

1 Data management of clinical trials during 2 an outbreak of Ebola virus disease

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23 **Abstract**

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

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

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

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

47

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

50

51 **1. Introduction**

52 West Africa experienced the largest outbreak of Ebola Virus Disease (EVD) in history
53 between March 2014 and June 2016. After 12 months, two vaccination trials were
54 started while infection rates had started to fall (WHO situation report date 25.03.2015
55 [1]). In order to stand a chance of seeing outcome cases, the clinical trials had to be
56 started as quickly as possible (Figure 1). The data management strategy was one of
57 the key issues that would make the trial succeed or fail. Working in Guinea during the
58 EVD outbreak posed a unique set of challenges, some of which this paper describes
59 along with our solutions during the trials.

60 **1.1. The EVD vaccination trials in Guinea**

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

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

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

81

82 **2. Methods**

83 **2.1. Requirements for the electronic data capture system (EDC)**

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

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

105 **2.2. Network Infrastructure**

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

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

130 **2.3. Choice of electronic data capture software**

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

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

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

141 **2.4. Set-up and support of the electronic data capture system**

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

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

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

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

159 **2.5. Structure of the trial database**

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

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

172 **2.6. Prerequisites for the data management centre in Conakry**

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

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

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

182 **2.7. The data management centre in Conakry, Guinea**

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

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

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

206 **2.8. Randomisation process**

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

216 **2.9. Data flow**

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

224 **2.10. Data validation**

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

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

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

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

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

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

257 **2.11. Export and reporting**

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

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

277 **2.12. Post study**

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

282 **3. Results**

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

294 Table 2 provides an overview of the accumulated data in the trial databases. In the
295 ring trial, 119 rings were defined encompassing 12,252 participants entered in the
296 database between 1 April 2015 and 31 October 2016. For the frontline worker trial,
297 2,115 participants were recruited between 23 March and 27 October 2015. This
298 resulted in a total of 14,620 recorded participants.

299 First data entry was done on 27 March 2015 and the last change was made in the
300 database on 14 April 2016 (Figure 1). Follow-up visits were scheduled using the trial
301 databases as a management tool. Therefore, data required for scheduling and
302 management purposes was prioritized. Further records were entered as fast as
303 possible. Still, data entry was quick with median completion of data entry between
304 one and two weeks (Table 3). Completion time varied in the first two months of the
305 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

330 January 2016 (while rings were being included) and then declined as the frequency
331 of follow-ups was reduced.
332

333 **4. Conclusion**

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

352 As the saying goes, hindsight is a wonderful thing. Thus are there certain aspects that
353 could have been improved (Table 4). Certain decisions were made given the
354 emergency situation. Often, this pressure results in compromises regarding
355 documentation and compliance to predefined processes. Although deviations from
356 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.
362

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389 **Tables**

390 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 participant	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 participant	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 participant	if applicable	if applicable	if applicable

391

392

393 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

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

396 ² per contact with a subject one form was completed

397

398

399

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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402

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.

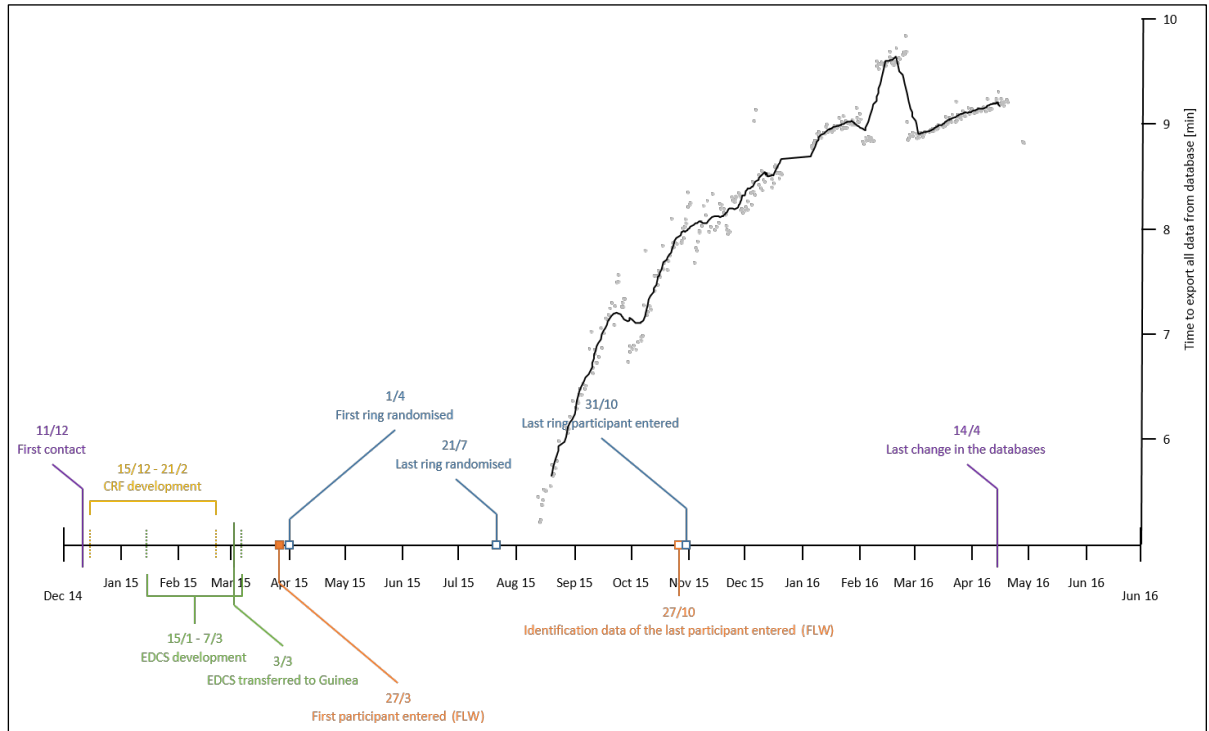
404

405

406

407 **Figures**

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



409

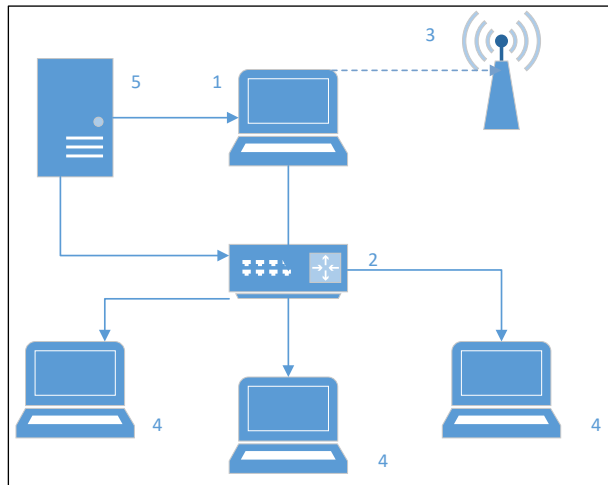
410 The black curve shows the accumulating amount of data over time using moving
411 averages of time required for individual exports (grey dot). Note that export time was
412 only recorded for exports via the application programming interface which was
413 implemented in August 2015. The peak in February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

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416

417

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



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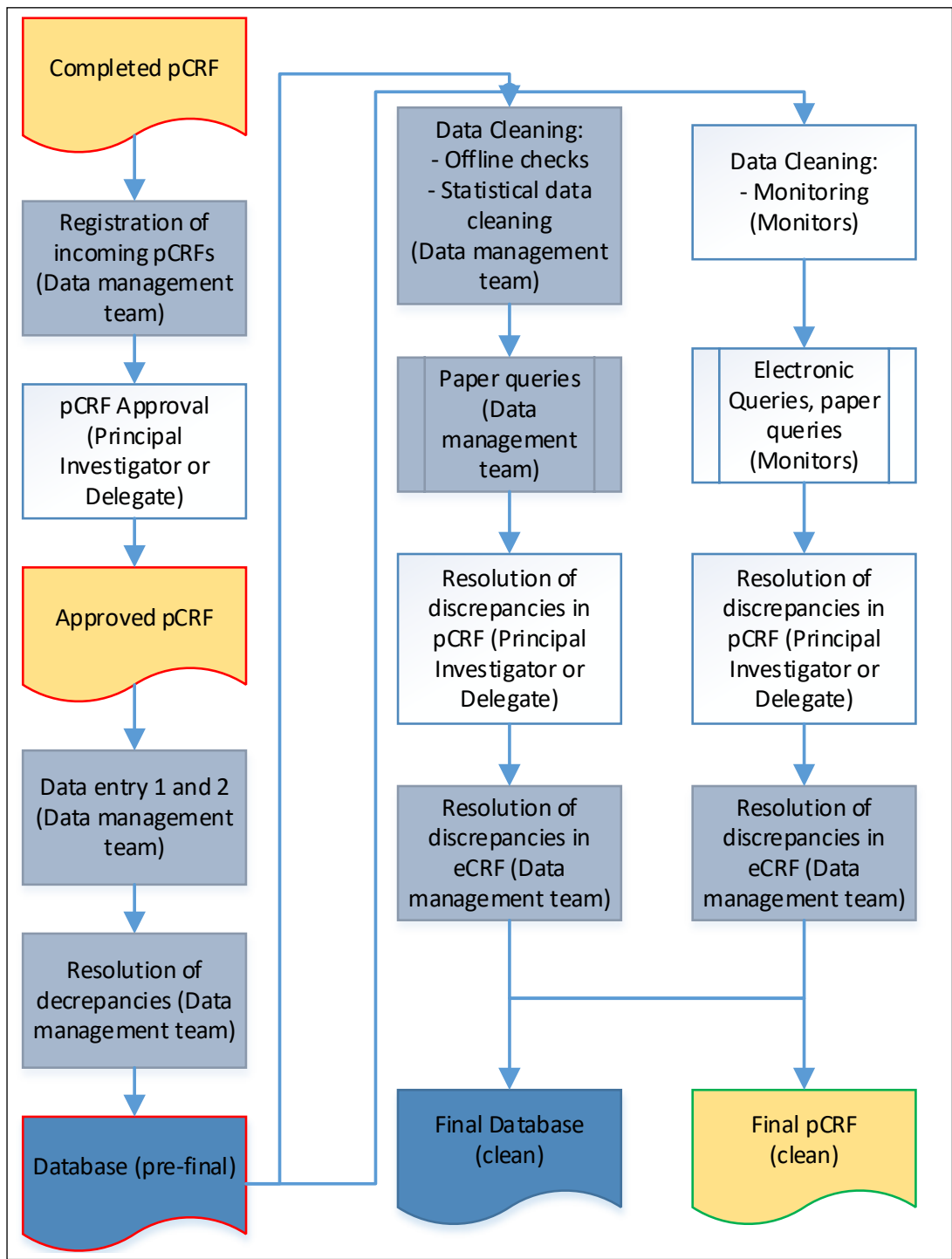
420 The MacBook¹ served as REDCap server and was connected to a network switch²
421 and intermittently to a WiFi router³. Client workstations (windows laptops⁴) were also
422 connected to the network switch. The uninterruptable power supply (UPS⁵) was
423 mainly used for the network switch and the router.

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426

427 Figure 3. Schematic data flow

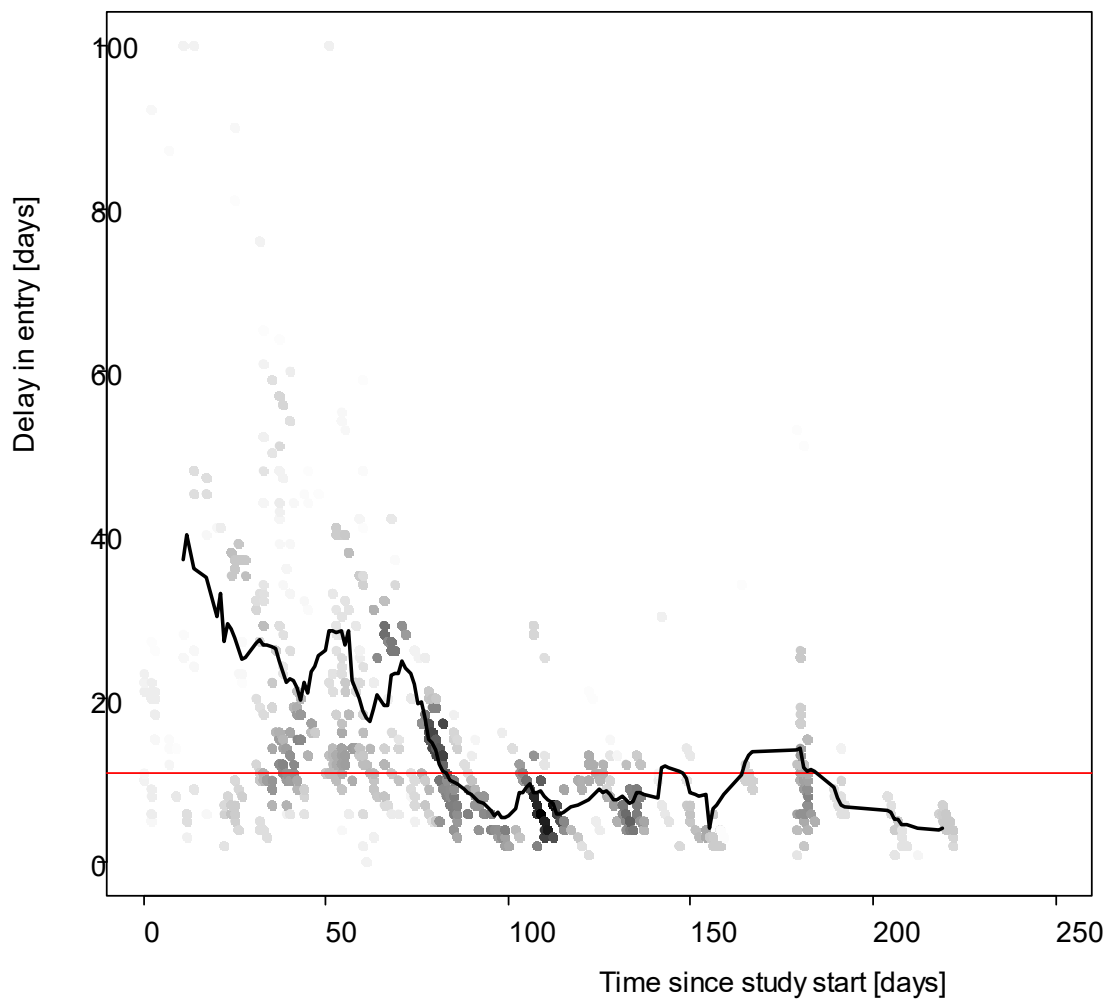


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431 Figure 4. Example of the time to data entry for the inclusion case report form.



432

433 The red line indicates the median time for data entry of the inclusion form (11 days).

434 The black line represents the moving average to show the trend. 111 points were
435 capped at 100 days.

436