eClinical: Imaging Solutions

Gunter Bellaire, Kevin Jaynes and Bill Byrom at Perceptive Informatics evaluate different medical imaging systems to improve productivity and efficiency of clinical trials utilising core medical imaging components and eClinical integration points

During the past decade, the medical imaging community has been challenged over how to work smarter, more efficiently and have the ability to report nearly real-time metrics. While there have been tremendous strides with the creation of workflow technology tools that allow for better workflow management, imaging chain of custody oversight and image quality control, the race to formulate an overall integration of all available technologies that affect a clinical trial is far from over (1).

Currently there are three main components of technology that manage the study-specific image workflow and independent review process. These components are: image visualisation software, image tracking application and the independent reviewer analysis application. The objective of these medical imaging systems is to closely shadow the implicit workflow of particular evaluation criteria such as RECIST, WHO or Cheson (2,3,4). These three technology components may be fully integrated within the medical imaging domain, but there is a real need to integrate with other clinical trial technologies (such as IVRS or EDC) in order to improve quality and reduce time, resources and cost. For example, real-time IVR subject visit data is of enormous value to the imaging tracking application as it provides an early indication that new image files are expected, and an alert for the staff managing image collation when these are overdue. However, since these three components are highly integrated into an assessment criteria-specific independent review, 'analysis system,' it would be completely out of the clinical EDC system's scope to provide the described functionality to independent reviewers. An EDC system is mainly designed for the clinical portion of a trial and especially built for multi-user support, and is not intended for a few niche medical imaging reviewers with specific support needs.

KEY COMPONENTS

Image Visualisation

Image visualisation software is the backbone of qualitative and quantitative analysis of medical images. The visualisation software contains various tools that allow the end-user to perform various functions to a study image, such as launch different image formats (DICOM and TIFF, for example), perform image zoom functions, perform image calibration, perform image measurements or statistics and image contrast adjustments. The three most critical functions of the image visualisation software are its ability to perform accurate measurements, post measurements or other related quantifications directly to a project-specific imaging database, to maintain a direct link between the image file and the analysis measurements and annotations, and to capture all audit trail information related to the imaging data as well as the images. The image visualisation software is a critical piece of the workflow for the internal staff of the imaging CRO as well as the independent reviewers that are conducting primary and/or secondary endpoint analysis.

Image Tracking and Management

Tracking applications are classified as a 'catch all' for the life of an image. Parameters that are captured within a tracking application include, but are not limited to, site contact information, imaging modalities, key image acquisition date/time stamps and scanner settings, current processing status of the image (that is, image received, processed, masked and cropped), image query information and automated tracking of all associated audit trails that are required for regulatory compliance. The end-users of these tracking applications are the internal staff of the imaging core lab that performs the site management and image processing duties on the trial. The alternative to a project-specific tracking application would be the use of multiple spreadsheets that are uncontrolled, prone to human data entry error and lack proactive error handling with the imaging data, which consistently leads to rework and repetitive cycles of reconciliation.

Image Analysis

The analysis application's primary function is to capture the critical data points that are being assessed on the image visualisation software by an independent reviewer (such as a radiologist or oncologist) for a specific protocol or therapeutic area, as well as to manage the workflow for a particular assessment. The analysis application is tightly integrated with the image viewing software and tracking application to ensure a seamless workflow. It is critical that the independent reviewers focus their time and energy on performing the clinical or scientific evaluation of an image or data point, and not spend needless time filling out paper case report forms or spreadsheets. The analysis application is considered an electronic case report form (eCRF). The electronic analysis application's main benefit is the ability to programmatically build in up front edit checks which prevent the reviewer(s) from making errors such as missing fields, analysis criteria deviations or mathematical typos from measurements, which at the end of the study would result in delays and expense to fix.

The current state of integration is limited to the image visualisation software, tracking and analysis application where

the data points (images, visit designations and so on) captured in the tracking system are automatically populated for the reviewer to perform the assessment. Essentially, all the eCRFs 'talk' to each other as one system.

FIRST INTEGRATION EXPERIENCES

IVRS and Imaging Integration

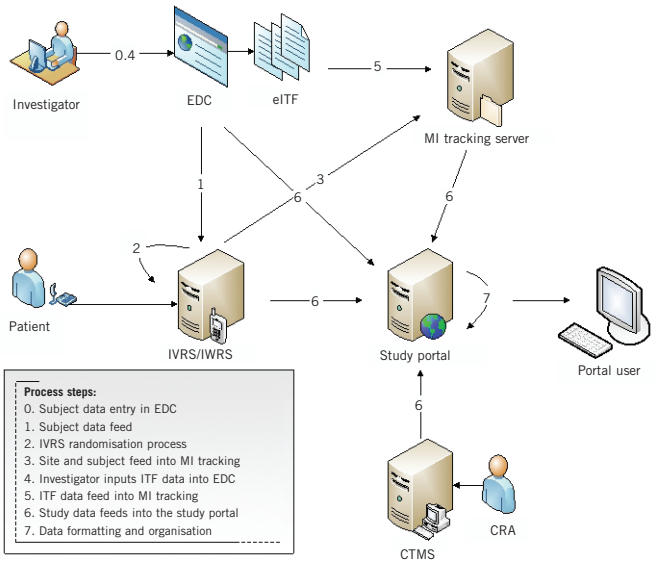
In many trials, IVR systems give a real-time indication of patient enrollment and discontinuation in addition to other defined patient visit events at which medication is dispensed. Particularly at baseline, the most important imaging timepoint, it is essential to follow-up as early as possible on missing data. The follow-up scheduler is a key tracking system functionality to support the CRO teams in approaching sites regarding visit related missing image data. The feed of tracking information from IVRS to the internal imaging systems (tracking system) would initiate the follow-up scheduler and keep the teams proactively informed. In addition, IVR systems can be used to limit the inclusion of patients not meeting the study inclusion criteria. In this case, IVR randomisation approval can be triggered by receipt of eligibility confirmation from the imaging CRO.

Image Upload

EDC usage supports the site's capability to use the internet (via sFTP or HTTPS, for example) to upload study image data directly to the imaging CRO. The advantages of the electronic image transfer are as follows:

- Cost savings due to reduced shipment cost: for example, an average Phase III trial might have approximately 1,000 patients each with four to five imaging visits. This would require up to 5,000 shipments each, amounting to $20 to $25 depending on the site location leading to around a $100,000 inbound shipment cost.
- An intelligent workflow could even mean the upload ends up right the first time: to receive the required anatomy and image parameters of the intended study patient.
- The need of an individual login to the image upload system will emphasise the chain of custody. This means in the non-technical world it is much easier to delegate the image media shipments which often lead to problems.

Figure 1: Integration workflow of current studies



- Image loss or damage due to shipment issues continues to be an issue.

EDC and Imaging Integration: e-Image Transmittal Forms

When images are shipped manually from site to the central imaging lab, the image is provided on CD along with a paper image transmittal form (ITF). The ITF contains information describing the image, including site details, patient number, visit and image details. These data should match the information stored in the DICOM header. The integration of the paper image transmittal form (ITF) into an EDC system (e-ITF) offers several opportunities.

First, there is data quality. As mentioned above, query resolution is an expensive and time-critical process. This general statement also relates to imaging queries. Image query resolution is in some cases cumbersome, since the risk of failure increases tremendously with regard to time spent after acquisition, especially for queries which require access, retransfer or even rescan of patient images.

Secondly, an e-ITF includes all the mentioned advantages of an e-CRF. Edit checks, pull-down menus, radio buttons, completeness checks, dynamic forms if required, and others. Many of the data items to be entered in a paper ITF are implicitly already available in the EDC system, such as site number, patient number and visit information. The query number is expected to decrease by at least 30 to 50 per cent.

Finally, the e-ITF is automatically part of a patient's electronic study file: there is no need to file a paper carbon copy. The clinical research associates (CRAs) are informed to control imaging data on site.

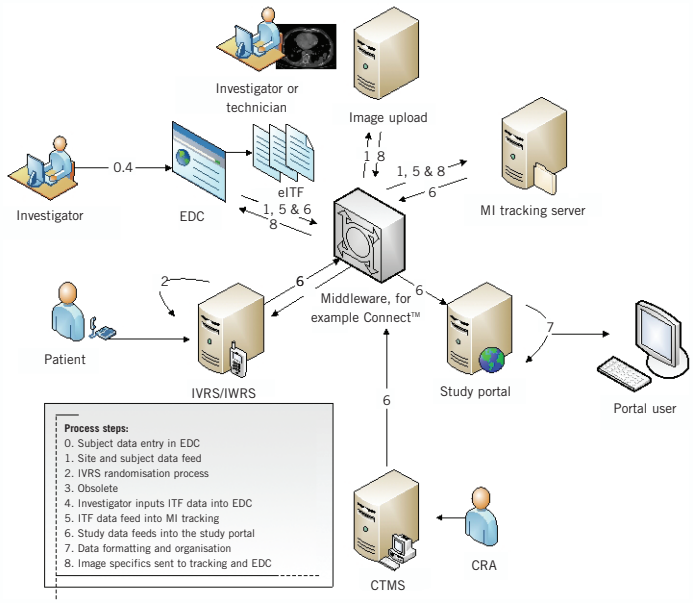
This does not eliminate possible reconciliation errors as the workflow for an imaging study dictates that the DICOM header information is entered by the radiologist using the imaging equipment, and this must be reconciled with the e-ITF data. However, this approach improves the quality of data recorded on the ITF in the ways described above.

Many EDC systems have built in an integrated workflow which require a CRA's final freeze of a CRF page before the page can be imported into the clinical database. From an imaging perspective, this will lead to the CRAs involvement in resolving imaging queries from the beginning. Ownership and general understanding will also start from the first steps. Late surprises such as review delays due to open queries will decrease.

A NEW MODEL FOR INTEGRATION

In the case example of Figure 1, the integration of EDC, IVR, medical imaging, CTMS and portal applications was achieved through point-to-point

Figure 2: eClinical approach using middleware



connections between solutions. In this model, to connect one system to another requires an individual connecter between the pair of solutions to be created, making them tightly coupled. One system connecting to multiple applications would require multiple connecters to be built and supported – for example, the IVR application would require three connecters, one each for EDC, imaging and portal, and ideally a fourth for CTMS. This approach has a number of disadvantages, not least that every time a connected system is upgraded or modified, each of its connecters must be tested and changed where necessary. In addition, the performance of each connection needs to be monitored independently to ensure the integrity of the connection and the data transferred, which provides a support challenge when operating with multiple point-to-point connections.

An alternative to this point-to-point model is the use of a middleware platform, in this context termed a 'clinical technology integration platform' (see Figure 2). This middleware concept has been well developed in many industries in order to provide robust and efficient integrated solutions. Middleware serves as a platform hub, controlling all the interactions between two or more systems. Its efficiency arises from the fact that now only a single connecter is required for each application, independent of how many other applications it will share data with. This has the advantage that when a software upgrade is performed on one application, only a single connecter needs to be reassessed. However, the middleware benefits are much greater when you consider the activities required to ensure visible, robust and reliable integration between clinical systems.

In particular, the clinical technology integration platform truly manages all the interactions between systems. The middleware catalogues all the systems it interacts with and knows the specific requirements of each. In our case study, when a patient is randomised using IVRS, the middleware platform receives information about the event such

Case Study

Figure 1 shows an integration set up recently implemented, providing a high integration of IVR/IWR, EDC, medical imaging and the presentation of study metrics, including key performance indicators (KPIs) in a study portal. In this integration workflow, the following steps make up the integration activities:

- Subjects are enrolled and screened using the EDC system. This provides screening event and subject identification data to the IVRS, which requires confirmation, not re-entry during the randomisation event
- The IVRS provides patient tracking data directly to the image tracking application – specifically the patient screening (received by the IVRS from EDC) and randomisation events
- When images have been collected, site staff enter ITF data into a patient-specific eCRF within the EDC system
- These data are transmitted automatically upon form submission to the image tracking system, where the e-ITF data are automatically uploaded
- When the image itself is physically received by electronic transfer, it can be cross-checked against this information by the imaging CRO personnel.
- The IVR, EDC, (internal CRO) CTMS and imaging applications all provide study progress data and metrics for presentation to CRO and sponsor management staff through the portal application

This integration provides certain benefits:

- Early notification of expected images using real-time event information from the IVRS. This enables staff managing image receipt and quality assessment to be proactive in managing sites and identifying missing data
- No data differences and time-consuming reconciliation activities between EDC, IVR and medical imaging applications, ensuring that all patient identifiers and data are consistent between each application
- High quality ITF data due to eCRF logic checking and auto-population with certain data points
- Full visibility of the study progress, including enrolments, data collection and image status through a single application (portal).

Despite these benefits, there are improvements that can be made in how these solutions are integrated, and these provide greater value to the imaging laboratory and study sponsor.

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as site ID, patient ID, time, date and medication pack allocated. This information is then distributed to the applications requiring it: the medical imaging tracking application receives the event data to flag that an eITF and associated image are expected; the portal and/or CTMS receives event data for high level study progress reporting; and the EDC system may receive pack allocation data to present in the dispensing log for that patient. All this is managed by the middleware configuration from a single event – patient randomisation. In addition to this, the middleware hub indexes and audit trails every transaction it manages. In this way it is possible to demonstrate the complete traceability of all data that is exchanged between systems, and provide a full account of all data if queries arise. This is difficult, if not impossible, to achieve with multiple point-to-point connections. Finally, another advantage of the middleware approach is unscheduled data handling. Say, for example, the IVR system has randomised or screened a patient that is unknown to the EDC solution as the patient's enrolment data has not yet been entered into the eCRFs. In this case, the hub will retain these data until the EDC system is able to receive them. This is visible to the technical support personnel managing the systems integrations, as the middleware solution should also contain an administration interface that provides a full real-time picture of all the data exchanges and should provide the ability to diagnose and remap any failed transactions.

Going back to image upload for a moment, as stated previously, the site/radiology facility would have the ability to upload the study images from the interface of the EDC system directly to the project-specific image repository. At this point in the process, it would be extremely advantageous to perform automatic image header verification. For example, the system would verify in the digital image properties that the correct patient is being uploaded, the correct visit designation is depicted, the correct scanner was utilised, and the correct slice thickness and other study-specific scanning parameters were utilised appropriately. All of these up front edit checks could occur prior to the patient leaving the CT/MRI scanner or, at a minimum, leaving the clinic, to prevent valuable data from being lost or inadequate for a proper analysis. It is important to remember the cost for one study patient and that every piece of data lost wastes time and money.

Within our example, it is clear to see that the middleware model to systems integration provides a more efficient, visible and supportable solution – all vital properties to ensure data reliability and robust solutions for today's clinical trials.

References

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