Paper TS10

Online Endpoint Adjudication in Oncology

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ABSTRACT

In oncology trials the primary and secondary endpoints are commonly time-to-event endpoints such as: overall survival, progression free survival, and time to progression. To minimize any process-driven variability on endpoint results and to ensure an unbiased review process resulting in enhanced accuracy, it is recommended to involve an independent adjudication committee of experts to review the data related to the endpoint. Clinical trials increasingly rely on this endpoint adjudication to better assess patient outcomes. One of the downfalls of centralized endpoint adjudication is that it is a time-consuming process which might jeopardize study timelines for analysis. Online endpoint coordination and adjudication software offers one solution and makes it easier to manage endpoints in a time efficient manner. Online coordination provides adjudication committee members, sponsors, and other authorized users real-time access to complete and accurate source data and endpoint results, reducing clinical trial timelines. With online software rather than a traditional paper process flow, potential safety risks and efficacy signals can be detected more rapidly and decisions to retain, close a trial, or close or enrich a treatment or dosing arm, can be made more quickly.

INTRODUCTION

The increased trend towards the use of centralized endpoint adjudication is being driven by regulatory authorities. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend centralized endpoint adjudication to assess safety risks of new drugs.[1,2] Endpoint adjudication can be a complicated process involving multiple steps and stakeholders. To eliminate process delays, a web-based endpoint adjudication system was developed by Merge which is integrated as a module in eClinical OS.[3] This paper will demonstrate how this endpoint adjudication module within eClinical OS can be used in oncology clinical trials to follow up on the evaluation of typical oncology clinical endpoints and will explain the advantages the process brings along with it.

ONCOLOGY CLINICAL TRIALS

ENDPOINTS IN ONCOLOGY

The gold standard clinical endpoint for demonstrating the clinical benefit of an oncology compound is overall survival (OS). However, evaluating OS in a clinical trial has several drawbacks. An analysis of OS requires large patient numbers and much longer follow-up compared to other accepted primary efficacy endpoints. In addition, OS may be confounded by subsequent therapies. Endpoints such as time to progression (TTP), progression free survival (PFS) and objective response rate (ORR) do not have these disadvantages and are thus often used in oncology trials. These tumor assessment endpoints are based on subjective evaluations such as clinical or radiological observations and thus are not as objective as OS. This is one of the reasons why standardized response criteria have been developed by experts. Standardized response criteria describe disease response definitions and advise which techniques and measurements or assessments are needed to evaluate the response. In addition to using these standards, certain design features can be incorporated into a clinical trial to minimize bias and increase precision and accuracy of potentially subjective observer-dependent assessments. To increase uniformity of efficacy endpoints based on tumor assessments, special attention must be given to blinding of patient data and the use of central (external) review committees is recommended. Without independent central review, bias stemming from the sponsor or study's monitor's familiarity with particular patients may influence endpoint assessments. Moreover, the validity of the conclusions drawn may be questioned if stringent processes are not in place to reduce bias.

DATA COLLECTION OF TUMOR LESIONS

Tumor lesions are identified at the baseline visit by using different methods of assessments such as: CT, MRI, PET, Endoscopy, and Bone Marrow Biopsy. Each identified tumor lesions is reassessed and followed up on subsequent visits. On each of the visits an evaluation of response is determined at the site. The site will report these results in the source notes and the eCRF. If an Independent Review Committee is involved, the images and all relevant source data are also submitted to the IRC that will also review all available data to assess the endpoint.

ENDPOINT ADJUDICATION PROCESS IN ONCOLOGY

An Independent Review Committee (IRC) is a panel of independent, unbiased, third-party experts charged with centrally reviewing and classifying suspected endpoints, verifying whether they meet protocol definitions, and providing standardized endpoint outcomes for the purposes of statistical analysis. Endpoints in oncology are often image-based and thus independent radiologists and oncologists are part of this independent review process. The clinical site submits the images taken at the visit, as well as any relevant source documents, and all relevant clinical data to an Endpoint Coordinating Center. The endpoint coordinator verifies the information that has been received on completeness and accuracy and performs a quality control check. Any non-blinded information will be blinded and any non-English documents are sent to a translation company. Queries will be raised by the coordinator to the site which on their turn will provide the necessary or missing information. The exchange of all this information is often still done by paper and fax and is a very time consuming process. Trackers are kept manually at both the clinical site and at the coordinator center to verify which information has been received and which information is still missing. In addition to the documents sent by the clinical site, it may also be necessary for the coordinator to receive additional clinical information from the trial database (including lab data, info on AE/SAE etc...). (See Figure 1) When all information has been collected, one single dossier is compiled by the coordinator so the independent review process by the experts of the central reading committee can be initiated.

Figure 1: Example of process flow of endpoint adjudication

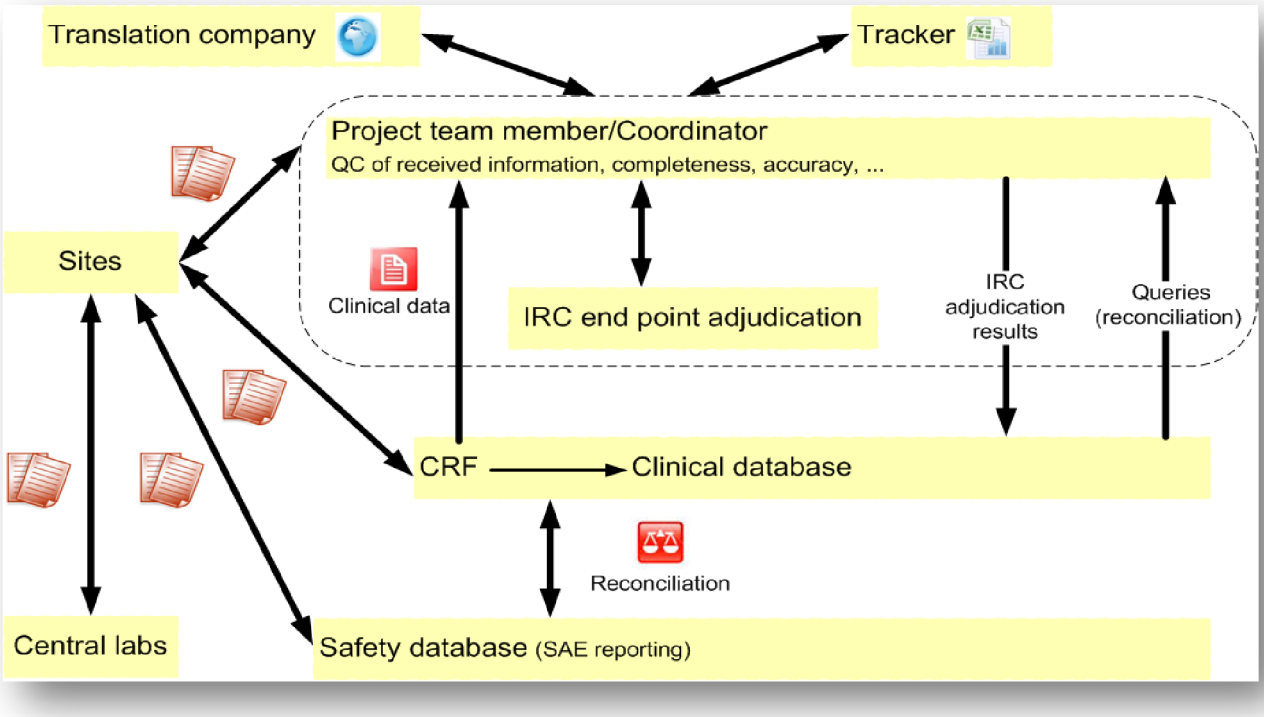
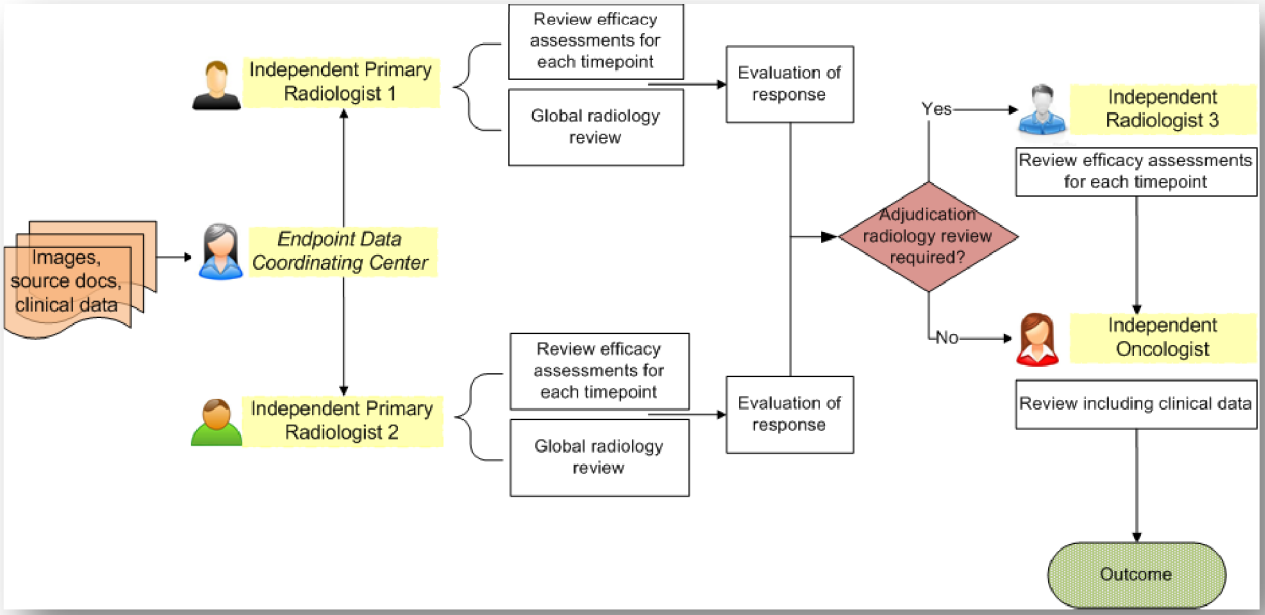


Figure 2 illustrates possible endpoint adjudication flow for oncology trials. Two independent radiologists will review the images of each time point and perform their measurements and assessments. Based on the tumor measurements and assessments the radiologist will determine the disease response of the specific time point. In addition, the radiologist will also perform a review on a patient level for all time points and assess an overall evaluation of response. If the evaluation of response of both radiologists is different, a third independent radiologist will review the images and accept the data of one of the radiologists. If the independent primary radiologists do have the same evaluation of response, no adjudication by a third radiologist is needed and the oncologist can directly perform his review by using the information of the radiologist(s) and the clinical data of the patient. The information of each assessor is captured in the clinical database supplementary to the site evaluation in the eCRF.

Figure 2: Example of independent review process within oncology clinical trials



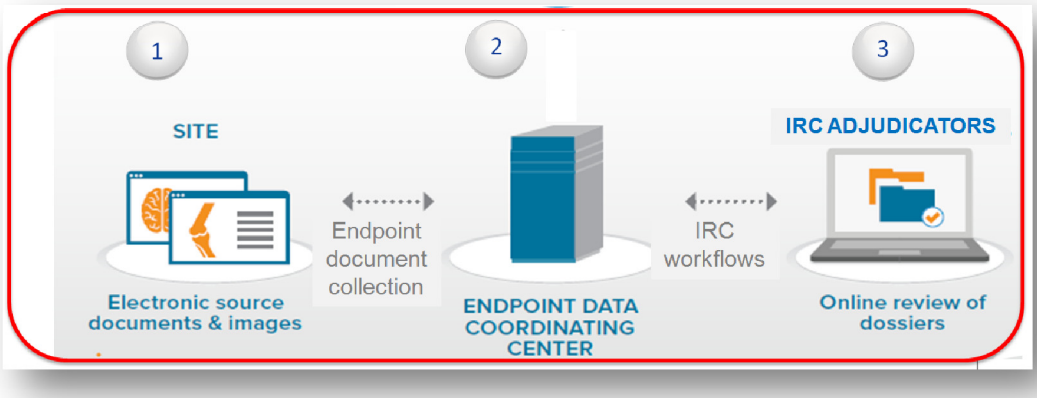
ONLINE ENDPOINT ADJUDICATION

Sponsors and Contract Research Organizations (CRO's) face pressure to reduce costs in clinical trials and to shorten clinical timelines. Contradictory to this, endpoint adjudication is a time-consuming process due to the many manual steps involved and it can be a huge bottleneck when it comes to timelines. As a result, all parties are looking for ways to increase the efficiency, streamline workflows, better facilitate business processes, and reduce complexities of endpoint management. Online software allows real-time visibility and helps to more efficiently manage endpoint coordination and adjudication processes.
Advancements in worldwide technology adoption have made document sharing easier as most clinical sites can now provide source documents in digital format and transmit them over high bandwidth Internet connections. Many endpoint adjudication systems (EAS) also have added interoperability capabilities that enable data sharing. In addition, new web-based tools allow for paperless review and processing of endpoints.

ENDPOINT ADJUDICATION MODULE (EAM) IN ECLINICAL OS

eClinical OS is a unified, cloud-based system developed by Merge that offers all of the EDC and study support capabilities.[3] One of the features within this web-based system is the Endpoint Adjudication Module (EAM), which is a web-based tool that integrates endpoint management and adjudication workflows into a single, seamless system. The EAM gives all involved parties online access to all relevant study documents (see Figure 3). It not only automatically compiles an electronic dossier of all required endpoint details and source documents, it also allows any authorized user to see the original documents.

Figure 3: Online endpoint coordination and adjudication process



The clinical sites will upload source documents and images of any format into the EAM of eClinical OS. Any relevant clinical data needed for the endpoint adjudication can be entered in the eCRF or uploaded as well. Once the site indicates that the data is complete, the coordinator can start reviewing the collected data needed for the endpoint adjudication and perform a quality control on the documents. Any documents that are not blinded can be blinded directly in the EAM by the coordinator. Non-English documents can also be submitted to a translation company via the EAM. If any queries are needed, then these can be addressed to the clinical site within the system. Once all data is collected, the clinical data, source documents and images can be compiled into one single dossier which is then immediately available for adjudicators review.

Independent adjudicators can review the data online in parallel and request additional information and send queries in the system to the site if needed. The adjudicators will complete the adjudication specific eCRF and this data is, together with the data completed in the eCRF by the site, transferred to data management for review. If the process requires adjudication by a third assessor like in the example above, then it can be foreseen in the EAM that adjudication outcomes of the first two adjudicators are compared automatically by the system, generating a dynamic step if there is a difference in outcome. The third adjudicator will then be automatically notified and also completes his/her review.

A dashboard overview is accessible at anytime and will provide information on how many endpoint adjudication events are initiated, in which phase they are, and how many events were assigned to each user (coordinator and adjudicators) (see Figure 4; example provided for endpoint adjudication for AE). For each endpoint adjudication event one can see its progress throughout the adjudication process (see Figure 5). Access to each form is dependent on the rights and roles assigned. For example, the site will only be able to manage and view the forms that they have completed in the EAM, while the third independent adjudicator will have access to each of the forms and can only make updates in his own adjudication form.

Figure 4: Dashboard overview of the endpoint adjudication events within this trial

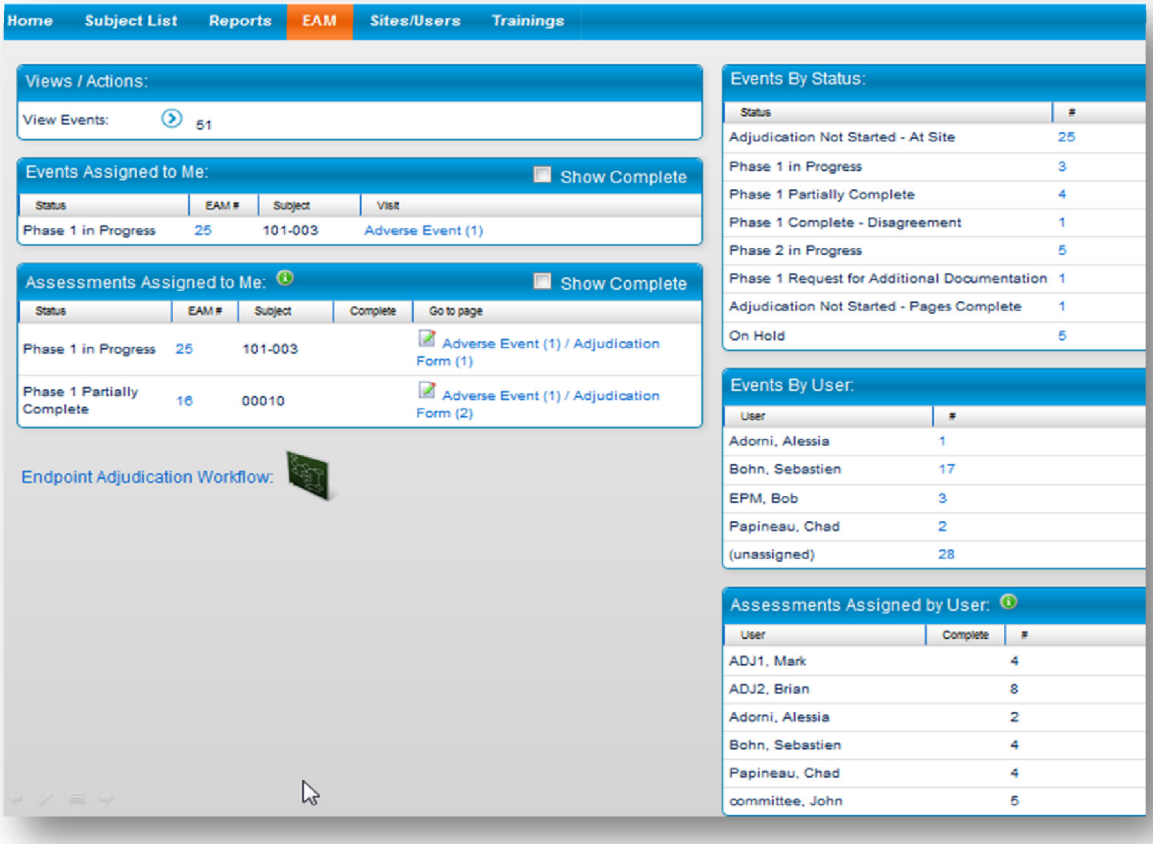
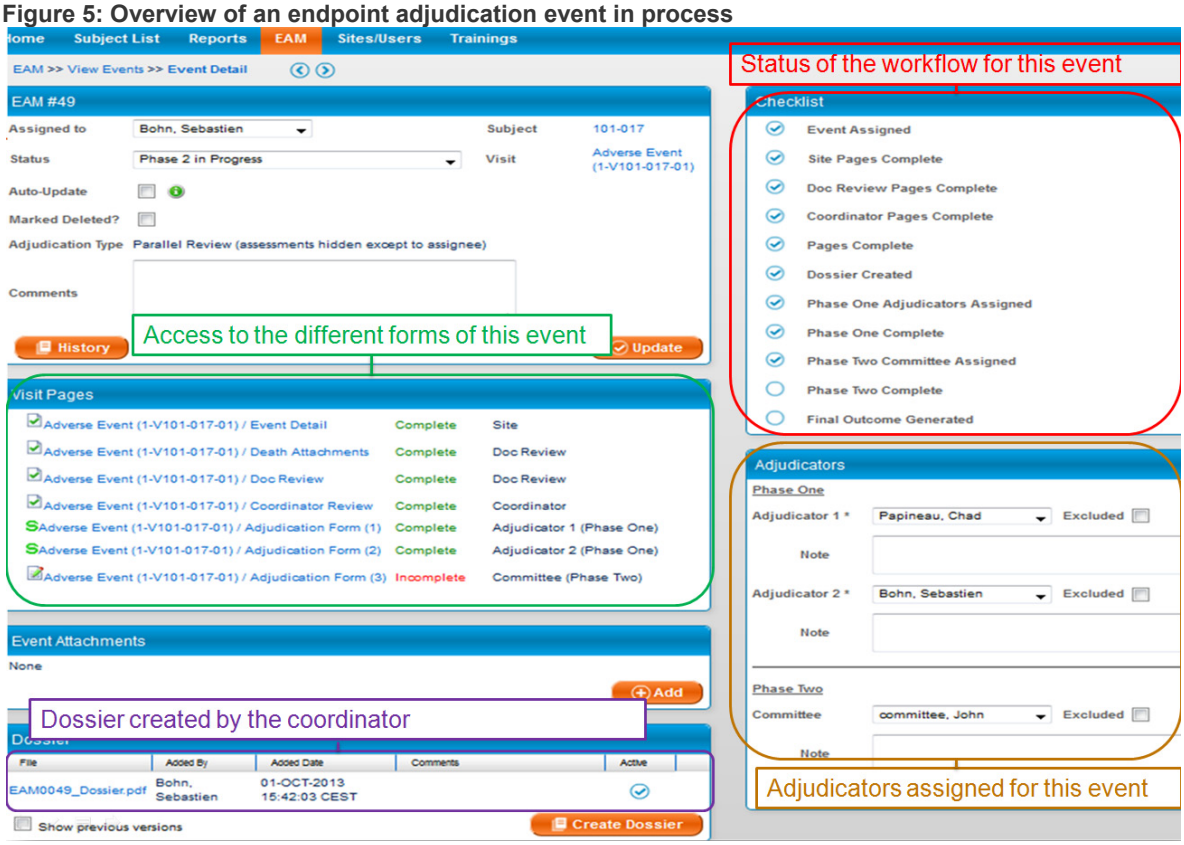


Figure 5: Overview of an endpoint adjudication event in process



BENEFITS OF ENDPOINT ADJUDICATION

A major benefit of performing all endpoint process steps within one single system is that all workflow components are linked in an integrated system process map. This approach improves process consistency, governance, and quality by eliminating manual handoffs and reducing reconciliations traditionally driven by multi-source data capture. In comparison to the old paper process, use of online adjudication technology brings a number of logistical and financial benefits. It reduces the manual labor associated with processing of endpoint data and documents and decreases the volume of data and statuses which need to be tracked manually. It also lowers project costs by eliminating courier and fax costs which have traditionally been required to transport paper documents from sites to endpoint coordinating centers to the independent review adjudicators. In addition, this approach reduces, and in some cases eliminates, travel costs which have traditionally been required for regular face-to-face review adjudication meetings.

CONCLUSION

The use of an online endpoint adjudication system technology enables the implementation of an end-to-end, transparent endpoint workflow. It creates significant cost efficiencies and reduces cycle times by offering a collaborative workspace for all relevant stakeholders, by partially automating the process steps with a flexible electronic workflow and integrating all components of the endpoint management and adjudication workflows into a single, seamless system, imbedded within an EDC platform. Knowing the time consuming process of a manual endpoint adjudication process and knowing the incentives of regulatory authorities to use endpoint adjudication outcomes rather than investigators outcomes in the analysis, it can only be expected that more and more oncology trials will start implementing an online system to incorporate the endpoint adjudication process in order to meet timelines for study analysis.

REFERENCES

1. www.fda.gov (August 29, 2014)
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3. www.merge.com (August 29, 2014)

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