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► To cite this version:

Candice Estellat, Florence Tubach, Yolande Costa, Isabelle Hoffmann, Jean Mantz, et al.. Data capture by digital pen in clinical trials: A qualitative and quantitative study.. Contemporary Clinical Trials, Elsevier, 2008, 29 (3), pp.314-23. <10.1016/j.cct.2007.09.007>. <inserm-00202203>

HAL Id: inserm-00202203

<http://www.hal.inserm.fr/inserm-00202203>

Submitted on 4 Jan 2008

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Data capture by digital pen in clinical trials: a qualitative and quantitative study

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Keywords: Clinical Trials/methods; Data Collection/methods; Interviews; Qualitative research; Internet

Word Count: 3 169

Funding – This study was funded in part by a grant from the Fondation pour la Recherche Médicale, and authors' work was independent of the funders' involvement. We did not receive any financial support from Hewlett Packard™ or Kayentis™. They took no part in initiation, design, realisation, analysis or report of this study. Authors declare no conflict of interest

Acknowledgements – We thank Caroline Quintin, Estelle Marcault, Delphine Prieur and Sophie Bougouin the study monitors who participated in the focus group and all the investigators who took part in the study.

Abstract (288 words)

Objectives. To investigate the use of the digital pen (DP) system to collect data in a clinical trial. To assess the accuracy of the system in this setting.

Design. Qualitative study based on semistructured interviews and a focus group. Quantitative study comparing the DP system and a double manual data entry system in accuracy of acquiring data by variable type (tick boxes, dates, numbers, letters).

Setting. An ongoing randomised multicentric clinical trial in tertiary care in France.

Participants. 27 investigators involved in the trial (anaesthetists) who did or did not include patients, 4 study monitors and the study coordinator.

Results. Six key findings emerged: 1) the DP system was easy to use; its utilisation was intuitive, even for investigators inexperienced in informatics; 2) despite its portability, the DP was not always used in front of patients; 3) the DP system did not affect patient recruitment; 4) most of the technical problems of the system occurred during setup (compatibility, password access, antivirus software); 5) the main advantage was quickness of data availability for the study coordination staff and the main hindrance was the extra time required for online verification; and 6) all investigators were ready to use the system again.

The investigators had to check 16% of data obtained by the DP system during the verification step. There is no relevant difference between the number of errors for the DP and the double manual data-entry systems: 8/5022 versus 6/5022 data entries. 5 out of 8 DP-system failures were due to the intelligent character recognition system.

Conclusion. The DP system has a good acceptability among all investigators in a clinical setting, whether they are experienced with computers or not, and a good accuracy, as compared with double manual data entry.

Difficulty in patient recruitment and quality of collected data are two important issues in clinical trials [1-4]. They could be influenced by how data is collected and investigators' motivation which is a very sensitive area [2, 5, 6].

The classical pen-and-paper case report form (P&P-CRF) has been widely used for many years in clinical trials. Investigators are used to it and it can be completed, as a medical record, in front of the patient. However, until study monitors visit each site, the study coordination staff remains unaware of what is going on in sites, with a lag in time from point of data capture to the central database and analysis (CRF collection, data entry and consistency checking).

Advances in the field of technology and communication have opened up a new and exciting avenue to enhance data collection in clinical trials. With electronic CRF (e-CRF), study coordination staff has immediate access to all data, and some monitoring can be done online, which can increase the quality of data collected because inconsistent or missing data can be resolved on an ongoing basis when investigator still has the patient in mind and access to all patient's data [5, 7-12]. Moreover, data are potentially ready for data management and analysis in a matter of seconds. However, electronic data capture is time-consuming and diverts the attention of investigators from traditional duties: usually they have to use immobile desktop PCs [13], which requires a powerful and permanently available Internet access [10], and the system often interferes with the investigator-patient relationship [7]. Thus, despite many theoretical advantages, the acceptability of e-CRF among investigators is questionable [13] and may, because of the extra work required, have an unwanted effect on investigators' motivation to recruit patients to the study.

The new digital pen (DP) system captures electronically all data written by use of the pen on a special printed paper. Mimicking the P&P-CRF system, it aims not to change investigator habits but also allows for immediate online availability of the data for the study coordination staff. The use of the DP system has been evaluated in just a few clinical settings and in a pilot study [14-17], but to our knowledge its use has not been described or evaluated in a clinical trial setting. We aimed to evaluate the acceptability and accuracy of the DP system for data collection in a clinical trial. For this purpose, we conducted an ancillary qualitative and quantitative study within an ongoing trial (STRATAGEM) that used the DP system for data collection, exploring investigators' acceptability of the system and the system's accuracy in a clinical trial setting.

Methods

Context

STRATAGEM is an ongoing randomised, double-blind, sequential trial comparing two antiplatelet therapy strategies in the peri-operative period (ClinicalTrials.gov identifier NCT00190307). The trial takes place in a tertiary care setting and is funded by a grant from the French Health Minister clinical research program. All data (approximately 300 variables per patient divided among six visits), including lab data, are captured by investigators (anaesthetists) using the DP system.

The DP system comprises four components: the Hewlett Packard™ (HP) digital pen 200; CRF with paper printed (on HP color LaserJet printers) with a special pattern, based on dots slightly displaced from an orthogonal grid, unique for each page and each CRF (Anoto™ technology); the software HP Workflow Connect 200; and the Vision Objects™ Intelligent

Character Recognition (ICR) system. This complete information system solution is provided by Kayentis™, a system integrator of digital writing solutions dedicated to clinical studies (Figure 1).

The investigator is pre-warned about any data transmission error or interpretation. Incomplete mandatory fields, data out of bounds (defined by the main investigator), or data recognised by the ICR engine but with a level of confidence under a predetermined threshold are automatically flagged on the electronic CRF replica until the investigator checks them online. By clicking on each data he opens a new window where he can confirm or correct it (verification step). The predetermined threshold of confidence required (sensitivity) of the ICR engine can be adjusted for each data type, higher for dates than for other variables in this trial. At any time, investigators have an electronic access to all CRF already transmitted from the study site, to their ICR interpretation and to a summary of the ongoing study for each patient.

The study monitors are in charge of checking that the data conform to the source documents and for their consistency, immediately on the Web site and periodically at study sites. They can provide technical support about the DP system by phone or when visiting sites. Study monitors went to each site to install the DP system software and to explain its use to investigators. Two DP systems with user's guides were given to each site.

When this ancillary study began, 134 patients were enrolled in the trial, at 18 sites, with one to four co-investigators for each site ("active" sites). For the other 13 sites, no patient had yet been enrolled in the trial ("non-active" sites).

Qualitative data collection:

We collected data from various players involved in data capture in a clinical trial to compile an exhaustive view of the acceptability of the DP system [18]: semistructured interviews with investigators from active sites and non-active sites; and a focus group with study monitors and the trial coordinator.

Interviews

All interviews were conducted by phone between March 2006 and May 2006 by an interviewer (CE) not involved in the trial. They typically lasted 10-15 minutes. Interviews were individual and followed a prompt guide (available on request) developed after literature review and discussions between assessors (CE and YC). We interviewed all leader investigators of active sites, asking them to describe how they used the DP system and to explain its benefits and drawbacks, including role in patient enrolment. Investigators were also asked about their previous experience with clinical trials and their willingness to re-use the system in another trial or another setting. We contacted by phone a random sample of leader investigators from non-active sites, until redundancy was reached, to ask them specifically about the DP system in comparison to the other system in terms of patient recruitment.

The interviewer pursued themes as they arose and sought clarification or elaboration as required. From the analysis of first interviews, the guide was periodically enhanced for subsequent interviews to further explore emerging themes. Interviews were audiotaped with

the participants' consent, transcribed verbatim, and then coded independently by the 2 assessors to ensure reliability.

Focus group

To further explore organisational and monitoring issues with the DP system, we held a focus-group session in May 2006 with study monitors and the trial coordinator. One of us (CE) conducted the focus group, facilitating discussions with an open-ended list of questions covering the same topics as in interviews with investigators but emphasizing organisational and monitoring issues. The session was audiotaped and then coded independently by CE and YC.

Analysis

We analysed data by an inductive method [18]. The two assessors read the transcripts several times, indexing and cross-indexing themes and categories. Then all data relevant to each category were identified and pooled to examine them by constant comparisons and to obtain final comprehensive analytical categories. In each of these steps, themes were synthesised to develop cohesive conceptual descriptions. Periodic discussions between assessors ensured consistency of coding and helped to reach agreement on final descriptions. Results of analyses were presented to participants of the interviews and focus group to incorporate their reactions to study findings.

Quantitative data collection

For all baseline visits and for each type of data variable (tick boxes, dates, numbers, letters), we obtained the number of verifications required from the investigator during the verification step of the DP system.

We also explored the accuracy of the system's data acquisition on a sample of 54 baseline visits (all patients enrolled from sites in the Paris area). We sent a copy of the CRF completed by investigators with the DP to an external company to perform blinded, double manual data entry of the CRF data. This database was compared to that obtained with the DP system. We reported mismatches (*e.g.*, for mismatch in date: "19/08/2005" with the DP system *versus* "29/08/2005" for the CRF data) for each type of variable. For each mismatch, we checked the correct answer on the copy to determine which acquisition process was wrong: manual data-entry failure, DP-system failure, or uncertain because data were unreadable. Then we attempted to describe the DP-system failures: ICR failure, transmission failure (data written on the paper CRF but not visible on the electronic replica) and online correction (during the verification step) not reported on the paper CRF.

Results are described with numbers and percentages. Database comparisons involved use of the software R 2.2.1.

Results

Qualitative analysis

Table 1 shows characteristics of investigators interviewed. Four study monitors and the trial coordinator attended the focus-group session.

Qualitative analysis of interview and focus-group data yielded six major themes: utilisation learning, DP-system performance, patterns of use, impact on patient recruitment, perceived drawbacks and advantages, and future use.

Utilisation learning

Most investigators reported that they learned to use the DP system when the study monitors came on site for the study setup. Few reported having consulted the user's guide. If they encountered a difficulty, they preferred to call the study monitor and were satisfied with this quick on-line counselling.

Almost all investigators, even those who considered they had no specific skills in informatics, said the system was very easy to learn. They said that its mechanism was intuitive even if a short lag time was necessary to get used to it.

"It's so easy! I'm not so talented in informatics and truly I found this pen was as easy as pie."

Some investigators had enrolled several patients in the study before they started to use the DP system. They were waiting to have time to learn how to use the system and thought it was more important to first enrol patients.

"I'm not able to do everything so I thought it was important to enrol patients as fast as possible and to capture data on CRF later on. ...I'll be on call this weekend so I planned to fill in all my CRF this weekend."

Only one investigator mentioned being afraid to use the DP system:

"2 or 3 times I asked the [study monitors] to explain to me again how [the system] works, to explain to me again because I was a little afraid of using it, yes. I twig it after many attempts ... but perhaps it's me."

DP-system performance

Users usually found that the DP system worked properly. The most commonly mentioned comments were about the ICR system (mandatory verification step, *cf. drawbacks*), the size of the pen, and the time required to download data from pen to computer (1 to 2 minutes).

Some technical problems occurred, mainly during setup, but all were resolved. Problems included password problems, compatibility with hospital informatics system or with existing

antivirus software, or failure to download data on the first attempt. Some investigators complained of poor ergonomics of the Web-site user interface.

Patterns of use

Although portability was a major advantage of the DP system, some investigators did not use it in front of the patient, especially for the first patients they enrolled. In these cases, they wrote down data differently (by pencil on the CRF, photocopy of the CRF, notes on the patient medical record or patient anaesthesia record, separate draft) and then recorded data by use of the DP. This pattern of use, although not encouraged, is possible in STRATAGEM.

“I wanted to see how it works for the first CRFs, but I think for the next I’ll do it directly with the DP”

Explanations given for this pattern of use were managing the availability of the DP between co-investigators in a site, becoming familiar with the DP system and the study protocol, and not having the DP at all times in their pocket.

Impact on patient recruitment

No investigator interviewed, either from an active or inactive site, thought that the DP system had positively or negatively influenced the number of patients enrolled in the trial, as compared with the P&P-CRF system:

“To be clear, in our site, it’s not because of [the DP] that we do have not recruited patients.”

Even in the few cases in which investigators encountered technical problems, they continued to recruit patients.

Drawbacks and advantages

The box lists the drawbacks and advantages of the DP system mentioned by investigators.

Only two investigators had experience with a previous clinical trial that involved use of an e-CRF. Both were disappointed by the amount of extra time required to capture data online with an e-CRF and clearly preferred the DP system.

“It’s very quicker than an Internet data entry! I’ve the experience of an Internet data entry and it was tedious, terrible, horrible, time-consuming, what else can I say ...? But the pen it’s fine, it’s like a normal pen, it’s the same as filling in a form and then you just have to click ... no, it’s great, really.”

Future use of the DP system

All investigators declared that they were ready to use the DP system again in another clinical trial. Many would like to use the system in a clinical setting, for example to complete the anaesthesia visit form or the patient medical record.

Quantitative analysis

Among the 12 462 total data entered with the DP system (from 134 baseline visits), 1994 (16%) needed to be checked by investigators at the verification step (Table 2). The higher rate of checks occurred for dates (994/1206; 82%).

We compared the two databases (the DP system and double manual data entry from the CRF copy) for 5022 data (54 baseline visits), mainly tick boxes and numbers (Table 3). Mismatches in data occurred between the two systems in 19 (0.38%) data, with no relevant difference in error rate between the 2 systems: 6 (0.12%) versus 8 errors (0.16%). In 5 cases, data were unreadable and the error was not attributable to any system. 5 out of 8 DP-system failures were attributable to an ICR error.

Discussion

To our knowledge, this is the first study to investigate the use of the DP system to record patient data in a clinical trial setting. The system seemed easy to use for most investigators, whether they were experienced with computers or not. Investigators did not feel that, compared with the classical P&P-CRF system, the DP system affected patient recruitment. Some were disappointed by the secondary mandatory verification step (16% of data). There is non relevant difference in accuracy between this data entry method and the double manual data entry system, considered the reference system [19].

We performed qualitative and quantitative analysis of the DP system. Semistructured interviews and a focus group were appropriate to investigate and better understand different views about this new device [18]. Observational method seemed unrealistic because of the unpredictability of patient recruitment and modifications in the use of the system. Even if we attempted to collect comprehensive views of the system [18], we may have missed some data from investigators reluctant to use informatics and who initially declined to take part in STRATAGEM. To some extent this may have biased our findings.

Our quantitative analysis of the accuracy of the DP system included objectively quantifying the extra work required in the verification step. We also evaluated data-entry accuracy with minimum biases because we compared two different data-acquisition processes from a unique data collection.

It is also important to underline that we assessed acceptability and accuracy in the worst case scenario: in this trial, all data were collected by the investigator with no help from a study nurse or a clinical research associate.

We could not investigate all the advantages and drawbacks (*e.g.* quick availability of the database for statistical analysis) of the DP system in a clinical trial because the STRATAGEM trial is ongoing. However, we considered it was important to know early in the trial the acceptability of a new device and not to miss some specific learning-phase patterns of use.

Cole *et al.* showed during an experimental data-capture session that the DP system is a fast and easy-to-use data-entry method, with an accuracy of captured electronic data that is not optimal but better than a secondary, single, manual data-entry system [16]. In a “real-life” clinical trial setting, we confirmed the ease of use of the DP system and its good accuracy as compared to a double manual data-entry system.

Despont-Gros *et al.* implemented and assessed the DP system in a clinical care setting and reported satisfaction of users [14, 20]. The authors also reported that the system was easy to learn and use and did not interfere with patient-physician relations. The accuracy rate they reported (96%) was lower than ours (99.8%), but the DP-system components they used were still in development at the time of their study and not commercially available. Moreover, their clinical setting contained no study monitor, and users were less familiar with collecting data than those in a clinical trial. As in our study, the authors also pointed to the need for data verification to enhance the reliability of this technology. However this step of verification is cited as the main drawbacks of DP system by investigators.

In each setting, the best level of sensitivity of the ICR system must be found: more verification required by the system does not necessarily mean better quality of data, because study monitors have pointed out that some investigators overwhelmed with verification extra work may unintentionally confirm erroneous data.

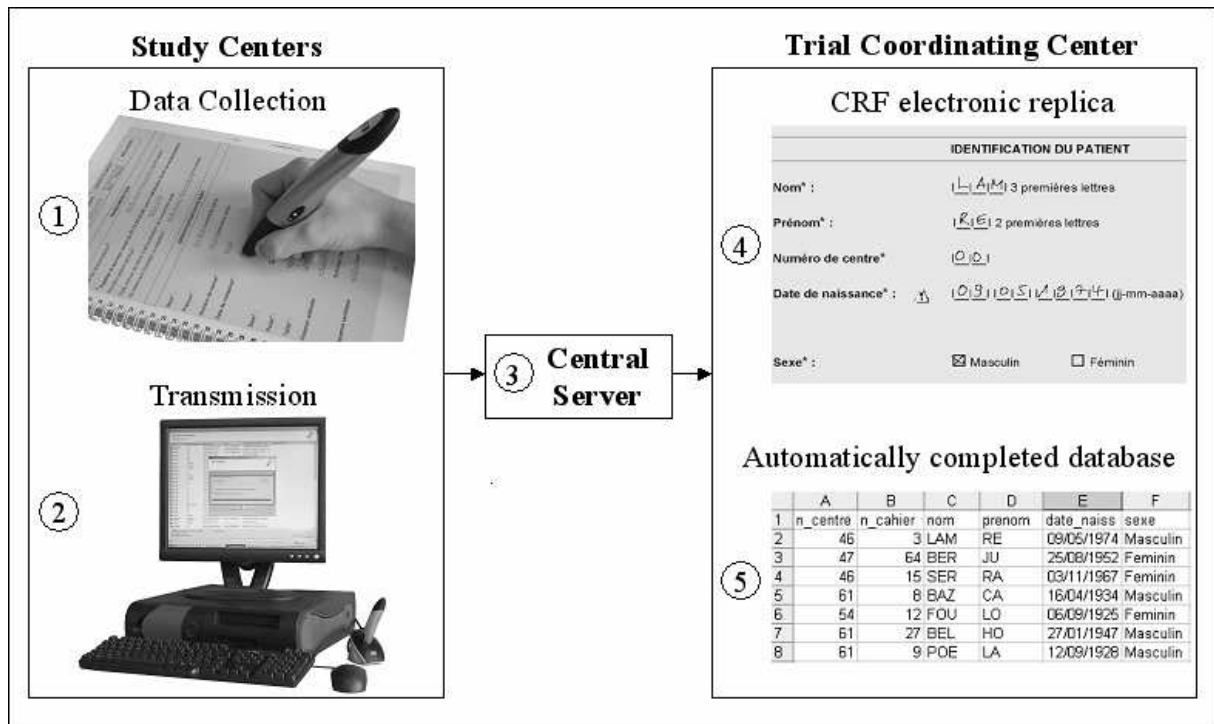
The DP system combines many advantages of the P&P-CRF and e-CRF systems (Table 4), but no single process is ideal for all studies [21]. The DP system is useful in multicentric and/or sequential trials and when most of the data must be collected in front of the patient when a computer is not always available. Other devices such as Personal Digital Assistant (PDA) or tablet PC could be useful in the same setting, but other drawbacks may limit their use: small screen size, stylus writing difficulty, memory and battery capacities, and complete lost of data in the case of an informatics bug [16, 22] or if the device is lost. Because the DP system is nearer to the classical P&P-CRF pattern of use, it has a good acceptability among all investigators and requires little new learning. Moreover, in the case of an informatics bug or if the DP is lost, the paper data remain and can be entered manually.

The DP system could enhance online data availability for trial coordination staff without altering investigator data collection practices and patient relations. Besides its use in clinical trials, the system may also have a future in other medical settings: pharmacovigilance, electronic medical records and public health surveillance, to name a few.

On the basis of our qualitative findings, we suggest a fixed-response survey among investigators of different trials and different data collection devices to help further determine the device most appropriate for a trial depending on trial characteristics.

Figure

Figure : Digital pen system



The digital pen (length 17.5 cm; diameter 2.5 cm; weight 50 g) is a ballpoint pen equipped with a small camera. (1) While the investigator is completing the case report form, the digital pen “reads” the unique pattern of print on the paper to record any pen tip movement made on it. (2) Once docked on an Universal Serial Bus (USB) cradle linked to the investigator’s computer, the pen is authenticated against the central server and (3) transmits the encoded information to the data processing application (central server) for this trial over the Internet. (4) The trial coordinating center receives an exact electronic replica of the handwritten page, and (5) an intelligent character recognition system instantly converts captured information into time-stamped clinical data stored in an automatically completed database.

Box

Investigators' feedback on drawbacks and advantages of the digital pen system in comparison to the classical pen and paper system.

- Logistics for the trial coordinating staff

"If I was the main investigator, coordinating all the clinical trial staff, I'd really appreciate to have live access to all CRF [data] as soon as the data entry is done, I guess it's a huge advantage, of course."

- Fun, user friendly

"We really enjoy it so we make a tick and we send it! (laugh)."

- Readability of the progression of the study

"Little advantage: we have access to all enrolled patient's data, I mean we have live access to all our patients' CRFs on the computer. So from this point of view it's an advantage because we are quickly able to find a data and correct it ourselves if required."

- Data of better quality (concentration, rereading during verification step, quick notification of error or missing data)

"I find at least there is a retro control ... It's better than seeing this 6 months later with the [study monitor] ... It's better, ... we can correct almost right away and this is good."

"In fact it's like a double data entry: you have the data entry -- pen/paper -- and the entry -- pen/download. We have a feedback on the second data entry, which possibly allows modifications, a retro control for investigators in fact."

- Evidence of seriousness

"It's an evidence of seriousness. We are confident that data will not be lost and will be analysed quickly."

- Enhancement

"The pen is a link"; "It's a way of meaning that we are involved in a national study; everybody who used this pen belongs to a multicentric thing, and I like this."

- Extra time required by the verification step:

Most respondents found the verification step a bit bothersome but acceptable, especially

in this trial, in which the number of data to collect was reasonable.

“Well, it’s a bit tedious.”

“If you did it well, if you are concentrated on writing, then it doesn’t take much time.”

Some even thought the data verification was security

“It doesn’t bother me. I prefer it. It’s like a security.”

Others were quite upset by the extra time required for verification.

“If you do not pay attention you’ll have all data to verify, because even when you pay attention you have some.”

“... this is a way to take the [study] monitor’s place, and, as I have already told you, I’m upset doing the monitor’s job, secretary’s job, many jobs I didn’t sign for!”

- Organisation, need to manage pen availability

“It’s a matter of organisation; at the beginning we didn’t know where to put [the pen], how to put it... I don’t know if we have found the best solution.”

Tables

Table 1: Description of participants and trial sites in analyzing use of the digital pen system to record data: investigators from active (had enrolled patients) and non-active (had not enrolled patients) sites in the STRATAGEM trial

	Active site (n=18)	Non-active site (n=9)
Age (years)		
25-39	4 (22)	4 (44)
40-54	10 (56)	5 (56)
55 +	4 (22)	0
Gender, male	11 (61)	8 (89)
Medical position		
Consultant full time	17 (94)	5 (56)
Specialist registrar full time	1 (6)	4 (44)
Clinical trial experience*		
High	4 (22)	-
Intermediate	9 (50)	-
Low	5 (28)	-
Informatics experience*		
High	3 (17)	-
Intermediate	8 (44)	-
Low	7 (39)	-
Patients enrolled at the site		
0	0	9 (100)

1-4	10 (56)	0
5-9	4 (22)	0
10 +	4 (22)	0
Time since site opening (months)	10 [8-12]	10 [7-11]

Results are presented as N (%) or median [range]

* data from qualitative interviews. Only available for investigators from active sites.

Table 2: Number of data requiring verification from the investigator

(N=134 case report forms, only baseline visit data)

	Number of data	Verifications required
All variable types	12 462	1994 (16)
Tick box	9246	407 (4)
Number	1742	469 (27)
Date*	1206	994 (82)
Letter	268	124 (46)

Results are presented as N (%)

*sensitivity of the automatically generated signal is higher for dates than for other variable types

Table 3: Mismatches in data acquisition by digital-pen and double manual data-entry systems
(N=54 case report forms)

	Variable type				
	Overall	Tick box	Number	Date	Letter
Total number of data	5022	3726	702	486	108
All mismatches	19 (0.38)	5 (0.13)	4 (0.57)	9 (1.85)	1 (0.93)
Unreadable	5 (0.10)**	1 (0.03)	0	3 (0.62)	1 (0.93)
Digital pen system failure	8 (0.16)	2 (0.05)	3 (0.43)	3 (0.62)	0
ICR failure	5	0	3	2	0
Transmission failure	2	2*	0	0	0
Online correction	1	0	0	1	0
Double manual data entry failure	6 (0.12)	2 (0.05)	1 (0.14)	3 (0.62)	0

Results are presented as N (%)

ICR: intelligent character recognition system

* not mandatory fields

** for 4 out of 5 unreadable data, an automatic signal asked the investigator for a verification.

Table 4: Advantages of use of pen-and-paper case report form (P&P-CRF), electronic CRF (e-CRF), and digital pen system (indicated in bold) in clinical trials as mentioned by interviewees.

P&P-CRF	e-CRF
<ul style="list-style-type: none"> • Usual practice • Good integration with clinical activity • No need for special equipment • Availability of an Internet connection not required during data collection • Regulatory requirements (a set of CRF kept on the site, no need for electronic signature) 	<ul style="list-style-type: none"> • Predetermined ranges, online reminders and help • Early detection of out-of-compliance site • Early detection/correction of errors or missing data • Detection of adverse events not declared • Ongoing CRF adjustment • Closer identification of data needing monitoring • No need for secondary data entry • Quick availability of data • Sequential analysis facilitated

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