDs, these elements help ensure that the clinical integrity of the system is matched by a stringent level of regulatory compliance as embodied by the term system integrity (See Figure 2).

Management Control

PED system integrity begins with management staying in control of the PED system throughout its life cycle. The control must exist from its development as a basic PED platform by the supplier, through its specification and configuration for a specific study protocol, deployment to the sites and subjects, and finally, to its retirement at study close out. Standard operating procedures (SOPs) are needed for specifying, configur-

ing, deploying, and using PEDs during clinical studies and for the processing of PED data and compliance metadata. These and other SOPs define management’s process for staying in control of the PED system.

Two essential components are part of the management control to ensure PED system integrity. First, documented requirements specifications to configure the PED for each new study protocol must exist. Second, a strict change control process must be in place to limit modifications after the PEDs have been configured. Frequent software modifications give rise to unreliable systems and data handling operations and the opportunity for data corruption, potentially leading to a system that functions, but may not function as expected or collect the right data. When specifications are clearly written at the start, the configured PED will meet study needs in a consistent and reliable manner. Taking time up front for proper specification saves time and money through the rest of the life cycle and is the best way to ensure management control of system integrity.

The change control process for PED units and software configuration must be documented and practiced, and all changes tested and results logged prior to deployment. On a per study basis, the SOP for how to deliver changes to the sites and subject PEDs needs to be defined and followed. The clinical team must consider the statistical and data integrity implications for any configuration changes requested prior to their implementation.

System Reliability

The ability of a computerized system to perform its required functions again and again is a hallmark of system reliability. Testing the PEDs with a wide variety of expected kinds of patient experience data will document the system’s reliability. Testing the PED with invalid inputs and stressful environmental conditions will document its “robustness” or ability to function correctly in the presence of errors and stress conditions in the subject’s lifestyle situation. For example, a

<p>Management Control</p> <ul style="list-style-type: none"> Documented PED Life Cycle Requirements spec. per study protocol Problem handling & site support Security practices & change control Site & subject training 	<p>System Reliability</p> <ul style="list-style-type: none"> Testing of basic PED platform PED testing per study configuration Staging of units prior to deployment Written patient instructions Change control testing Spare units for replacement/backup
<p>Data Integrity</p> <ul style="list-style-type: none"> Built-in entry & processing checks Password & code security Verification of critical data & data uploads Patient training & built-in prompts Audit trail for data entry & edits 	<p>Auditable Quality</p> <ul style="list-style-type: none"> CSV Package for PED platform CSV Package per study configuration System specification per study config. Metadata DB for entry & edits Patient training materials & records

FIGURE 2. The PED system integrity matrix.

subject's small child may play with the PED, a teenager may try to hack into the parent's PED to use other capabilities of the device, or the PED might drop off the bed on to the floor. These examples of possible stress in the subject environment suggest that physical as well as logical testing of PEDs be performed during the staging of electronic PED units prior to sending them to the sites or replacing a subject's broken unit.

Data Integrity

As shown in Table 2, there are five key quality metrics required of any Good Clinical Practice data used for submission to authorities in support of a product claim. PED data must meet these metrics and the PED configuration must preserve the integrity of PED data during their electronic handling at collection, uploading, database storage/retrieval, system backup/archival, and during any data analysis or reporting.

Password and code security on a PED support the "attributable" metric by identifying the subject doing the recording of data. Instructions to the subject about not sharing password and code are important to enforce

this metric. Date and time stamps on the PED support the "original" metric for time-based compliance data. Built-in real-time edit checks, user prompts, and alarms support the validity of the data by helping the subject describe his/her experience in protocol-relevant terms. A PED designed to have scheduled and random alarms with defined windows of opportunity for data entry provides support for compliance metrics in PED data that can never be approached by paper diaries. The improved data quality associated with PED data includes guaranteed legibility, which cannot be matched by paper-based methods.

TABLE 2
The Food and Drug Administration's
Quality Metrics for Data

Patient diary data must be:

- **Attributable**—data are identified with a specific patient and a specific recorder
- **Original**—data are recorded for the first time
- **Accurate**—data are correct
- **Contemporaneous**—data are recorded at the time they are generated
- **Legible**—data are readable by humans

The compliance metadata collected by the PED have the audit trail information for edits and changes as well as the contextual information described earlier in this article. All of these aspects of the electronic data can be used to verify subject compliance and data integrity when the PED system has documented system integrity.

Auditable Quality

The whole focus for audits and inspections is to examine the documented evidence for quality practices being followed in regulated operations and to assess the adequacy of those efforts in comparison to expected quality standards. If PED system testing was performed, but no test plan, test records, or test summary report was kept (37), then the testing has no evidence to show it ever took place and no 21 CFR Part 11 credit can be given during an audit or inspection. Without a configuration requirements document, there is an opportunity for multiple PED changes that, in turn, could jeopardize data quality. With proper change control logs for change request, change delivery, and change testing, the PEDs are in control, have system integrity, and the PED data are then deemed reliable and of use in support of a regulatory submission.

With appropriate subject training records, examples of subject instructions for PED use in a study, and the existence of standardized training materials, the resulting data are more likely to be of auditable quality. In addition, the security, data upload, and data management practices for the data and meta-data databases need to be described in a work instruction, SOP, or data management plan.

The computerized system validation package for an electronic PED system needs to have the same elements as the computerized system validation package for a clinical data management system, but package items are scaled to the size of the respective system. The PED configuration for a specific study protocol needs computerized system validation work comparable to that of an electronic

case report form configured for a specific study protocol.

The auditor/inspector perspective is the following: If quality practices are not documented, they did not happen. If quality practices did not happen, the process/system is out of control. If the process/system is out of control, the data are suspect. If the data are suspect, they are inadmissible for regulatory approvals. If data are inadmissible, the trial would have to be repeated using documented quality practices. However, when documented quality practices are in place, the audit or inspection confirms the PED team's pride in performance (38).

CONCLUSION

Clinical integrity ensures that there are good data for the electronic PED system to handle, but even good clinical data will not be admissible unless there is also PED system integrity to ensure a validated environment for computerized data handling. The combination of the two raises the bar for the quality of diary data and enables successful real-time capture of patient experience data. In short, clinical and system integrity are both essential for a computerized system that collects data from subjects in a clinical study. While clinical integrity helps to ensure that the right data are collected at the right time, system integrity helps to ensure that the PED system itself is robust and trustworthy so that electronic data are safely handled and protected from corruption. A PED system with both clinical and system integrity has been empirically shown to deliver on the promise of high-quality diary data.

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