



44TH
Annual Meeting



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Electronic Patient Diaries: Validation in an Unsupervised Setting

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Refining Patient Reported Outcomes



Validation in an Unsupervised Setting

21 CFR Part 11 distinguishes between open and closed computer systems

- All ePRO systems are open systems
- Not all open systems are created equal...



Electronic Patient Reported Outcomes (ePRO)

Two main scenarios:

In-Clinic Assessment	Everyday Assessment
<ul style="list-style-type: none">• Patient completes questionnaires at clinic visit.• Typically recall over 1 – 4 weeks• Supervised setting	<ul style="list-style-type: none">• Patient takes diary away, and uses at home, work, etc.• Recall over day, shorter period, or here and now• Unsupervised setting



ePRO in an Unsupervised Setting

- Ensuring that it is the patient who completes the diary
- Ensuring that entries are made at the intended times
- Ensuring that entries are valid
- Ensuring that the data are correctly transferred to the clinical database



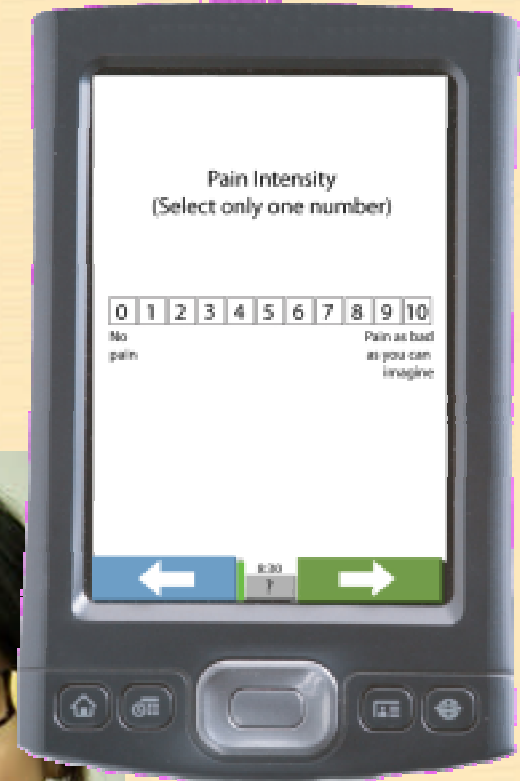
Example: Bank Security

- You have something
- You know something



Patient Identification

- You have something
- You know something



Patient Identification

- You have something
- You know something

- There must also be a system for dealing with forgotten or compromised PIN numbers



Validity of Entries - Paper

5	S/A	1	2	3	F
6	10/20	1	2	3	F



Validity of Entries - Paper

Not at all

Could
~~Couldn't~~
be worse

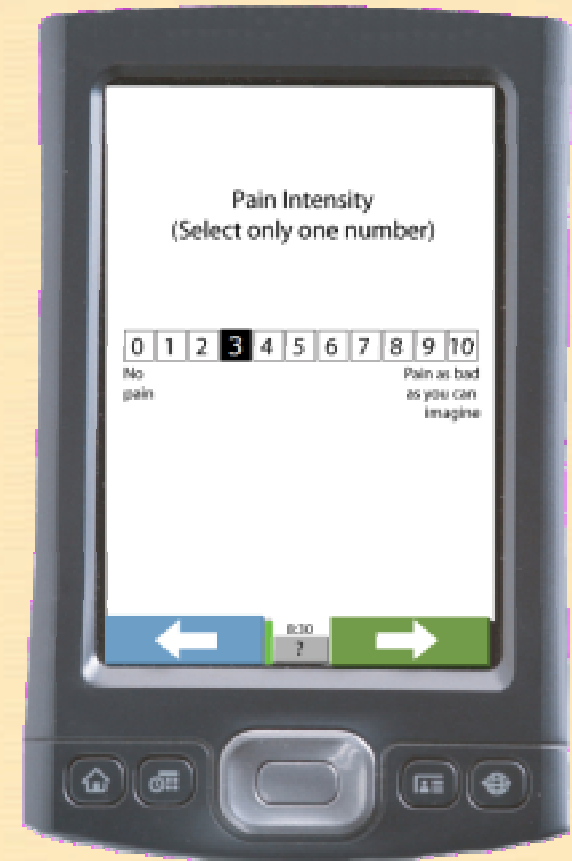


Validity of Entries

Up to 80% of paper diary cards contain significant errors (Quinn et al., 2000)

- Marks between boxes
- Added comments
- Illegible entries

These problems do not occur with electronic diaries



Investigations of Paper Data

Objective measure	Compared to	Example (N of studies)	Finding
Doses recorded on instrumented inhaler	Daily paper record of doses taken	Simmons et al., 2000 (4)	True compliance ~30% lower than recorded on paper
Peak flow recorded on instrumented meter	Peak flow entered on daily paper diary	Verschelden et al., 1996 (2)	Around 40% of paper entries were invented by patients
Opening of instrumented paper diary	Entries in paper diaries and patients' record of compliance	Stone et al., 2002 (1)	Claimed compliance, 90%; true compliance 11%, about 30% of entries invented.

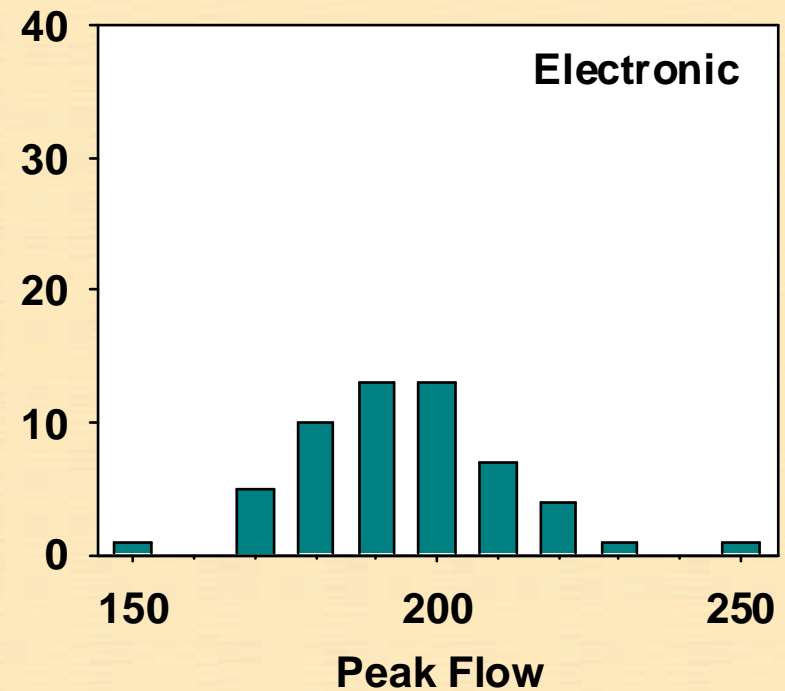
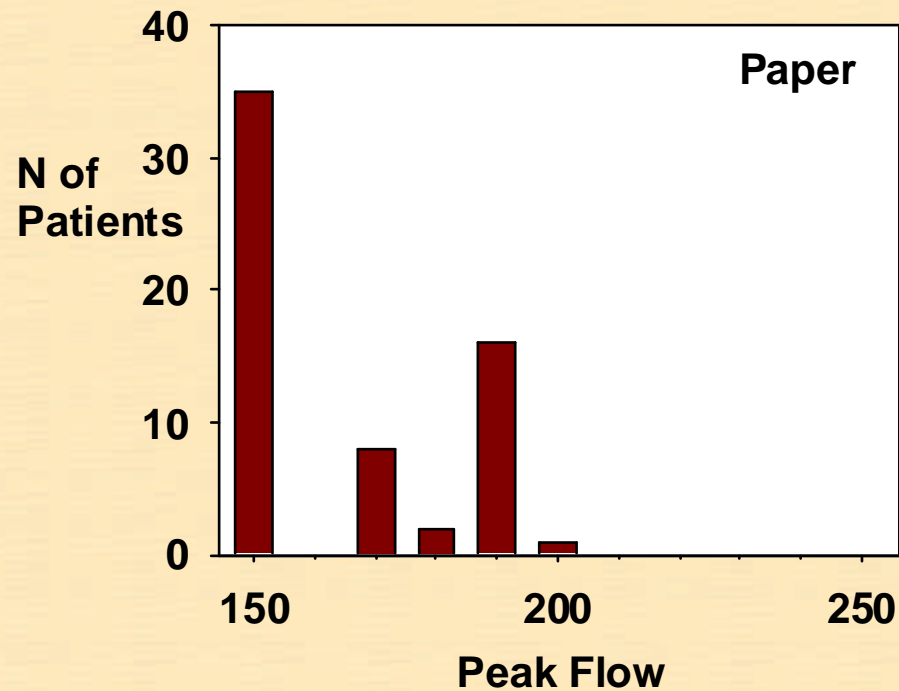


Electronic Patient Diaries

- Time tools prevent data hoarding and document actual compliance
- Reminders help patients follow protocol
 - In the Stone et al (2002) study, electronic diary compliance was over 90%
 - Compliance over 90% regularly obtained in clinical trials
- Improvements in data quality often seen



Quality of Diary Data

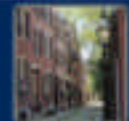


Source: Tiplady et al. (1995)



ALCOA and diaries

	Paper	Electronic
Attributable	Handwriting + sign-off	Patient passwords, digital signatures
Legible	Often problematic	Ensured
Contemporaneous	Violations common	Time/date stamping
Original	Patients can make changes after the fact	Patients cannot change the data once submitted
Accurate	Many invalid responses	Only in-range values can be entered



Contemporaneous

If a patient diary or some other form of unsupervised data entry is used, the FDA plans to review the protocol to determine what measures are taken to ensure that patients make entries according to the study design and not, for example, just before a clinic visit when their reports will be collected.

Source: FDA Draft PRO Guidance Feb 2006

How would you do this for paper?



Compliance for ePRO

- Documenting Compliance
 - Patient identification at login
 - Date and Time stamping of records
- Improving compliance
 - Time windows during which entries can be made
 - Alarms and reminders
 - Feedback from monitoring of study data



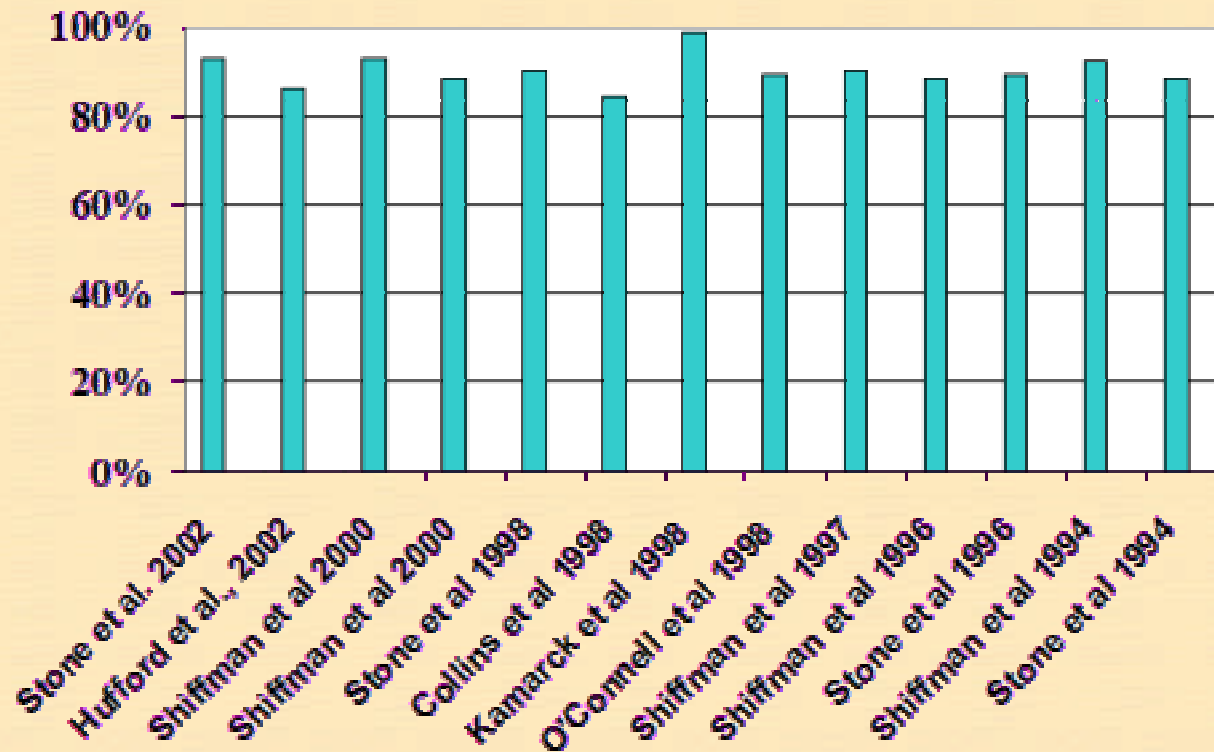
Importance of high compliance for data validity

- Reduced opportunity of bias
- More precise outcomes
- High compliance can be consistently obtained with ePRO
- ePRO documents true compliance rates



Compliance in published ePRO studies

Consistent compliance: average of 93%



Data Transfer

- Real-time connection to server during entry
 - Requires network coverage at all times
- Store-and-forward, with frequent update during study
 - Transmission after each entry
 - Daily transmission, typically at night
- Store data on device and upload at end of study



Store and Forward



- Cradle combines charging and data transmission function
- Same PDA model can be used either for landline or wireless transmission
- No patient involvement with mechanics – PDA placed on cradle at night, transmission is automatic



Data Security



- Data transmitted regularly to secure server
 - Potential for lost data much less than for paper
- Data stored on device
 - Backup in case of transmission problems



Data Security

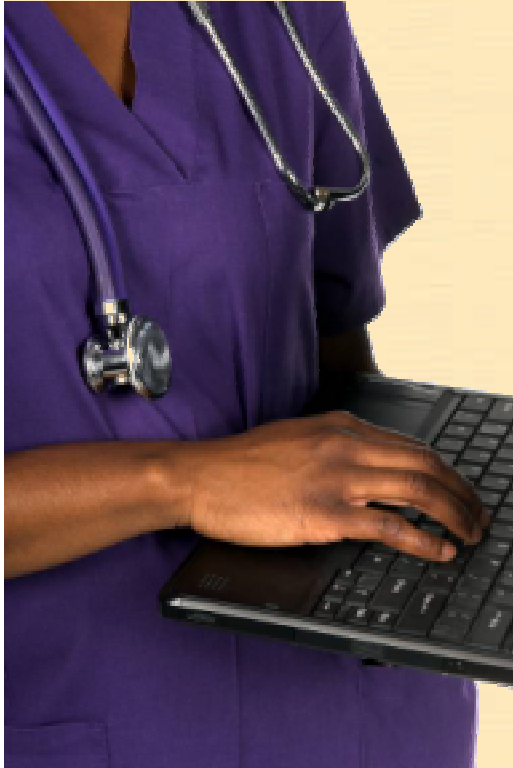
- Encryption
 - Essential when open networks are used
- Data cannot be viewed on device
 - Useful for sensitive topics
- Metadata to support eSource
 - Device ID
 - Transmission time



Data Review

Web browser means data are immediately available to investigator and study staff

- Following study progress
- Site management
- Patient management
- Data integrity



Web Report Example

 [Log Out](#)  [Print](#)  [Help](#)

[< Home](#)

Site Information

[Site Information Dashboard](#)
[Visit Status by Subject](#)
[Compliance Summary Report](#)

Subject Information

[Subject Information Dashboard](#)
[View Subject Data](#)
[Medication Use Summary](#)
[Migraine Episode Summary](#)

Data Clarification Forms

[View All DCFs](#)
[Create DCF](#)
[Resolve a DCF](#)

Site Comments

[Create a Site Comment](#)

My Information

[My Profile](#)
[Change Password](#)

Compliance Summary Report

Protocol Number: Study 01: Protocol 2468


Version: 1

Site Number: 01001 - A Jones

Current Date: 22 Oct 2007

Subject ID	Migraine Episodes Completed in Last 7 Days	Evening Reports Completed in Last 7 Days	Date of First Study Med
01001002	1	7	08-May-2007
01001003	3	7	22-May-2007
01001004	0	6	None
01001005	2	7	None
01001001	Completed	Completed	Completed

Select a Site

Next Site 

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Data Review

- Compliance
- Data query resolution
- Help desk usage

Prompt review allows early identification and resolutions of problems that may arise



Unsupervised but Secure

- Patients
- Entries
- Process

Photo source: <http://hpwren.ucsd.edu>



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