All clinical trial data are ultimately digital. The pathway to this digital database is not always as connected as one might expect in this technological age. The backbone of clinical trials is now Electronic Data Capture (EDC), and this is not yet synchronous with the other major aspects of data collection, such as medical imaging. With the need for more streamlined processes, this paper explores the combination of medical imaging with EDC and provides the future paradigm for the trialist in the digital age. This will not only ensure an earlier final database lock, which is a key milestone, but during the trial data quality control (QC), and specifically image data QC, and evaluation can be performed in a more contemporaneous fashion with immediate feedback to those managing the study and the local investigator site. The ultimate goal is to unify all the essential data in a standardised format to expedite submissions and to increase the quality of those submissions.

Introduction
The use of medical imaging in clinical trials has seen an exponential growth in the last decade due to increased use of technology and improved computing power (1). This use continues to grow, particularly in early stage development when the latest techniques can aid in the early go/no-go decisions in new pharmaceutical/biotech product development. Examples of new techniques which are starting to be more commonly used in Phase I and II are listed in Table 1. For completeness, the more common applications that are used in Phase III are listed in Table 2, although the techniques are not exclusive to the phases listed.

The need for an imaging core lab (ICL) has been described elsewhere (2) and is now a standard part of the team of the vendors in clinical trials (3). The days of leaving the image interpretation and analysis to the local investigator site have long gone due to the loss of data, reduced precision and lack of standardisation. The local investigators’ radiological department’s work is optimised for image acquisition and image interpretation for patient management, but not for the safety and efficacy reads.

Along with the increased use of medical imaging in clinical trials, electronic data capture (EDC) has progressed significantly, so that in 2008 more than 50% of all trials used some form of EDC (4). The obvious question is raised about how to integrate the medical imaging and EDC into one system or process. This challenge is being addressed on many fronts. Historically the two processes have been managed independently, and the ICLs have been separate entities from the EDC companies. The reason for this is twofold: 1. medical imaging is memory-, storage-, and transport-heavy, with some image files exceeding 10MegaBytes (MB) in size, and 2. the requirements in the radiology department are such that they either do not have access to the EDC system or the technologists do not have the knowledge to transfer the images to a system that takes them outside their institutional firewall.

Convergence of the two processes is now starting to take place, although complete integration is highly unlikely for the immediate future due to the challenges mentioned. However we can anticipate some immediate developments and envision the full integration paradigm with the corresponding advances and improvements.

This paper will discuss the concept of maximising the value of combining EDC and medical imaging, the utilisation of the synchronicity and working with ICLs and an EDC vendor with the current technology. A brief exploration of the mid-term future potential will also be entertained.

Medical Imaging and Electronic Data Capture
In most hospitals or clinics, medical images are available in a digital format, and even plain X-rays are obtained using digital X-ray although there are still some centres supplying plain film X-rays. The more technically savvy investigational sites will have the ability to submit the images to the imaging core lab via new technology processes such as those developed by AG Mednet (5). Not only are the images being sent electronically, but the data transmission information is sent and the images are anonymised. While this does not seem unreasonable in the current environment, there are still logistical and technical issues with some investigator sites, even beyond the issue of those sites still using film. Furthermore, the initial cost of setting this service up will be more than remaining with the well tried and tested method of sending the images via courier.

Interestingly, using overnight courier services versus an electronic method only gains a few hours in the time of receipt of the images at the ICL, since many sites send their images at the end of the business day, regardless of which methodology is used. Therefore for the direct electronic transfer method the images will arrive at the end of the ICL’s working day and so will start being processed on the following work day. If the images are sent by courier they are routinely delivered by 10 or 11 am the following

“The information delivered by AG Mednet and others is not yet integrated with EDC systems, therefore the investigator site can provide information via the EDC system to the core lab about the incoming images”
morning to the ICL, providing a net increase of time of delivery of less than four hours compared to the direct digital delivery system. However, there are additional advantages and disadvantages that have to be carefully considered with both methods; these are summarised in Table 3.

The information delivered by AG Mednet and others is not yet integrated with EDC systems, therefore the investigator site can provide information via the EDC system to the core lab about the incoming images. Also, many EDC systems are tied in with interactive voice response systems (IVRS). If these are set up correctly, the ICL can receive notification at patient screening or randomisation, alerting them to the fact that there are screening images inbound, and they can be ready for the required rapid turnaround for eligibility of this data.

Medical imaging endpoints are used primarily for efficacy, but are being used more for safety evaluation, e.g. bone density assessment in trials, like the ATAC study for breast cancer (6) or isotretinoin in acne (7). Medical imaging is also used as part of the eligibility criteria. The tie into EDC therefore becomes more critical, and the need for the ICL team and the EC team to discuss the trial data flow is important. It will no longer be acceptable to have these two groups working independently, since with the optimal logic built into the EDC, the imaging will take on a bigger role. EDC will capture the results of the patient management and safety reporting with adverse events. The results of the safety reads and possibly the efficacy reads will need to be entered to provide the comprehensive picture. EDC programming is not just a matter of entering the questions from the CRF but building a complete logic sequence to the data capture. If this is provided as a combined team, the correct logic sequence can be applied, ensuring that the principal investigators (PI) and study site coordinators can be “steered” through the process to ensure there is no missing data.

Table 1. Novel Imaging Techniques used in Phase I/II Studies
Molecular imaging techniques:
- Positron Emission Tomography (PET)
- Novel PET tracers,
- Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI),
- Magnetic Resonance Spectroscopy (MRS),
- functional MRI (fMRI)
- Finite Element Analysis (FEA)
- Active Shape Modelling (ASM)
- Hip Structural Analysis

Table 2. Imaging Techniques more Commonly Used in Phase III Studies.
- X-ray
- Plain film
- Digital X-ray (DXR)
- Angiography
- Computerised Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Ultrasound
- Echocardiography
- Doppler Ultrasound
- Intima Media Thickness (IMT)
- Dual Energy X-Ray Absorptiometry (DXA) or bone densitometry
- Single Photon Emission Computerised Tomography (SPECT)
- Fundus photography
- Optical Coherence Tomography (OCT) for retinal imaging

Table 3. The advantages and disadvantages of courier v direct electronic image transfer

* Some older techniques require a “black box” to be installed and linked into the PACS system. This has been found to be unworkable at the site.
Furthermore the logic should prevent incorrect data being entered. The author has experienced this first-hand in a complex osteoporosis study where with some round table discussions, the logic and performance of the EDC was enhanced and reduced the data entry at the site, while capturing the same information.

The blinded reads that are conducted by the ICLs are, in most instances the two central radiologists (or readers, since they can also be rheumatologists, cardiologists etc) reading the images in isolation of all the data, with a third to adjudicate any differences (8). However, in oncology the readers need to know if the patient has had a resection or radiation therapy, depending on the study. This information should be available in real time to them via the EDC system. Many oncology reads often go on to a so-called “global assessment”. This is the process where a central oncologist will review the images with one radiologist and a set of clinical data that has been determined a priori. This provides a trial overview of the data and ensures there is complete congruity of the images and clinical data. Obviously the use of the EDC system makes this process much more seamless and the global assessment can potentially be captured in the EDC system. Historically these kinds of global assessments have been rate-limiting to the end of the study: the clinical data had to come into the data management department of the sponsor or the contract research organisation (CRO) and, once cleaned, shipped to the ICL for integrating into the read system. Only then could the final global read be conducted, often weeks or months after the last patient, last visit (LPLV) time point. With an integrated EDC system this process can be moved up to occur within days of LPLV and not slow down the data integration and database lock.

Another aspect that has been gaining ground is the development of Adaptive Clinical Trials. These can only work if EDC is being used. In some of the more complex versions even the imaging may change depending on the arm or the inclusion criteria. This requires a very close relationship between the EDC vendor and ICL in the setup stages to ensure everything is captured in the correct sequence.

As more imaging is used in Phase II, the cost-effectiveness of using the right EDC vendor to work with the ICL becomes increasingly important. Pressure on the pharmaceutical industry to develop process improvements at all levels has dramatically increased. Phase II studies are probably the last area to feel the pressure to compress timelines. EDC has formerly been seen as this cumbersome technology that requires months of programming and therefore not suitable to the Phase II/I environment. This is no longer the case and within an eight week lead time, EDC and imaging can be set up in an expeditious manner to provide clean and rapid data with the right partners.

The Future
As we conceptualise the future, combining a robust EDC platform with even some of the basic medical imaging technologies that are now being deployed will allow the image management to be built into the EDC component. The images can then be reviewed by the ICL and can be sent to the blinded read all within the same software platform. All the reads are then captured in the same EDC software platform.

As we look into the future not only does this EDC synchronicity provide an elegant one-stop shop solution but it provides image data handling in the same environment as the other electronic data. Furthermore with proper planning and programming, the monitors and sponsor can have all this information in dashboard format providing advanced monitoring tools.

Conclusions
In the next 36 months or so, we can anticipate that medical images will be transferred electronically to the core lab as a de facto standard, and the courier will be relegated to the smaller investigator sites, new sites, or those sending X-rays. We can anticipate that those EDC vendors who are forward-thinking and linked in with ICLs will exploit the relationship and further improve the logic and questions in the EDC process. There will be a much closer tie-in with the IVRS and notifications to the ICL will result in a more rapid follow-up and knowledge of the incoming images. This will further reduce the losses of images that occur in clinical trials.

The ultimate goal is to unify all the essential data in a standardised format, to expedite submissions, and to increase the quality of those submissions. With the advent of the e-clinical space, over time, medical imaging will become a specialised extension of this rapidly growing technology, rather than a stand-alone facet •

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