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Data management of clinical trials during an outbreak of Ebola virus disease

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Abstract

Introduction: Clinical trial data management (DM) conducted during outbreaks like that of Ebola virus disease (EVD) in West Africa, 2014–2016, has to adapt to specific, unique circumstances. CTU Bern was asked to set up a safe data capture/management system that could be launched within a few weeks and cover two different vaccine trials. This article describes some of the challenges we faced and our solutions during the two different trials.

Methods: Setting up a DM system was split into four phases/tasks: 1) quick set-up of the (electronic) data capture system (EDC) and mobile infrastructure in Bern, 2) moving the EDC and infrastructure to Conakry, Guinea and implementation of a local data management center (DMC), 3) running the DMC, and 4) data cleaning. The DMC had to meet the following criteria: 1) quick implementation, 2) efficient maintenance and handling of data, and 3) procedures to guarantee data quality. The EDC (REDCap) was setup as a local area network. In order to ensure high data quality, double data entry, and then review of inconsistencies and offline plausibility checks were implemented.

Results: From the start of CTU Bern's involvement to the productive EDC took 11 weeks. It was necessary to adapt processes for dealing with data continuously throughout the trial conduct phase. The data management team processed 171,794 case report form pages from a total of 14,203 participants in the period between March and December 2015.

Conclusion: Data management is a key task supporting trial conduct. For trials in emergency situations, many of our approaches are suitable, but we also provide a list of aspects that might be done differently.

Key words: Clinical trial, data management, data management centre, electronic data capturing system, REDCap,

1. Introduction

West Africa experienced the largest outbreak of Ebola Virus Disease (EVD) in history between March 2014 and June 2016. After 12 months, two vaccination trials were started while infection rates had started to fall (WHO situation report date 25.03.2015 [1]). In order to stand a chance of seeing outcome cases, the clinical trials had to be started as quickly as possible (Figure 1). The data management strategy was one of the key issues that would make the trial succeed or fail. Working in Guinea during the EVD outbreak posed a unique set of challenges, some of which this paper describes along with our solutions during the trials.

1.1. The EVD vaccination trials in Guinea

Ring trial. The randomized controlled ring vaccination trial tested the efficacy of rVSV-ZEBOV vaccine in preventing EVD in contacts and contacts of contacts of recently confirmed EVD cases (index cases) in Guinea [2]. The trial used a cluster-randomization design in which clusters were built around each EVD index case. This required two different levels of data capture: at the cluster level (EVD index case), and the participant level (contacts and contacts of contacts of the index case). The basic case report form dossier per participant consisted of 575 variables. Certain events triggered additional data collection; if a participant became an EVD case, 648 additional data points were required to be recorded, 190 for each serious adverse event (SAE), and 10 in case of a pregnancy. To record epidemiological characteristics of the different clusters, each contact and contact of contacts had to be recorded independent of being eligible and willing to participate, or not. The case report form

contained not only variables for analysis, but also data collected to support (administrative) trial processes.

Frontline worker trial. The frontline worker (FLW) trial was a single-arm trial of whether the vaccine provided frontline workers charged with treating potential and confirmed EVD cases protection against EVD. In addition, and in contrast to the ring vaccination trial, the trial involved collection of blood samples for immunological analyses. The same set of variables used in the ring vaccination trial was used for the clinical part of this trial.

2. Methods

2.1. Requirements for the electronic data capture system (EDC)

Previous experiences suggest that direct electronic data collection in the field is feasible in comparable settings [3]. It was clear for us, however, that data collection in the field had to be paper based. Although we discussed collecting data in the field electronically with later synchronization to the trial database, this idea was discarded mainly for reasons of flexibility, reliability, and security. Also, using an electronic data capture system hosted at CTU Bern with data entry in Guinea via the Internet turned out to be impossible given the available Internet connection. The initial idea, then, was that field workers collect all data on paper case report forms. The case report forms would then be scanned at a central facility and send to CTU Bern for data entry into the trial database. Eventually, it was decided that CTU Bern sets up a data management system in Conakry and all data entry tasks be done in Guinea by local staff which resulted in several challenges:

- Initially, no IT infrastructure was available at the facility.
- Power cuts are frequent in Conakry.
- As time was short, the whole system had to be planned, installed, and tested at CTU Bern before the final setup in Conakry.
- The electronic data capture system had to run with minimal external and internal IT support.
- There would be no compromises regarding data security and protection.
- Good Clinical Practice standards of CTU Bern and WHO would be complied with.

2.2. Network Infrastructure

A generator was installed to overcome the frequent power cuts at the data management site. Because its reliability was unknown we set up the electronic data capture system relying on a battery-based uninterruptable power supply (UPS). A local area network with a MacBook Pro as a server and 20 windows notebooks was built (Figure 2). The choice of a powerful notebook as server had several advantages compared to a fully featured hardware server. Maintenance is simple and manageable for non-IT specialists. It could be set up and tested in Bern and brought to Guinea as personal baggage without unpredictably long travel. It ran almost noiselessly and did not require a separate server room. Most importantly, the notebook server was not affected by power cuts and did not require a large UPS. The local network was not connected to the internet. Data security was carefully taken into account by using fixed Internet Protocol addressees and the https protocol within the network. We also set up all notebooks in such a way that only the electronic data capture system was accessible by using appropriate group policies and changes in the basic input/output system (BIOS) such as deactivation of WiFi and USB ports. The server was protected by a firewall and the data drives and backup drives were encrypted using FileVault. Data preservation was guaranteed by hourly backups on an external drive. Every evening a daily backup was stored outside the data management centre using 14 different drives for two week backup cycles. A spare MacBook Pro mirroring the main server notebook was installed and ready to be used in case of failure of the dedicated server. The restore functionality using a backup drive and the spare hardware using Carbon Copy Cloner software was tested prior to the setup in Guinea. The restore

process was easy, reliable, and could be done by the local data manager within an hour.

2.3. Choice of electronic data capture software

There are numerous electronic data capture systems available [4]. For the purposes of this project, the system had to be:

- Easy to use
- Supportable by CTU Bern
- Affordable
- Capable of running offline
- Compliant with Good Clinical Practice using the ECRIN standards as a benchmark [5]

We used Research Electronic Data Capture (REDCap, see https://projectredcap.org), a secure web application for capturing data [6].

2.4. Set-up and support of the electronic data capture system

Setting up and maintaining an appropriate security infrastructure for the LAN was not feasible and we therefore restricted Internet connection. Using REDCap in offline mode was possible by writing scripts, e.g., for user management. REDCap was running on OS X with an Apache web server, MySQL as database and PHP as scripting language.

In REDCap, individual trials are managed in what are called projects. First, the REDCap project for the trials was created at CTU Bern in order to develop case report forms in collaboration with WHO. The same project was then installed on the

MacBook Pro server. A local area network was created in Bern to set up the security features on the server and the router, and to test the hardware infrastructure. Third, a CTU Bern staff member brought the server and router to Guinea to set up the final local area network.

Support for the whole system was provided by CTU Bern using TeamViewer software. Because the data capture system ran offline in Guinea, the local data manager had to connect the server with the Internet manually if support was requested. For regular checks, software update, and data exports, scripts were written to allow quick access to the server during the night at specified times.

2.5. Structure of the trial database

The electronic data capture system had to accommodate two different trials and, for the ring vaccination trial, the hierarchical structure of the data. In the end, the system consisted of three *REDCap projects*: one for the front-line worker trial and two for the ring vaccination trial. One of the two projects for the ring trial contained data of the rings (cluster level) and the other of individuals (participant level). Randomization was implemented in the ring database. The link between the two ring trial databases was achieved by a unique identification number. Otherwise, the structure followed standard set-ups for longitudinal projects in REDCap in which each visit constitutes an *event* in the system.

Data that were required for planning and management purposes were made available for clinical trial personnel via regularly run reports. Eventually, minimal data on nonparticipants were also collected within the participant database.

2.6. Prerequisites for the data management centre in Conakry

One requirement of the Guinean government was that data stay in the country while trials were conducted. This led to setting up a data management centre in Conakry. The centre had to fulfil the following criteria:

- It had to be set up (very) fast.
- To deal with the expected amount of data, it had to be very effective.
- It had to guarantee data quality.

To accommodate this, most strategies, standard operating procedures, and processes were developed remotely. The different elements were put together after arrival in Conakry and adapted during the early conduct phase as required.

2.7. The data management centre in Conakry, Guinea

An initial version of the case report forms and an initial set of standard operating procedures was defined initially in Switzerland. Early on during the trial it became clear that the procedures were not exhaustive and that most of the operating procedures required adaptation.

Only seven days elapsed between the arrival of the CTU data managers in Conakry and the inclusion of the first trial participant (frontline worker trial). Within those seven days, the data management centre infrastructure was installed and tested, the local team was compiled and trained, trial material was organized, and systematic data export and data check systems were put in place. Shipment of materials and infrastructure delayed parts of the set-up process and the will to improvise was indispensable. Some tasks that are usually completed in the set-up and implementation phases of a trial had to be extended into the conduct phase itself.

Processes had to be developed and improved gradually. Initially, paper case report forms were printed at the centre on standard printers with manually inserted carbon paper. At the point of first data entry, the centre began with four data entry clerks who had to be trained on the REDCap system with the data of the first participants. Fifteen days after inclusion of the first participant in the front-line worker trial, the first ring was included and randomized. Eventually, the centre staff consisted of 23 data entry clerks, 3 local data managers, and one statistical data manager from CTU Bern. In addition, the following CTU Bern staff made regular visits to the centre: a project manager, a statistician, and a quality manager. A CTU Bern data manager, one located in Bern (AH) and another in Singapore (AS), was available remotely to support the centre 24 hours, seven days a week.

2.8. Randomisation process

Upon identification of a new Ebola virus disease case, a field team went to the patient's home to map the ring (contacts and contacts of contacts) around this index case. By mobile phone, the team at the data management centre was informed about basic characteristics of the ring as soon as it was defined. This information was immediately entered into the REDCap system where the rings were then randomized to either immediate or delayed vaccination in a 1:1 ratio. The randomization result was passed to the field team by text message and by an additional phone call to avoid misunderstanding. This immediate information exchange with the field team was required to allow the recruitment process to begin right away.

2.9. Data flow

Considering the large number of individual case report form pages (N=171,794), registration and tracking of individual case report forms was critical to avoid loss of data (Figure 3). Initial registration of incoming paper forms was transferred to a set of MS Excel tables. Movement of dossiers in order to locate them was documented in a registration book. Paper case report forms also went through an initial quality check by the principal investigator or a delegate. After double data entry and review of incongruities, the forms were filed in a dossier.

2.10. Data validation

A multilevel data validation approach was implemented to ensure data consistency and validity [7], which included:

1. Registration of all incoming paper case report forms
2. Approval of paper forms by the principal investigator or a delegate
3. Real-time data validation within the REDCap data entry forms (plausibility checks)
4. Quality control using double-data entry and independent resolution of any discrepancies
5. Monitoring by independent monitors for external and independent data validation
6. Statistical data cleaning

Real-time plausibility checks were implemented in the database using functionality available in REDCap: branching logic (variables that appear, or not, based on the values in others), range checks, and regular expressions. Regular expressions were

used for dates and certain string variables where the standard built-in checks would not work. Offline checks were implemented in Stata to compare inconsistencies between forms such as time between follow up visits because REDCap can only handle within-form consistency checks. With more than 12,000 participants, and a ring containing many participants (median = 82.0, IQR = 66.0-114.8), regular reports were required to check consistency of the data, maintain an overview of the studies, and provide assistance in conducting the studies. These checks were run at least daily during data entry.

Because no other source such as patient charts was available, paper case report forms were considered the source of the trial data. An independent monitoring team did a 100% source data verification by comparing mainly data collection forms with the data in the trial database.

Statistical data cleaning was done at CTU Bern using exported data. During cleaning, we identified a bug in the REDCap version we used: When the first variable on a form was a radio button (single-choice question), the field was active when the form was opened and it was possible to enter any text into it via the keyboard. In order to find variables containing implausible entries, a custom R script was written to search all radio button variables and check that all entries were valid for that variable.

2.11. Export and reporting

Exporting data from REDCap is generally very simple. Exporting in Stata format worked very well for the first month or two until the volume of data required a large amount of memory to form the export files. Because of the relatively complex visit structure (10 visits and 14 different forms, see Table 3) exports contained a lot of

empty cells. REDCap stores data in tables containing only a few columns (record ID, event name, variable, value, data (time), and user). Because data are stored in this way, the data points for an individual's visits must be reshaped from this long format into a wide format where each row is a unique participant-event combination (e.g., the identification visit for participant 1). The process of converting from long to wide format requires a relatively large amount of memory when there are a lot of empty variables. Ultimately, we could no longer use the predefined export tools in REDCap and had to resort to another method. REDCap ships with an application program interface (API) which allows interaction between REDCap and other software (e.g., R or Stata). Using a custom R script, it was possible to export the data via the API in batches of 2000 individuals and then append the batches, together, in R. The combined dataset was then exported to CSV for utilization in other programs. It was also possible to restrict the dataset to nonidentifying information depending on the intended purpose (for example, working lists required names and place of residence, while analysis data sets needed to be without identifiers).

2.12. Post study

After the trials in Guinea were completed, data were prepared in Switzerland for transfer to WHO and Doctors Without Borders/Medecins sans Frontieres. Again, Stata (initially version 13, later 14.0) was used to convert the long data (one row per visit per participant) to wide data (one row per patient).

3. Results

The plan of developing the project at the CTU in Bern, using the local REDCap installation for the creation of the eCRFs, setting up the server and the router, and testing the LAN before transferring the hardware to Guinea was successful. It allowed the creation of eCRFs long before details of the infrastructure in Guinea were known and was crucial to the timely setup of the trials (Figure 1). The choice of a portable, battery powered solution with UPS support for the router and switches turned out to be the right choice since the local generator reset the settings each time it started during the installation and test phase in Guinea. The EDC ran smoothly for 15 months with almost no interruption except a few hours of downtime due to memory issues in the MySQL database. No other hardware- or software-based interruption occurred during the trial.

Table 2 provides an overview of the accumulated data in the trial databases. In the ring trial, 119 rings were defined encompassing 12,252 participants entered in the database between 1 April 2015 and 31 October 2016. For the frontline worker trial, 2,115 participants were recruited between 23 March and 27 October 2015. This resulted in a total of 14,620 recorded participants.

First data entry was done on 27 March 2015 and the last change was made in the database on 14 April 2016 (Figure 1). Follow-up visits were scheduled using the trial databases as a management tool. Therefore, data required for scheduling and management purposes was prioritized. Further records were entered as fast as possible. Still, data entry was quick with median completion of data entry between one and two weeks (Table 3). Completion time varied in the first two months of the trial due to adaptations in processes but also exemplify the learning curve of all

306 involved personnel (Figure 4). We also consider these figures as key performance
307 indicators for the organization of the data management centre and a proof for the good
308 local organization. It also exemplifies the engagement of all team members. Certainly,
309 the emergency situation and the fact that all local team members were directly
310 affected by the outbreak helped.
311 By comparing two double data entries and the reviewed record we quantified the rate
312 of incorrect data entry for selected fields. For questions with options (dropdown), at
313 least one double data entry value differed in the comparison in 1.62% of values in the
314 eligibility form. Three variables regarding vaccination (vaccinated yes/no, left/right
315 arm vaccinated, and date and time of vaccination) had errors in 3.71% of values.
316 Conversely, in text fields used for locating participants, differences were found in
317 41.84% and of values. The entire vaccination form, including those variables already
318 mentioned as well as a number of free text variables for vaccine tracing (e.g., batch
319 number) had errors in 10.17% of values. During on-site monitoring, 3,855 queries
320 were created and resolved in the query system of REDCap. This number, however,
321 should not be taken at face value since many queries were treated in direct contact
322 outside the system without any formal documentation. The average time for query
323 response was 4.2 days. Due to data cleaning activities, 10,160 forms were unlocked
324 and relocked during the data cleaning process. This number can be interpreted as the
325 minimum amount of queries generated by data cleaning activities and proof their
326 importance.
327 The code used to export the data produced a log file. As a proxy for data volume, we
328 used the time required to complete the export of the participant database to depict the
329 quantity of data collected over time (Figure 1). Data volume increased rapidly until

January 2016 (while rings were being included) and then declined as the frequency of follow-ups was reduced.

4. Conclusion

The work on the two vaccine trials showed that data management strategies in such a setting have to be dynamic and flexible. We were able to set up three databases including electronic case report forms in very short time as well as a highly motivated local data management team. The team eventually consisted of 26 local staff members and three nonresident staff. Mechanisms were planned remotely, implemented locally, and further developed based on experiences and changes of circumstances. We regard using both a local area network and REDCap as two major choices that made the data management succeed. The data management centre managed the data and also supported the work in the field with planning of follow-up visits. Intensive collaboration between the field and data management teams also was a key contributor to a successful trial. The experiences made are in line with other trials in comparable settings especially regarding the importance of local staff and training [7]. Finally, although we aimed at complying with regulatory standards we are aware that the data management was not fully compliant with established standards. Validation of the system was the major concern and led to some initial discussions within CTU Bern. Time constraints, however, prohibited adequate validation. Nevertheless, an independent auditor successfully audited the data management processes.

As the saying goes, hindsight is a wonderful thing. Thus are there certain aspects that could have been improved (Table 4). Certain decisions were made given the emergency situation. Often, this pressure results in compromises regarding documentation and compliance to predefined processes. Although deviations from structured processes or less documentation spares time short-term in a given

357 situation our experience shows that it does not pay off mid- to long-term for the trial.
358 The more persons and institutions are involved in a task/process the more
359 pronounced this shift becomes. It is, however, not only an issue of efficiency but might
360 also compromise quality. Therefore, the challenge is to find the optimal balance
361 between structure and flexibility.
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Tables

Table 1. Visit schedule of the different trials or trial arms

Visit Schedule								
	VISITs with timeline >							
	Vaccination			Follow-up		Unscheduled visits		
	Baseline data	Vaiccination	Reactions after 30 minutes	Follow-up	End of follow-up	Serious adverse event	Pregnancy	Outcome case
Participants in the immediate vaccination arm	day 0	day 0	day 0	day 3 day 14 day 21 day 42 day 63 day 84	last contact with the particpant	if applicable	if applicable	if applicable
Participants in the delayed vaccination arm	day 0	day 21	day 21	day 24 day 35 day 42 day 63 day 84 day 105	last contact with the particpant	if applicable	if applicable	if applicable
Participant in the frontline worker trial	day 0	day 0	day 0	day 3 day 14 day 28 day 84	last contact with the particpant	if applicable	if applicable	if applicable

Table 2. Amount of subject's data in the ring database

Data	Number
Total subjects entered[1]	36,487
Deleted subjects	1,388
Final subjects	12,088
Total entered forms[1,2]	515,284
Final entered forms[2]	171,703
Forms per person (mean (95% CI))	14.5 (14.3 to 14.6)
Forms per person (min - max)	4 - 32
Values per person (mean (95% CI))	100.4 (99.2 to 101.6)
Values per person (min - max)	29 - 448

[1] includes double data entry. Most forms (and therefore subjects) were entered three times (double data entries plus a review). Reviewed data represented the final data.

[2] per contact with a subject one form was completed

400 Table 3. Times to data entry completion as key performance indicator

Visits	**Median (IQR)**
Vaccination (immediate arm)/inclusion (both arms)	11 (6 - 23)
Vaccination (delayed arm)	10 (7 - 12)
30 min reaction	9 (5 - 12)
3 day FUP	8 (5 - 13)
14 day FUP	6 (4 - 11)
21 day FUP	7 (4 - 13)
42 day FUP	6 (4 - 11)
63 day FUP	6 (3 - 10)
84 day FUP	6 (4 - 10)
End of study	6 (4 - 11)

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403 Table 4. Learnings and potential improvements

System validation	The REDCap system was tested but could not be formally validated. This is a step that should usually not be skipped. Although a full system validation might be impossible in certain emergency situations, more extensive documentation of testing should be achievable.
Process definition	To improve data quality, the processes were adapted during the trial based on accumulating experiences. Regular updates of the process descriptions would have made the DMC team's work easier.
Data exports	By default, REDCap exports all data simultaneous. Rather than using this default behaviour, it would have simplified many aspects of the reporting process to have exported individual forms and events, although this would result in a larger number of individual export files.
Monitoring	The on-site monitoring could have been extended or partly replaced by field visits to improve the quality of data at the point where it was collected.
Version control of script files	Many script files were created and sporadically updated during the study either locally or remotely. Because the technical support was based in Switzerland, but the working copies of scripts were based in Guinea, there were regular mismatches between the versions. By using a version control system such as SubVersion or Git, harmonization could have been simplified.
Data transfers between sites	A good process for the request, transmission, and receipt of data would improve logging and transparency. In practice, the approach of CTU Bern performing data preparation did not work as well as was hoped. It might be more consistent to transfer unmanipulated datasets to involved parties e.g. for statistical analysis. This has the advantage that the sites

	receive data in a fixed format (as defined by REDCap), which is consistent with the data dictionary, and can tailor the data to their own purposes without requiring a middleman to arrange the data. It would increase the amount of work for the other parties, but ultimately is more transparent.

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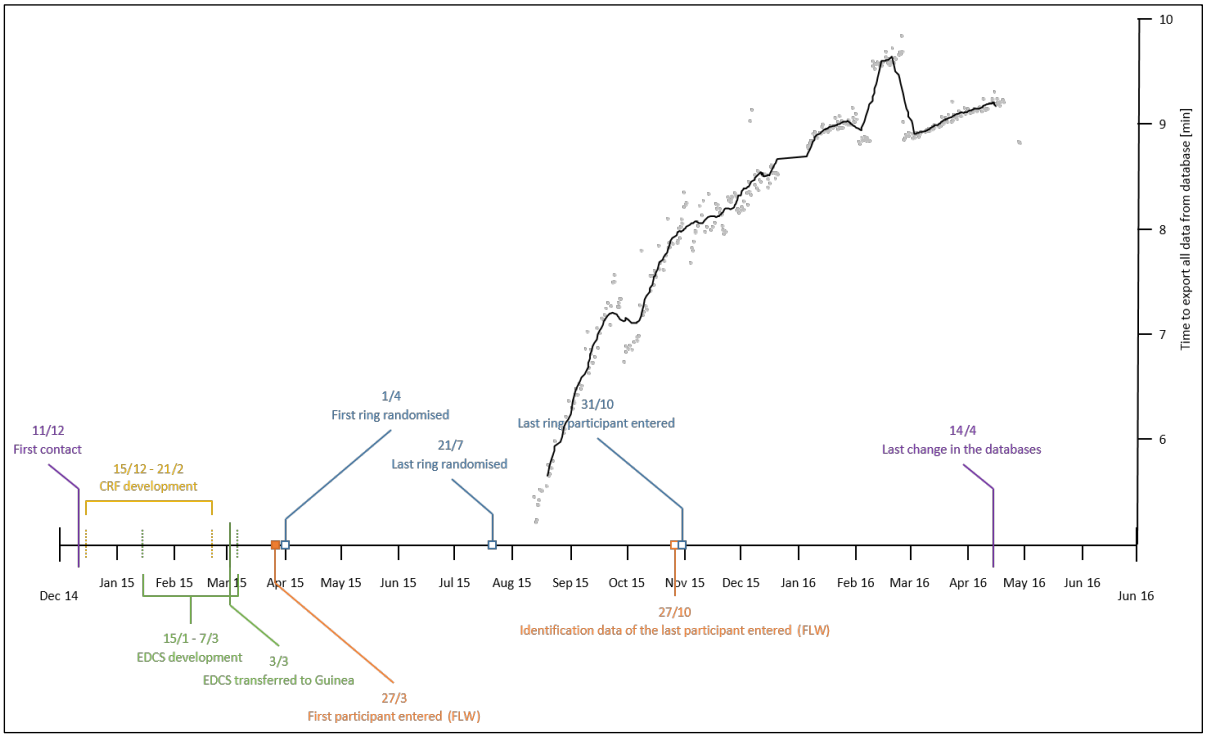
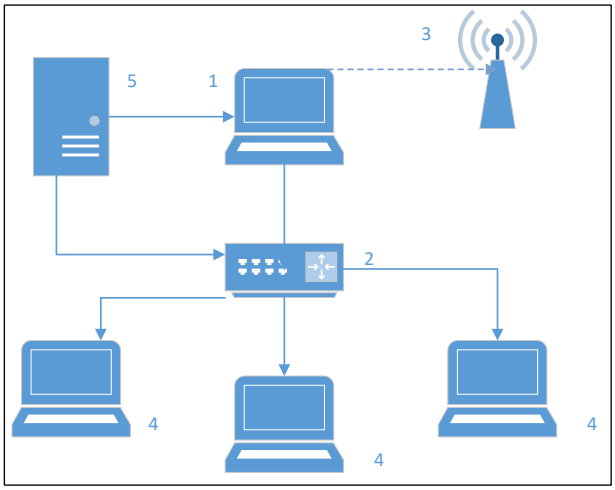
Figures

Figure 1. Time course of the trials with regard to data management.



The black curve shows the accumulating amount of data over time using moving averages of time required for individual exports (grey dot). Note that export time was only recorded for exports via the application programming interface which was implemented in August 2015. The peak in February 2016 was related to connection issues.

418 Figure 2. Local Area Network Structure in the data management centre.



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420 The MacBook[1] served as REDCap server and was connected to a network switch[2]
421 and intermittently to a WiFi router[3]. Client workstations (windows laptops[4]) were also
422 connected to the network switch. The uninterruptable power supply (UPS[5]) was
423 mainly used for the network switch and the router.

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Figure 3. Schematic data flow

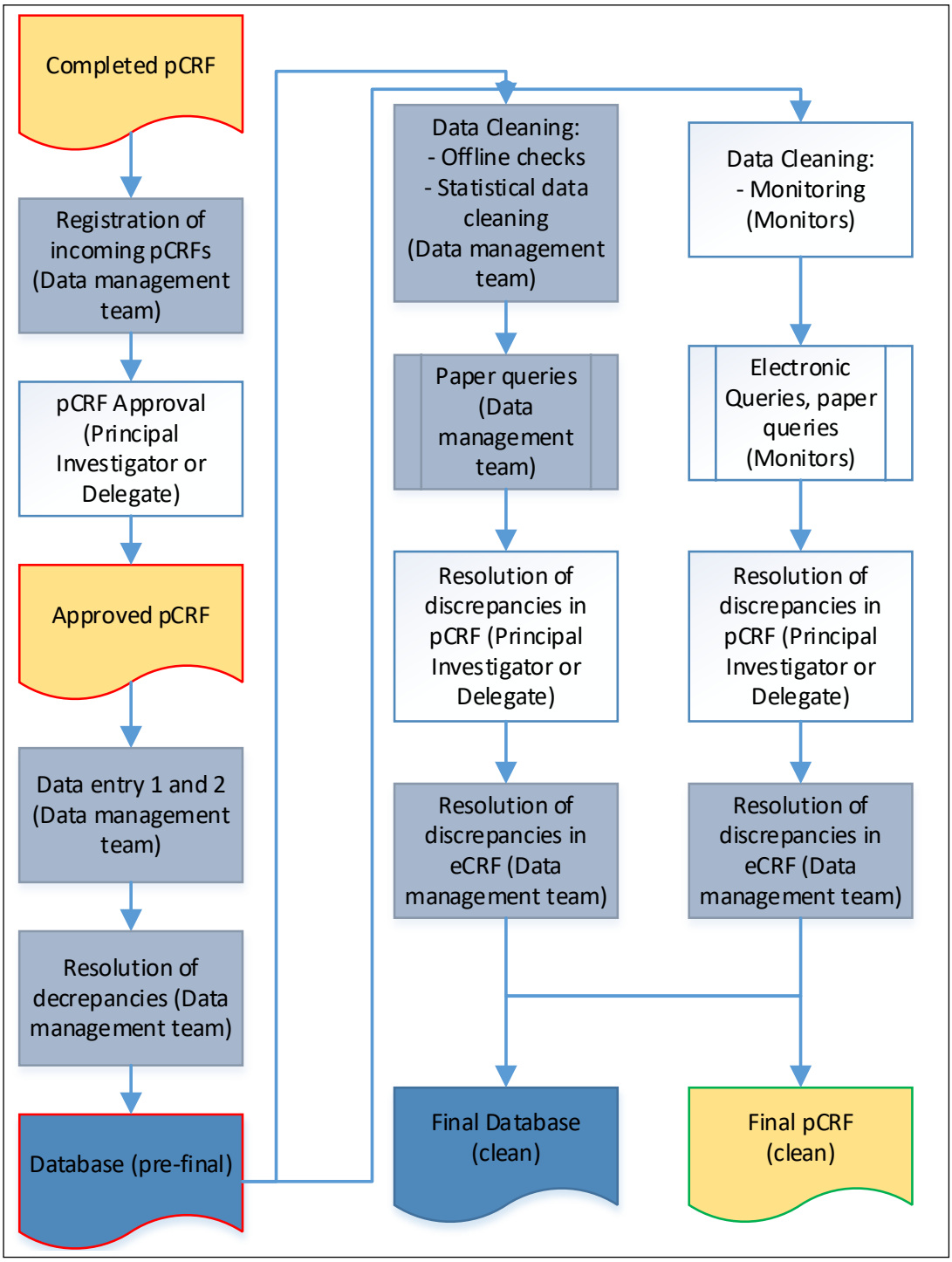
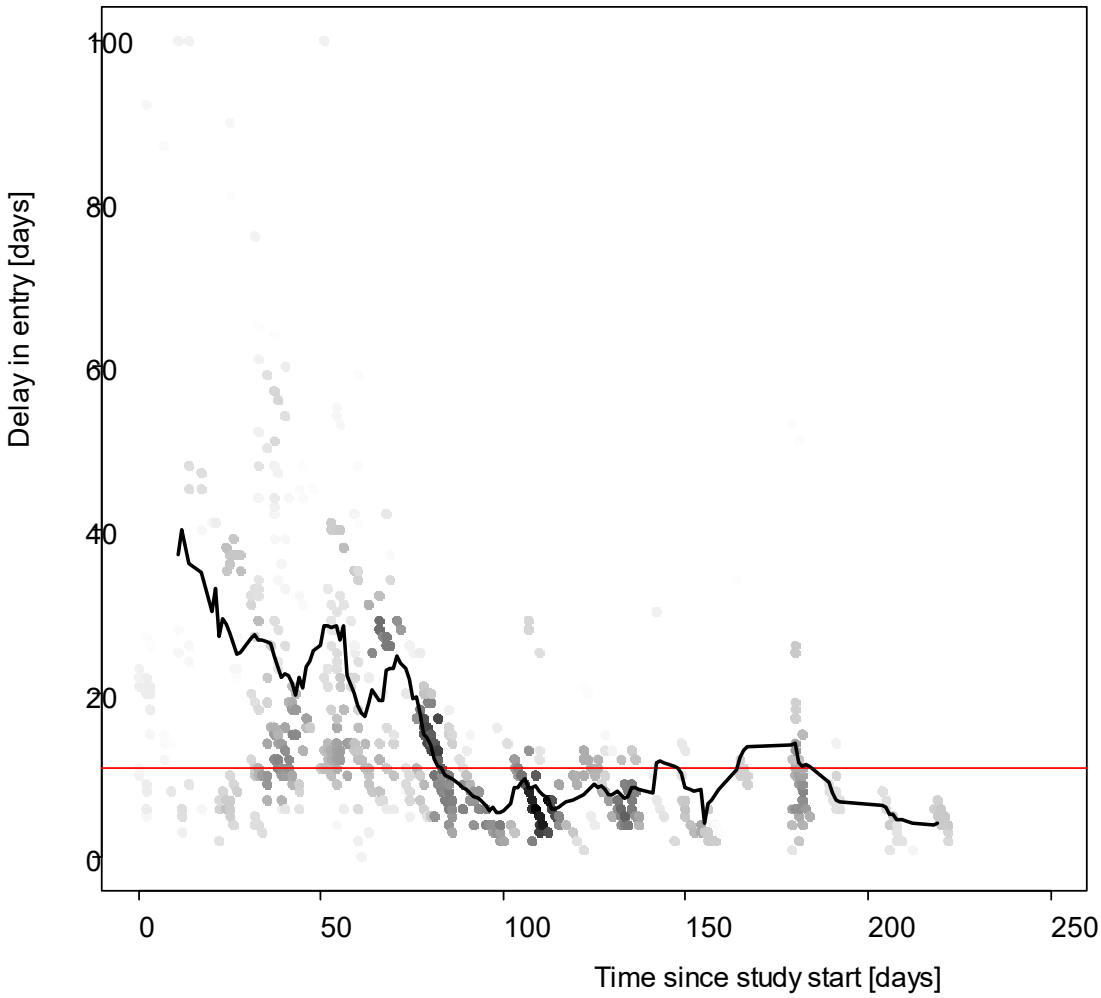


Figure 4. Example of the time to data entry for the inclusion case report form.



The red line indicates the median time for data entry of the inclusion form (11 days). The black line represents the moving average to show the trend. 111 points were capped at 100 days.