Author’s response to reviews

Title: Comparison of two data collection processes in clinical studies: Electronic and paper case report forms

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Author's response to reviews: see over
The authors are indebted to the reviewers for their thorough review of our manuscript and for their useful suggestions. We have addressed to the best of our possibilities their comments and provide a detailed answer to each point. We have revised the abstract and the manuscript accordingly.

Sincerely,

The authors
Reviewer 1: Zhao Ling

Reviewer's report:

Major compulsory revisions:

1. The purpose of this paper is to “compare objective and subjective efficiency of pCRF and eCRF use in clinical studies”, but in fact, the research studies collected in the paper were sponsored by the Paris regional hospital consortium AP-HP. So, the results are representativeness?

The research was multicenter and involved hospitals throughout the country. The fact it was sponsored by the APHP only means that the principal investigator is a physician working in one of the 37 APHP Paris hospitals. The studies included were financed by the French ministry of Health following a national call for proposal. They were publicly financed and the use of the allocated budget was in accordance with the rules of public accounting. The results are therefore representative of research projects that are funded by public or not-for-profit institutions.

In addition, studies sponsored by the APHP represented 40% of France’s publicly funded studies and resulted in over 8,300 scientific publications in 2012 (http://portail-web.aphp.fr/drcd/IMG/pdf/Rapport-DRCD-2012.pdf).

2. This is a retrospective study and how to implement the quality control during the process of survey? Moreover, how to judge the quality of responded questionnaires?

I am afraid that I do not understand this remark. The aim of the survey was to elicit preferences from users of CRFs. Despite the fact that the quantitative study was retrospective, the qualitative part (survey) concerned the ongoing practice of investigators, data managers and clinical research associates who are all still working in clinical research and using p and eCRFs. It is therefore not a retrospective survey.
Minor Essential Revision:
All the tables in the paper should modify to three-line tables.

*We have used the BMC recommendations to format tables: “Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. “*

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

*We disagree with that statement. All clinicians involved in clinical research as primary investigators devote major efforts to motivate the other investigators and the research teams. Filling out CRFs requires time and attention; the logistics must therefore be flawless in order to keep recruitment and the study running. The choice of a CRF is an important issue and should be the result of an informed decision.*

**Quality of written English:** Acceptable

*The article was reviewed by a native American speaker*

**Statistical review:** Yes, and I have assessed the statistics in my report.

*We did not find the corresponding report*

**Declaration of competing interests:**

I declare that I have no competing interests.
Reviewer 2: Kamala Thriemer

Reviewer’s report:

Major comments:

The main concern is that the comparison of the two methods include different studies and is therefore potentially biased. The authors describe this in the limitation section, however I would suggest to reduce the comparisons made through the paper as much as possible and stick to descriptive findings of both methods in the different studies included. E.g. the objective (last paragraph introduction) could be changed from “to compare” to “to describe”. And in the primary endpoints “to describe satisfaction among stakeholders”, “to calculate average cost for both methods” etc. Or e.g. in the results “the mean cost was higher than…” change “to the mean cost in group 1 was xy Euro and in group 2 xy euro.” In light of this I would also suggest to review the conclusion. I think the limitations of this data does not allow to state that “stakeholders support eCRF of paper”.

We agree with this important remark. When the study began, our assumption, and that of clinical researchers was that the choice of pCRF vs. eCRF was a matter of taste and habit and not a conscientious decision based on study characteristics. We found that studies with pCRFs indeed differ from studies with eCRFs and that they are not full substitutes.

We have changed the text to reflect that point, we limited the use of ‘to compare’ and used the verb ‘to contrast’ instead.

The ‘Results’ section of the Abstract was changed to: ‘The total cost per patient was 374€ ±351 with eCRFs vs. 1,135€ ±1,234 with pCRFs. Time between the opening of the first centre and the database lock was 31.7 months Q1=24.6; Q3=42.8 using eCRFs, vs. 39.8 months Q1=31.7; Q3=52.2 with pCRFs (p = 0.11).’

And its Conclusion was changed to ‘This study found that eCRFs and pCRFs are used in studies with different patient numbers, center numbers and risk. The eCRFs are more advantageous in large, low–risk studies and gain support from a majority of stakeholders.’
Minor comments:

Introduction:

At the end of the introduction it is stated that the objective was to evaluate the “efficiency” of the two CRF. However the definition of efficiency in this framework is not entirely clear. The primary endpoint is described with “satisfaction”. It would be good to streamline objectives and endpoints for consistency.

The end of the introduction was changed to: ‘Our objective was to formally describe the efficiency (measured by satisfaction, cost and duration of the study) of electronic and paper CRFs in the context of biomedical research conducted in hospitals.’

Methods:

For clarity I suggest to divide the paragraph “clinical studies” in two paragraphs: one “clinical studies” and one “cost estimation”.

The paragraph “cost estimation” was added

It would also be good to add one paragraph on how the open ended questions were analyzed?

The following sentence was added: ‘Answers to the two open-ended questions were classified by topic using word clustering for the question about key features of an optimal data collection form, and by topic clustering for the open remarks.’

Results:

The authors included 27 studies. It would be good to show how representative those are for all studies ongoing in the sector.

We included all studies that were completed at the time our study began. The only selection was that of the 6 research units and it was based on goodwill from these units’ heads. In order to check the representativeness of the sample, we looked at the topics covered compared with ongoing research projects (see figure below). Studies that are financed by public or not-for-profit organization and led by investigators belonging to public institutions are more often non-drug trials
(unlike trials sponsored by the Industry). The share of topics can be found at (http://portail-web.aphp.fr/drcd/IMG/pdf/Rapport-DRCD-2012.pdf)

The 27 studies that we selected were:

- Drugs: 15 (56%)
- No medical technology (observational or public health intervention): 6 (22%)
- Physiopathology: 2 (7%)
- Devices: 2 (7%)
- Cellular therapy: 1 (4%)
- Surgical Therapy: 1 (4%)

We added the following sentence in the Material section: ‘The research topics were representative of the ongoing publicly funded clinical research.’
The proportion of returned questionnaires is very low how can you exclude any bias due to this?

_We have no reason to believe that responders were self selected by their preference for one of the other CRF. Results are quite balanced between e- and pCRFs. We think that willingness to respond was more related to an individual’s interest for research than to their attraction to one or another type of CRF._

The cost estimate based on one software used in those trials. It might be good to add cost estimates when using other software.

_The laws of public accounting request that software is chosen following a call for tender. The price reported is the lowest for a given set of technical requirements. We modified the sentence in the Methods section as follow: ‘Since 2003, following a successful tender by TELEMEDICINE Technologies S.A.S., the AP-HP’s Department of Clinical Research and Development (Direction de la Recherche Clinique et du Développement; DRCD) has contracted with TELEMEDICINE for use of the software CleanWEB in eCRFs for clinical trials.’_

_LEVEL OF INTEREST: An article whose findings are important to those with closely related research interests_

_QUALITY OF WRITTEN ENGLISH: Acceptable_

_STATISTICAL REVIEW: Yes, but I do not feel adequately qualified to assess the statistics._

_DECLARATION OF COMPETING INTERESTS:_

'I declare that I have no competing interests'
Reviewer 3: Adam B Wilcox

Reviewer’s report:
This represents original work that is relevant to this field, and addresses an important issue. The authors worked well within the limitations of the study design, which was appropriate given the maturity of research in this field. As always, an RCT would have eliminated some bias issues that were present in the retrospective study and survey, but such an approach would have been inefficient and inappropriate.

We thank the reviewer for this comment and fully agree.

Major Compulsory Revisions
The main issue, which should be addressed in the discussion and not by changing the methods or the study, is that some clear potential biases were not noted or explained. Specifically, there were three issues that were not noted.

1. In the selection of the studies, only studies that completed use of eCRFs were used. What about studies that started with eCRFs (the newer approach at the time), and then after difficulties reverted back to pCRFs (the established approach)?

This is an important issue indeed, but this case did not occur. Two studies however used pCRFs prior to entering data in the eCRF. In our results, these studies were classified with eCRF. The reason was that investigators preferred to enter data in their usual pCRF but that the eCRF was available and the local research assistant used it to enter the data directly.

We added the following sentence in the Materials section: 'Moreover in our sample, two studies used pCRFs to collect data before entering it in the eCRF. These two studies were analysed in the eCRF group.'
2. The eCRFs were used for larger, multi-center trials, while the pCRFs were used for smaller trials. The difference in length of time until completion, as it was reported, was significant but could have been due to different types of trials being conducted. Investigative studies of rare conditions may take much longer to accrue patients, regardless of the CRF approach. This seems a more-likely explanation for the time difference, especially since the time from last visit of last patient to database freeze was not different.

We agree that the differences in recruitment difficulty might account for part of the differences in time for study completion. Following your comment we separated the studies by type of disease studied.

Studies using eCRF included patients with:

- ICU patients with mechanical ventilation (300 patients), ICU patient with sepsis (621 patients), ICU patients with resistant enterobacteria (917 patients),
- HCV infected patients (1,993 patients), patients with cirrhosis (355 patients)
- Emergency room patients with suspected infection (1,464 patients)
- Acute paediatric pyelonephritis in the ER (170 patients)
- Type 1 myotonia dystrophia (75 patients)
- Malaria-infected patients (573 patients)
- Children immunization for TB (47 patients)
- End-stage renal failure (48 patients)

Studies with p CRF:

- kidney transplant (280 patients)
- attention-deficit disorder (21 patients)
- multiple sclerosis (110 patients)
- urinary incontinence (phase 2 trial, 10 patients)
- thrombocytopenic purpura (65 patients)
- elderly patients failing to thrive (68 patients), elderly patients with multiple medications (665 patients)
- hypertensive patients (209 patients)
- ICU and SICU patients (50 patients)
- Children with steroid treatment (24 patients)
- Children undergoing eye surgery (80 patients)
- Duchene myopathy (30 patients)
- Nephritic syndrome (55 patients)
- education for helper in Alzheimer (172 patients)
- use of MTA® for premature tooth closure (34 patients)
- IV Ig for ANCA positive vasculitis, (Wegener, Churg & Strauss syndrome) (24 patients)

From this list, it appears that the only rare condition in eCRF studies was myotonia dystrophia, while pCRF studies investigated paediatric conditions (which are more demanding due to informed consent procedure) and rare conditions such as thrombocytopenic purpura, vasculitis and Duchene myopathy. It must be noted however that in the case of rare conditions the investigators belonged to the national reference centers for that condition. Average duration of recruitment was 26.5 (±13) months for pCRF studies and 22.4 (±9) months for eCRF studies (p value =0.34).

We added the following sentences:

- to the Methods section: ‘We estimated the duration of patients’ recruitment’
- To the Results section: ‘We found no difference in the average duration of recruitment (22.4 ±9 months with eCRFs vs. 26.5 ±13 months with pCRFs; p = 0.34).’
- And to the Discussion section: ‘Average duration of recruitment did not differ between pCRF and eCRF studies, despite a greater number of trials investigating rare and pediatric conditions in the pCRF group.’

3. Table 1 shows an interesting characteristic difference in the studies that was not addressed: Median number of variables in the CRF. This seems a very larger difference (1062 v. 396), but it wasn’t explained. This supports the hypothesis that the studies are more different than the other factors that may lead to a choice between eCRF and pCRF.

We fully agree that our initial hypothesis that p- and eCRFs could be substitutes was not verified and that studies differed by identified and (very likely)
unidentified factors. We found no explanation in relation to the characteristics of the studies and we can only assume that investigators using eCRF self limited. We added the following sentence in the Discussion: ‘In addition, unobserved factors must also influence the choice between eCRF and pCRF as can be assumed by, for example, the fact that the large difference in the number of variables between the 2 collection methods was not correlated to any of the characteristics of the studies that we investigated.’

Minor Essential

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer 4: Meredith Nahm

Reviewer's report:
This is a well written presentation of a survey of clinical investigators, CRAs and Data Managers. I liked that you included copies of the actual questionnaires used for your study.

We are indebted to the reviewer for this comment

Major Compulsory Revisions

1) Background section, paragraph 2, the assertion, “Despite their demonstrated usefulness, eCRFs have not become dominant.” Needs a reference.

The reference was added:


“Now in nearly half of all trials clinical data are captured electronically”

2) Results section: comparison because the size (in number of patients) of the eCRF studies was much larger than the pCRF studies, a comparison based on cost per patient is not valid. In large studies, the threshold / start-up cost is spread over a much larger number of patients. I suggest separating these into start-up costs, e.g., database specification, programming and testing, site training, versus ongoing data collection (entry and cleaning) costs for a more fair comparison. You describe this effect in the discussion section, but it should also be presented in the results section.

Start up costs included: eCRF and additional programming, training either by a subcontractor or by research associates, p CRF printing and local training. Start up amounted to 19% of total costs with the pCRF and 35% with the eCRF.

We added the following sentence in the results section: ‘ when total costs were broken down into start-up costs and ongoing cost of running the study, the former
represented 19% of total costs for pCRFs and 35% for eCRFs, or 10,885€ and 30,975€ on average for one study respectively.’

3) Results section: top of pdf document page 9, the statements, “more effective monitoring and ability to monitor data collection from their offices, better error prevention, …” need more characterization. For example, one usually defines monitoring in the context of clinical trials as including comparison of source documents to the data collection forms – this task can not be done from a CRA (monitor’s) office. Further, I do not readily see a mechanism by which eCRFs would lead to “more effective monitoring”.

We fully agree that monitoring data entry with comparison with patients’ charts cannot be done from outside the investigator’s center. What we meant by ‘more effective monitoring’ was that clinical research associates can prepare their monitoring work by viewing queries and abnormal entries before visiting the sites. They resolve discrepancies without going on site by asking the investigator to check directly on the patients’ charts. Thus their time spent on site is used more effectively on actual quality checks comparing source documents with patients’ charts.

Research associates do not have to spend time looking for missing data during their visits because this has been done either by mandatory data entry and feedback to the investigator or by automatic checks with pre -specified values ranges.

Similarly, the phrase, “better error prevention” needs more characterization – I assume you mean that on-screen real-time error checks facilitate data correction at the site while the data enterer has the source document at hand or is still in the patient encounter.

This is indeed what we meant and the sentence was changed to: ‘They based their preference for eCRFs on the more effective monitoring which allowed them to monitor data collection from their offices — for example by receiving queries of abnormal entries in real time—, the better prevention of errors resulting from this and from automatic checks, the easier electronic storage (as opposed to the
copious paper storage of pCRFs) and a greater efficiency in managing drug supplies.'

4) Results section: top of pdf document page 9, the statements, “generated fewer queries and less error” need further characterization / more explicitness. For example, were fewer queries generated because fewer data checks were programmed on average than the paper CRFs? Less error, likewise needs more explicitness, do you mean that the data were more accurate or that fewer queries were generated? I suggest either clarifying that the “fewer queries and less error” were data manager perceptions, or provide actual metrics.

We agree that the sentence is confusing and that is an important point. We were not able to retrieve the total number of queries for all studies and therefore did not attempt a comparison. It is indeed only the Data Managers’ perceptions. Given the fact that pCRFs tend to be used in higher risk studies and collect more variables than eCRFs, we cannot exclude that the fewer queries simply result from a smaller number of variables monitored.

Sentence replaced in Results by: ‘DMs preferred eCRFs (Figure 3) because fewer queries were generated and the database contained fewer errors before cleaning. Thus they saved time allowing faster data availability.’

And in Discussion by: ‘Data managers reported that eCRFs saved time and improved data quality, however we cannot exclude that the perception of fewer queries simply results from a smaller number of variables monitored;’

Minor Essential Revisions
Is it possible to also provide the data collection form for the structured data about each trial?

We have added it to the additional files: Additional file 6.xls. Data collection form regarding studies’ characteristics, variables and costs.
Discussion section: top of pdf page 10. The statement, “Whereas pCRFs were used in small drug trials.” Is interesting.

**Trials using pCRF included on average 60 patients (vs. 355 patients for eCRFs) and 5 centers (vs. 10 centers for eCRFs).** As we mentioned in the article, drug trials were equally prevalent in p- and eCRF studies but out of 8 high risk drug trials, 7 used pCRF.

*We changed the Discussion sentence to: ‘whereas pCRFs were used in high risk small drug trials, possibly because of the greater reliability of written documents.’*

Can you clarify whether the pCRF are recent, i.e., that there is no time component.

**The pCRF studies were initiated from 2001 to 2008 and the eCRF studies did not begin before 2004 (see figure below). For your information, the first eCRF implemented by APHP was in 2004 and pCRFs are still in use nowadays. We did not add this chart to the article due to space limitation.**

![Year of studies'beginning](chart.png)

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
'I declare that I have no competing interests