Promises, Promises

Andrea DeRosa of Airon Telematica (Air-Tel) critically evaluates the use of eCRFs, pointing out how site sponsors can completely miss the benefits of these technologies if they fail to utilise them properly

Back in 1983, I worked as part of the Medical Department at Roche, in Milan, Italy, to evaluate the costs of connecting several research sites participating in regulatory trials via cable. The results were an unpleasant surprise; the only way to connect the centres was to actually physically lay new telephone lines, costing the equivalent of hundreds of thousands of Euros, not to mention hardware and software costs. Needless to say, the entire project never got beyond the feasibility analysis stage. Fifteen years later, the internet took off and PCs became widely used; the old dream of connecting all centres participating in a clinical research programme returned with a vengeance. In 2000, after much analysis and testing, my first web-based electronic case report form (eCRF) – capable of safely collecting clinical data and in accordance to GCP – was finally launched.

Today, after more than 11 years spent in the world of eCRF, I am yet to see substantial evidence of the huge advantages promised by this revolutionary technology, at least as far as Italy and other European countries are concerned. The aim of this article is to identify the main reasons for these unkept promises and to find out why using an eCRF can end up increasing costs and making clinical research management more complex – the exact opposite of what one might reasonably expect.

OLD PROCEDURES & NEW TECHNOLOGIES

At the root of the contradiction between eCRF's potential and achievements is the tendency to use new technologies as a support for 'old' operating procedures. The classical division of tasks among CRO professionals has developed according to a sequential system (see Figure 1). In a first, often long phase, the procedure starts with a carbon paper-based CRF. The activities of both the clinical monitoring team and the investigators revolve around this document.

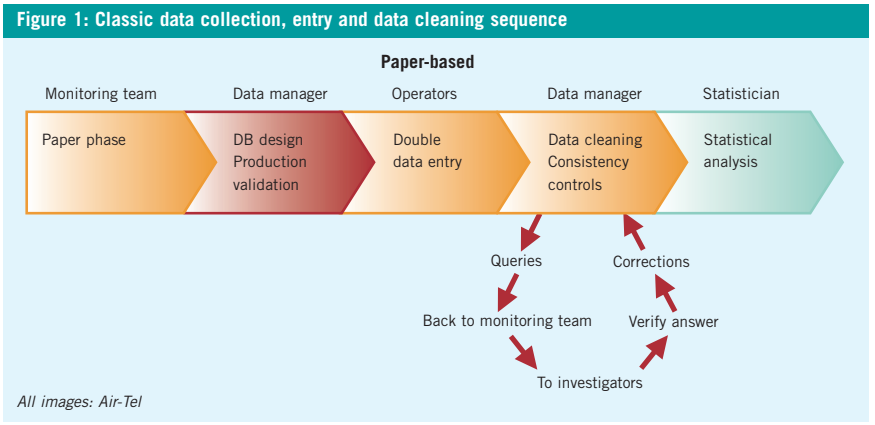
During the initial visit, the CRFs are distributed to various centres and then left there to fend for themselves, at the mercy of clinicians, until the first monitoring visit takes place. At this time, the monitors check the state of progress of the study and completion of the CRF, using source data documents to double-check the correctness and completeness of the data. This is a truly laborious job, especially because the monitors only have a few hours during visits.

After a stipulated period of time (and a certain number of monitoring visits) a copy of the CRF is sent to the CRO. The data managers now come into play; they create the database and organise data entry. To minimise entry errors, all the data are entered twice by different operators (known as double data entry), so that any differences from the original CRF will be highlighted and, if necessary, corrected. At this point, only entry errors are being checked, and not any errors made by the investigator.

Data cleaning can then begin; data managers subject the data to numerous types of analyses regarding completeness and, above all, consistency. They create and perform complex control procedures which will highlight any inconsistencies. All 'dubious' data serve as the basis for the issue and management of queries. Some can be directly solved by the monitoring team, while others must be sent to the investigators who will then provide the correct answers. Once 'cleaned', the database is converted into the format desired by the statistician and sent to him/her for analysis.

When using an eCRF, this sequence is no longer suitable as the database is designed and developed before the study starts. It is, in fact, an integral part of the eCRF, without which it cannot work. The interface can (and must) be designed to limit inconsistent data entry; all data (with rare exceptions) can be checked at the time of entry and illegible handwriting is a thing of the past. In fact, it is no longer necessary to wait for monitoring visits in order to have an idea of the quality and quantity of data flow, nor is it necessary to receive feedback from data managers in order to issue queries to investigators. In short,

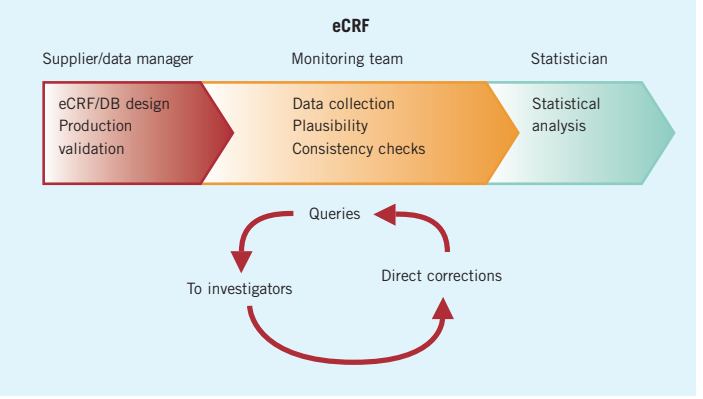
Figure 1: Classic data collection, entry and data cleaning sequence



All images: Air-Tel

not only does an eCRF enable the entire monitoring team to check the data directly, but also significantly simplifies the cleaning procedure (see Figure 2).

Figure 2: When using an eCRF, different processes take place at the same time



REDESIGN, DON'T ADAPT

Redesiging is only feasible provided that the eCRF is not simply an electronic transposition of the good old paper CRFs, even though, over the years, these have fulfilled their duty pretty well. Paper has its limitations and, unfortunately, you often come across these very limitations within an eCRF for which the paper version acted as a mould or template.

When thinking about the questions to ask in the eCRF, modify the sequence and show them only when appropriate – for example, only ask patients defined as 'smokers' for details regarding the number of cigarettes smoked. Also, avoid redundant questions that might generate inconsistent data (never ask for both date of birth and age), and directly code everything that can be coded in order to help investigators reduce inconsistencies.

Although it might seem obvious, it is difficult to imagine just how much resistance there is to modifying time-tested forms even slightly. For example, on a frequently used adverse events collection form, there are two separate definitions of 'severity'. There is the inevitable request to know whether an event can be defined as a severe adverse event (SAE). If it is, the question then asked is to indicate to which of the six standard FDA typologies reference is being made. But a few lines below, the question about severity, to which there are three possible answers (mild, moderate and severe), pops up. This stems from a failure to use the form when the SAE were better defined and standardised. This goes to show that such a form accepts that a SAE can be moderate (an inconsistency which will require the issue and management of a specific query).

There are two advantages to suitably structuring an eCRF: the first is a reduction in the number of input fields; and the second is the avoidance of page checks (one of the main causes of the 'slowness' of many eCRFs, especially if run on old PCs).

SUBSTITUTE & INTEGRATE ACTIVITIES

From the onset, one of the main promises of eCRFs was that they would reduce transport costs (due to a reduction in the number of monitoring visits made). Unfortunately, this rarely happens and is probably due to the fact that monitoring visits are at the core of the CRO's activity (and, of course, turnover) and it is difficult to change people's minds about how to perform their job. Remote monitoring, if well performed, often produces surprising results as each monitor can successfully observe hundreds (or even thousands) of patients. Added benefits include: plausibility and consistency checks in real-time; and alerting systems (via email or SMS) that are activated when a critical event occurs, such as new enrolment or randomisation, criteria violation, or SAE. These are all tools that help to strengthen the monitors' perceptive abilities, thus enabling them to monitor many more patients. This can considerably reduce the number of on-site visits, while simultaneously increasing their efficiency. Imagine if the entire problem-finding stage can be performed remotely, therefore meaning that the time spent at the centre can be wholly dedicated to problem-solving and the checking of crucial data. However, monitors only access eCRFs sporadically and usually only a few days prior to on-site visits.

INTERFACE FOR DOCTORS

The advantages of an eCRF only become tangible if it is completed by the investigators in real-time (or at least without much delay).

Another factor that comes into play is that clinicians generally dislike computerisation of their processes. They are busy with their jobs and expect to be provided with tools designed to make their lives easier, not more complicated. Therefore, the structure of the eCRF must be straightforward and follow clinical practices step-by-step. Unfortunately, this is not always the case and eCRFs often come with huge instruction manuals. A good eCRF should be designed to help clinicians save time, not waste it; pages should load quickly, and the overall response time should remain reasonable even when band conditions are weak or old hardware is being used. Fortunately, scientific data lends itself particularly well to this kind of activity as it is, by nature, highly 'condensed' (an entire battery of laboratory tests, including measurement units and normal values, only occupies a few kilobytes) and unaffected by the variation of secondary aspects (graphics, sounds or videos).

Clinicians often have a silent, though effective, method of 'grading' an eCRF: if it is simple and quick, they use it; otherwise they don't. A simple way of evaluating how clinicians respond to an eCRF is to check the data entry curves (traceability is a fundamental characteristic of eCRF). If data collection is steady, the tool has been accepted by the investigators. However, if data influx shows sporadic peaks of activity (which happens to coincide with monitoring visits), that means these data have only been entered 'under the gun'

Table 1: Example of data management activities usually integrated in eCRF costs (that is, necessary for eCRF design and production or automated)

Data management activities integrated in eCRF		
Activity	**Included**	**Comments**
Database design and creation	Yes	Initial step in eCRF production
Database validation (via software)	Yes	During eCRF validation process
Annotation of CRF with DB specification	Yes	Necessary to create the eCRF
CRF tracking and review	Yes	Necessary to create the eCRF
Check of step-down logic for dependent fields	Yes	Step-down logic helps data consistency (only expose needed fields)
Edit checks study and implementation	Partially	Most edit checks are standard and present in the eCRF, only a few left which are study specific
Data validation process	Partially	Edit checks and plausibility checks reduce errors
Data management status report	Partially	Statistics available in real-time give a full picture of input and cleaning rate
Queries generation, distribution and resolution	Partially	Integrated queries management, direct investigator corrections, form validation controls

or by the monitors themselves while at their site visit (which in actual fact is wasting their precious on-site time). This means that the main advantages of eCRF are nullified.

A NEW COST STRUCTURE

During the first studies conducted using an eCRF, the tool was considered and budgeted as a sort of 'add-on' – a fashionable 'must-have'. The only costs that were removed from standard quotes were those related to the production and printing of CRF on carbon paper. The rest of the costs remained the same (monitoring visits, data management activities, and so on). Conversely, eCRF should become the linchpin around which all the activities of a CRO revolve. This is what significantly increases efficiency and decreases the costs of a study. The number and costs of monitoring visits would decrease and a portion of the cost savings would need to be used for remote monitoring to ensure the overall quality. It is a question of monitoring data influx frequently, checking the data for automatic consistency controls and deciding whether to issue any queries. Furthermore, in order to ensure that queries are answered suitably, it is necessary to plan telephone interviews with the investigators. They should also encourage clinicians to collaborate, monitoring their degree of activity through periodic contacts via email and phone calls.

Furthermore, these 'new remote monitoring costs' can be drawn partially from the data management budget. In fact, as we have seen, a number of standard data management activities will be integrated in real-time remote monitoring activities (see Table 1).

WHAT ABOUT DATA TRANSFER STANDARDS?

From the inception of the internet, we have witnessed the rapid surge of new entities (Facebook, YouTube, Google and Skype) and new standards. Put millions of individuals in contact with each other at the same time and you will see a selection of standards occurring in almost real-time. This selection takes place at grass roots level and rewards everything that works well, while penalising everything that doesn't.

The picture is totally different when it comes to standards that have been developed 'from above', even if the work groups dealing with them are all top-professionals. For example, the Clinical Data Interchange Standards Consortium (CDISC) was to establish a few simple rules so that all clinical data would be defined unambiguously and used by any IT platform.

This idea has certain attractions: being able to establish a number of simple rules which would allow any clinical data to be defined unambiguously and, above all, used by any IT platform – and the dream of anyone dealing with clinical data files. However, as time has passed and after a couple of major modifications, the standard has not yet been fully implemented.

Fortunately, the problem of efficiently transferring data to the internet has been made much simpler thanks to a new language (Extensible Markup Language, XML) and it is not surprising that XML itself has been adopted by the CDISC work group.

Once data is collected in a research trial, it must be subjected to statistical analysis. As part of the eCRF design, data managers and statisticians should be consulted to see if programmes such as SAS, SAP or Oracle can use the raw data directly from the eCRF database or if it needs to undergo a conversion process. This will save a considerable amount of time and money, as this can be incorporated into eCRF design.

CONCLUSION

Organisations have tried to maintain a foothold in the past while trying new possibilities, and as a result they have not fully taken advantage of the revolutionary potential of eCRF. Indeed, it would seem that some have added to their costs because of an inability to relinquish past procedures. However, the 'miracles' of email and smartphones have shown us what technology can accomplish if we are willing to embrace it. Electronic CRFs are to here to stay; they offer the promise of saving time, money and increasing the reliability and quality of data collected. It is now time to let go of our past.

About the author

Andrea DeRosa is the founder of Airon Telematica (Air-Tel). He has over 10 years of experience in eCRF design and optimisation. After graduating with a Medical degree, he held positions as a Medical Manager at Roche, Italy and at Roussel Uclaf from 1981 to 1989. In the 1990s, as a founding member of the medical marketing and communication agency, Airon Communication, he began to take advantage of his expertise in information technology to support companies in their transition from traditional to web-based medical information. In 2000, he founded Air-Tel, a company dedicated to supplying eCRF SaaS (Software as a Service) for sponsored and non-profit clinical research. He is a Lecturer on the Post-graduate Master's degree programme in Clinical Research at Bicocca University, Milan. **Email:** a.derosa@air-tel.it