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OpenClinica's (low cost) eCRF, an Investigator-Initiated Study's Showcase

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OpenClinica (OC) was identified as a possible means to facilitate data management aspects of small(er) scale investigator-initiated/non-commercial trials. A Dutch investigator who was willing to share user requirements, was identified through the first author's professional network. This investigator was in need of an electronic CRF (eCRF) for a multi-center trial to be led/conducted by his team, at his own and three other sites in the Netherlands. [1]

During three rather brief face-to-face meetings and a couple of follow-up e-mail contacts, specifics of the trial and requirements for the eCRF were collected. It took the two authors a total of 45 hours to build the 12-paged eCRF in OC that comprised of 183 items. Input from the institution's statistician was collected as well, and basic e-mail alerts were programmed to ensure that any safety-related issues will reach the principal investigator, for appropriate reporting to the Ethics Committee and the Competent Authority.

Whereas initially OC ran on an external server, it was eventually hosted on a server hired and managed by the principal investigator's institution.

This effort shows that OC can be installed, set-up, hosted and maintained by a small team, and thus serve as a relatively low cost means to manage data, patient safety, and sites' progress in the field of investigator-initiated trials.

Introduction

A lean, low-budget, but at the same time solid electronic Case Report Form (eCRF) could contribute a lot to non-commercial, usually investigator-initiated clinical research projects. Nowadays, activities like forwarding spreadsheets to other participating investigators to collect the data, and putting together paper "CRFs" that actually and at best could be regarded as source documents, should be deemed unnecessary. eCRFs options have been around for quite some years now and carry the potential to cut away bureaucracy and to avoid data-sharing/data-entry processes often prone to error. The authors identified the open source application OpenClinica (see Box 1) and were offered the opportunity to put this to the test in an investigator-initiated multi-center randomized clinical trial, conducted in the Netherlands.

Box 1: OpenClinica, an Open Source Application

OpenClinica (OC) is the world's leading open source clinical trial software for electronic data capture and clinical data management. OC was and is brought to the community by Akaza Research LLC (https://community.openclinica.com/). The first version was released in 2005. OC comes in two versions, the Community version (unsupported) and the Akaza-supported Enterprise version. The former is free for download and use, the latter comes with set-up, hosting and consulting fees.

Within OC, the following roles can be assigned: "Study Director," "Data Manager," "Site User/Clinical Research Coordinator," '"Monitor," and "Investigator," each having a distinct set of authorizations. The Site User or Clinical Research Coordinator adds subjects, performs the actual data-entry, answers to "notes," and solves "discrepancies." The Monitor reviews the data, issues "notes" and "discrepancies," based on Source Data Verification. Moreover, the Monitor may

program his own ad-hoc data-sets. The Investigator has the same authorizations as the Site User, with the addition of placing electronic signatures on each of the CRFs.

Results and discussion

OC is rather easy to use, from the perspectives of the data entry person and the monitor. Such was the experience gained by the first author in a previous Phase I trial, conducted December 2009 – April 2011, to which he was appointed the monitor. Based on this experience, we asked ourselves if installing our own OC, building and maintaining an eCRF in it, would be feasible, easy-to-use for all sites involved, (more) compliant to current regulatory CA and EC requirements, and cost-effective.

Installing OC was performed following the documentation available on the OpenClinica website. Installing plus testing and securing the system took 24 man-hours, leading to a solid test environment which was next used to make the eCRF pages (see Box 2).

Box 2: Equipment Used and the Workload to Install OC

Initially, Certu BV expressed interest in this pilot and offered to install and run OC on their HP Proliant DL360, with an Xeon E5335 processor, four GB RAM operating on a 100 mbit Internet connection. The basic install took the experienced IT worker approximately eight hours. Testing this installation, installing the security certificate, and setting up the database backup took another eight hours. Finally, eight extra hours were put into more sophisticated security measures. However, it is anticipated that OC can run in a smaller environment: a shared virtual Linux server, on which Tomcat and Postgres are installed, with a memory "slice" of 256 MB and free disk space of about 500 MB would be sufficient for the study as described in this article. Soon after the decision was taken to transit the eCRF into production, the eCRF was moved to the VANCIS server (see Box 3).In the table below, the time spent on actually building the eCRF, alligning it to both study protocol and a small set of paper worksheets/instructions, is depicted per person/role. The time spent by the Sub-Investigator is relatively high as it was considered very beneficial by the Sub-Investigator herself, to review the eCRF extensively during this process, to make it match the protocol perfectly, rendering it suitable for the other sites.

Making eCRF pages was straightforward as well. The CRFs were made "from scratch" and the template eCRFs, that can be found on the OC website for everyone's use, were not used. Using MS-Excel sheets, it is easy to define the lay-out of the eCRF page, name and define the data fields and their entry specifications. Easy-to-understand error messages can be entered, and will be shown should an out-of-specifications entry be made. Also, tips or advice can be given, leading the data entry person through the eCRF, in a motivational way, resulting in cleaner data. Care was taken that the eCRF pages and fields closely matched the paper worksheets to be used by site staff.

At each of the local sites only limited laboratory assays are required, to be run in the local laboratory, the results of which are entered into the eCRF by the local site staff. At the same time, sub-samples are forwarded to the principle investigator's site for other (central) analysis, the results of which are entered by one person who will be assigned data entry rights for each of the local sites, but then only for these specific fields.

OC offers an audit trail that records whom entered or modified what data field and when.

	Hours
ES and GRV	45
Sub-Investigator2	20
Principal Investigator	2
Institute's Data Manager	2
Institute's Statistician	1
Total:	70

Box 3: Unveiling Other Dutch Academic Institutions' Interest in OC

Currently, OC is not only being explored and tested by ES and GRV in collaboration with the principal investigator's institution (VU University Medical Center, Amsterdam). During this pilot study, the authors were informed that the university hospitals of Maastricht, Utrecht, and the Academic Medical Center (University of Amsterdam) are currently looking into "rolling out" OC so it can be offered to their local investigators. While building the current eCRF, during which the OC community version was being hosted on a Certu BV server, the Center for Translational Molecular Medicine (CTMM) approached the team and offered cooperation and assistance. Since then, the "production," or "live" eCRF runs on a server hosted at VANCIS, and CTMM staff have registered the domain www.openclinica.nl. This server can be used for any Dutch investigator-initiated or non-commercial trial. Currently, it hosts a total of eight active trials, using OC community version 3.0.1.

In order for the principal investigator to be aware of the safety aspects at any time during the conduct of this trial, automatic e-mailing was programmed for each adverse event entered meeting the ICH-GCP criteria of "serious." Once alerted via e-mail of an SAE reported by a local site, the principal investigator can log into the eCRF, review the relevant information, and contact the local site, for example to advise on next steps to alleviate the event. This obviously would rely on a very timely completion of the eCRF data. The eCRF information can be matched with the paper SAE report to be forwarded to the principal investigator, and used for the step to follow; reporting the SAE or SUSAR to the Competent Authorities and the local EC via the online portal "ToetsingOnline."

The monitor's function/role present in OC can be used to source-verify the entries, issue queries, (collectively called "Notes and Discrepancies" in OC), review and approve the answers to queries and eventually "soft-lock" the data entered. In the current trial, this monitoring function has not yet been implemented, pending the finalization of a Monitoring Plan. It is anticipated that a delegate from the principal investigator's site will be assigned the monitor for current study. In OC, the Data Manager(s) too can issue queries.

At any time, any selection of CRF-items can be downloaded as "reports" in various file formats for ad-hoc review (e.g., for trends), without changing the data whatsoever. Formats available are SPSS, ODM or tab-delimited text.

In the Netherlands, each investigational study with human subjects requires prior and ongoing safety review by the Centrale Commissie Mensgebonden Onderzoek (CCMO; the central country Ethics Committee). The CCMO hereby predominantly acts as the Competent Authority, and as such keeps an extensive record of the Dutch "trials industry". [2] Of all trial applications (roughly 1,700) in 2010, nearly half (47%) can be categorized as investigator-initiated. Also, 1,063 applications were for studies to be run at more than one site (i.e., multi-center). Contrary to expectations based on more administrative demands that would be imposed on the academic investigator groups by the EU Trials Directive, the number of investigator-initiated studies is up as compared to 2009 figures (44% of the approximate 1,900 applications). Clearly, the "market" of investigator-initiated studies in our country remains important and solid. Not only because of its supported "real time" SAE alerts, that actually can be used to fulfill the Dutch Competent Authorities' wish to create better safety oversight in investigator-lead studies, [3] OC could be a meaningful addition to an investigator's research portfolio.

OC was piloted, reviewed and compared with other low-cost software solutions before, [4-5] but not so much with regards to its actual set-up and use. The work in this article was not meant to compare OC with other software but rather to see if it can be an attractive option to a small non-commercial research group.

In its view on near-term (bio-)pharmaceutical drug developments trends, [6] the Center for the Study of Drug Development anticipates a rise in pre-competitive partnering between large firms, smaller R&D organizations and academic research institutions, aiming to share risks, lower costs, improve resource management, and maximize investigative site performance. Individual academic investigators and academic research groups/institutions could improve their chances of gaining such partnerships by implementing and using the full benefits of OC, at rather low installation and running costs.

Footnote:

1. This is randomized clinical trial, enrolling 400 patients in the Netherlands. Ethics Committee approval was gained December 2010, with first patient enrolled 04 Jan 2011

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