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eClinical Systems Selection

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# eClinical Systems Selection

There are lots of clinical trial software systems around, all offering the 'holy grail' of solutions for conducting clinical trials. Software solutions exist for every facet of the clinical trial life-cycle and each solution comes with its own smart acronym set (eDC, CDMS, CTMS, eSAE, CDISC and iDAM). Almost every vendor claims simplicity of use, simple and fast configuration, robust reporting on clinical data, a team of experts to 'pull it all together' and the safe handling of data. It thus becomes very difficult for potential customers to understand what companies are really offering and how they (often subtly, other times markedly) differ from each other. Indeed, a great deal of knowledge in a multiplicity of domains is now required, in order to try and understand what is on offer. Fields include advanced clinical data management; clinical project management; clinical monitoring; QA; archiving; software development; testing and support; training; logic and computer and IT hardware. Thus, is it any wonder that poor choices and decisions are regularly made by intelligent folk, and that, as a direct consequence of this, there is a widespread and high level of dissatisfaction with clinical trial technologies? However, one thing should be made clear: it is not always the technology that is the problem. One could be excused for making a poor choice of technology for a particular trial setting, given the widespread prevalence of fluffy marketing, wildly unsubstantiated claims and a lack of accurate and comparable industry-standard facts. Put simply, your choice of technology for a particular project in a particular setting could easily have all the hallmarks of a Bollywood disaster movie! By the time a clinical team discover the inadequacies of their technology for their particular project, the only realistic option remaining is to 'work around' or 'make-do'. Of course, this usually entails a great deal of additional work and stress, which often leads to strained client-vendor relationships. **Caveat Emptor!**

These days, the buzz-word is E2E or end-to-end (note to self – shouldn't this be start-to-end?). This term manages to imply an interconnection of the suite of tools and applications that a vendor may offer and the concept is noble yet the reality is not, with phrases such as chalk and cheese, apples and pears and Jack of all trades and master of none springing to mind. There are, however, a few promising rays of light on the horizon.

Firstly, it makes basic sense that all components of any eClinical suite should 'speak the same language': the data should easily flow from one module into the next. This makes perfect sense for all vendors, in terms of interoperability. Each technology may develop a proprietary interface language for their own suite of components, yet it is not unusual for companies to acquire external and third-part technologies that do not necessarily 'speak' the same language. One solution to this is CDISC (Clinical Data Interchange Standards Consortium): if you suspect you suffer from TMA (too many acronyms), you'd better change career paths at this point! CDISC is:

*...a global, open, multi-disciplinary, non-profit organization that*

*has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata. The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability, in order to improve medical research and related areas of healthcare. CDISC standards are vendor-neutral, platform-independent and freely available via the CDISC (website1).*

Futhermore, it is apparent that CDISC is becoming the standard organisation of choice, in terms of clinical data.

## The Search: Conference Time

So, where does one begin their journey in choosing a suitable suite of electronic tools for a clinical study? Time to attend a few industry-orientated events...

It is surprising how little attention the topic of clinical trial technology receives at a clinical trial conference! The same presentations on the same topics are heard every year, discussing the impact of regulatory issues on timelines; risk management; data safety; how outsourcing will solve all of your problems; emerging markets to the rescue; labs; couriers, storage and logistics in drug supply and management, legalities and even ethical issues. All these are relevant and all have the potential to adversely affect all sides of the project management triangle of a clinical study. So, what about the choice of clinical trials technology and, more importantly, the practical application of the myriad of technological offerings? Paper, I hear you say: forget it. Like it or not, we are now immersed in the electronic era. Only 90 years to go to the 22nd century: plug in or tune out, paper is so dead! By the way, does your data management system support hybrid trials, just in case?!!

I recently attended an Adaptive Trials conference, one of several on the subject. Within an hour, I felt that I had regressed to my university years and was sitting dazed in one of my theoretical mathematics lectures as the professor at the head of the theatre filled board after board with integrals, ns and the characters of several Indo-European languages! What I am trying to say is that clinical project members want to know and learn the practical rather than the theoretical: we do have a day-job, you know! More conferences on clinical trials technologies and more practical, real-world, non-hypothetical presentations please. Now I feel we're beginning to understand one another!

However, if you thought that you had problems in your phase one single-site study in Western Europe or North America, just wait until you move to a phase three study in an emerging market. If you are not already managing a trial in an emerging country, you soon will be: that's what all the figures and daily digests keep telling us. Now Daragh, what exactly were you telling us about eDC: you see, I'm a clinical project manager and I need to run a global study across Asia, Africa and South America. You mentioned something about clinical trials technology? It's time to seek out the vendors and see what is on offer.

Of course, you may have already committed to a particular clinical

trial solution, or, worse still, your company or boss had done this long before you arrived on the scene. Within the context of this article, your choices are simple at this point: make-do and, if things get hairy, 'work around'. However, if you have the liberty of choosing a system from the start, then it's time to shop around.

### Doing the Right Study and Doing the Study Right!

As your clinical study gets underway, it is imperative that things go according to plan (you do have a plan, right?). Moreover, plans change and it is becoming ever more important that a clinical team manages such changes and is able to adapt. A good CTMS (Clinical Trial Management System) enables a team to track the progress of their study throughout the clinical project lifecycle and this is vital if a study budget and time constraints are to be honoured. Ideally, this system will not be a stand-alone application: it will interface with the other components of a clinical suite. The continuous interaction of clinical trial technology components, when combined with the most powerful database application, will not only enable you to 'stick to the plan' but will also enable you to modify your trial design and structure, should the need arise. This will ensure that your study is conducted in the safest and most efficient way possible.

### The Basics: Data Collection

In any electronic clinical data management system (CDMS), clinical data is inputted, transformed (cleaned) and stored in an electronic database. Eventually, this electronic data is outputted (exported) from the database for further analysis and then continues on its journey towards regulatory submission (its goal in life!) and archive (the retirement home!). Clinical data comes from many sources during a study: in a paper trial setup, the patient data will be captured onsite on paper case report forms (CRFs). A copy will normally remain at the site and another copy will be sent to the data management centre (Of course everyone knows this from their first few weeks on the job; this is Clinical 101). There may be other sources of data, such as print-outs from medical equipment and patient questionnaires, and additional data is often generated during the course of the trial, such as safety and laboratory data. Again, with a paper trial, all of this clinical data is recorded on paper and needs to find its way back to the CDMS, where it will be entered onto the electronic system. Any questions (queries) that arise as a result of entering and reviewing this data will need to come back out of the system and be sent back to the site. As we know, an electronic data capture (eDC) system enables us to greatly simplify this data transmission process by providing a means of remotely interacting with the CDMS (either by directly accessing the CDMS or by accessing an eDC system, which in-turn talks to (synchronises with) the CDMS system). However, for a remote trial in, say, Sub-Saharan Africa, is eDC really the 'holy grail'? Does it really speed things up and simplify the process?

### The Obvious: Connectivity

There are really only two kinds of eDC systems to choose from when it comes to connectivity: online and offline. Typically, an online eDC system enables site staff to interact with the electronic case report forms (eCRFs) via a web-browser, which necessitates a constant (unbroken) and appropriately sized (sufficient bandwidth) internet connection. Without this, there is nothing: an inability to see the data already entered, an inability to enter additional data and certainly an inability to verify that the data entered into the electronic database matches the original source of that data (source data verification or SDV). No, there is nothing wrong with your television set. Do not attempt to adjust the picture: just sit and wait!

The other choice of eDC system is the Offline system. With this system, copies of a site's eCRFs are stored locally, either on a dedicated clinical trial appliance (CTA) or on the site's computer, on which an eDC application has been installed. As the term offline implies, site staff can access the eCRFs, even when there is no internet connection (or any other form of communication link, for that matter). Some companies will claim to offer the offline feature; however, this is often little more than a cached browser store. It's a bit like seeing the Google search page in your web browser when you are not connected to the internet and this is radically different (and far inferior) to a stand-alone system with intelligent communications ability and full application support when no internet connection is present. That, my friend, is offline! Of course, a connection to the mother ship must be re-established at some point, so that communications may continue between the data management centre and the site. This way, site staff can continue to enter patient data and monitors can continue to monitor site data. Hakuna matata!

One further consideration regarding communication between remote sites (eDC) and the data management centre (CDMS) is the 'available and supported' modalities of communication, in order to enable system connectivity. The web has been described as a commonly-available mode of connectivity, yet web connectivity is typically poor, intermittent, or even completely lacking at remote sites and the installation of satellite units is one way to overcome this. However, practically speaking, these satellite units are slow and very expensive: if the copper cable has not already been dug up and sold, phone lines can offer a relatively slow conduit to the internet, via a dial-up modem. Finally, if your system can handle it (few can), you have the option of the ever-expanding GSM mobile phone network or even the relatively inexpensive mini-broadband global area satellite. These latter options assume that your system can function adequately over narrowband communication links.

There is another consideration for the sponsor at this point. Even with these systems offering a site the ability to enter data directly into the electronic database, practically all data is firstly recorded on a paper 'source sheet'. To anyone outside the clinical trials industry, this would sound insane! Is it not that the electronic system, with its pre-programmed error checking (validation checks), is designed to avoid the collection of poor and inaccurate data? Or perhaps it just exists to test the transcription skills of site staff? After all, the patient has long gone before the majority of site data is entered! In an ideal, futuristic setting, we would surely enter the patient data directly into the eDC system while the patient is still there and thus avoid the need for source data verification: double points! However, we are a long way from 'total eSource': as mentioned above, there are many other sources of clinical data, such as laboratory samples and medical device outputs. So, just what is stopping us from importing information electronically from these sources also? Well, nothing really; yes, you guessed it: it's whether your clinical trial technology can handle this!

### The Cool: Direct Data Capture

Subject 001 enters the doctor's office as they are taking part in a clinical study. A quick fingerprint scan of the subject, with the assistance of the study co-ordinator, and a picture of them and some basic details pop up onscreen, confirming that this is the same patient who electronically consented to take part in this clinical trial the week before. Over the next few minutes, the answers to a series of questions are directly entered (by the study co-ordinator) onto the CTA.

The nurse connects a vital signs machine to the patient and activates the device from the vital signs eCRF page. The readings are taken and automatically populate the eCRF (electronic case report form). Following a series of questions and responses from the study subject, the study nurse completes the eCRF and possible errors are flagged and addressed immediately in the eDC system. Behind the scenes, further checks on the data are continuously checked against other data from other study subjects and even other sites, and, if necessary, the appropriate staff are alerted (by e-mail or text message) to potential data and/or safety issues. Following the completion of a subject screening, the eClinical system analyses their responses and, depending on this analysis and other factors, may automatically randomise the subject to a particular cohort of the clinical study. Once again, the system is connecting (in the background) to the drug supply warehouse and, before the study subject has even left the doctor's office, has already placed an electronic order for the drugs required for that subject's next visit.

The nurse then takes a blood sample from the patient. A barcode is generated through the eDC system and is attached to the blood sample, which is then sent to a local lab for analysis. When the sample arrives at the lab, the technician logs into the eDC system and scans the blood sample barcode. He is then presented with an eCRF lab screen, onto which he enters the results: as a lab technician, he is blind to all other eCRF data. Indeed, it is not inconceivable that even the entering of lab data (whether local or central) may be automated and directly electronically loaded onto the eDC or CDMS systems. I'm thinking CDISC to the rescue once more!

As additional data populates the database, the clinical data is dynamically modelled using an adaptive trial data modelling algorithm. The results of this are fed back into the database as metadata, with possible instructions to alter a particular dose, increase the population of a cohort, or even terminate a cohort because of ineffectiveness or, worse still, toxicity! Sponsors now have real-time visibility of clinical drug developments and, more importantly, the right 'adaptive-ready' clinical trial system will enable any schedule changes resulting from protocol amendments to be auctioned remotely and with zero down-time. Real-time (and as such, early) identification of ineffective and potentially unsafe drugs is the name of the game: the regulatory agency loves it! Also, delivering safe and effective drugs quickly is the new modus operandi and sponsors love it! Welcome to clinical win-win. If you think that all of this is tomorrow's dream, think again: this is today's technology and tomorrow gets a whole lot more exciting.

## Potential Problems

This all seems too easy, so where could things go wrong? Well, let's consider an extremely remote study, where the patients are located over ten hours by dirt road with no electricity and no mobile phone signal. The first problem would be drug storage and the second the storage of samples, prior to analysis. There is also the consideration of skilled resources. A local village nurse may be able to administer drugs, take samples and even complete written source sheets, but will they have any experience in managing a eCRF on a CTA? The key here is not just being able to provide a solar-powered CTA in an offline mode and/or portable satellite access, but also being able to provide an uber-intuitive eCRF with possible on-screen dual language support. However, if the site has no drug and sample storage or analysis facilities, the only advantage of eDC over paper sources is real-time data visibility for the sponsor (not to be underestimated), as the samples will need to be transported to a centre in any case. Of

course, a mobile clinical trials unit with a truly portable eDC system, as described above, sounds like the perfect option! Remember, the physical transportation of anything (paper source, samples and supplies) to and from remote sites in the rainy season can be extremely difficult, if not impossible. To avoid some of these potential problems in remote areas, it is common for sponsors and sites to set up primary investigation centres (often referred to as centres of excellence): these sites control the drug supply, lab analysis and data entry for trials and manage a network of satellite sites through their field-based staff. Unfortunately, as there are very few true offline eDC systems, these field-based staff use paper sources when they could be using eDC and, at the same time, saving a lot of time and money and greatly increasing safety through the provision of sending more accurate and up-to-date data to the sponsor.

## Monitoring: Cheap and Easy!

Finally, there is monitoring: a necessary and often expensive component of a clinical trial. Need it be so expensive? Most clinical projects assume that monitoring will be conducted at fixed frequency intervals throughout the study, with perhaps an additional visit thrown in at the start (for initiating a site) and one at the end (for site close-out). There are several inefficiencies within this approach: firstly, where a clinical trial system does not give the study monitor access to real-time clinical trial data, the monitoring visits will rarely be as effective as they might be with prior access to the site data. Now, back to that remote site in Sub-Saharan Africa: it is a well established, proven fact that the monitoring of electronic clinical studies in remote sites can be extremely frustrating when the eDC system being used is reliant on an internet connection. I have multiple first-hand experience of monitors taking up to two weeks to conduct a two-day visit because of poor connectivity onsite and the resultant inability to access the database of a web-based eDC system, not to mention the frustration of ultra-slow page submission! The answer to all this is a system with offline capabilities and a suite of features that allows a monitor to complete SDV (source data verification) and raise electronic queries. Even better, let's suppose that this trial was being conducted as in the example above, using direct data capture or eSource (electronic source). For all the data that has been captured electronically from patient records, medical devices or from being directly entered onto an eDC system without first being written down, there is no longer a requirement for SDV. Naturally, the monitor will still need to review the data but they will have considerably more time to manage the site staff and drug accountability. Thus, they will only need to perform a site visit when there is a real problem with data or patient recruitment.

Intelligent data-centric targeted monitoring is the future of clinical studies. This, combined with a suite of sophisticated and intuitive interconnected clinical trial technologies, is the future of clinical trial research. Trust me, my boss is a doctor! ●



**Daragh Ryan**, is Business Development Manager at Cmed and has been with Cmed for over 8 years. Daragh has extensive experience in the clinical trials industry and with clinical trials software development. He was responsible for the project management of Cmed's clinical trials software until 2005. Since then Daragh has managed a multitude of clinical and commercial projects around the globe and has presented at many conferences on electronic data capture and management in clinical trials. Daragh is passionate about drug development the use of technology in clinical trials.

Email: [dryan@cmedtechnology.com](mailto:dryan@cmedtechnology.com)