Questions Received from the Audience: Interim Study Monitoring Webinar

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Webinar Recording can be accessed here

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Q1. From the way described, the CRO has to actively present the study data for upload (at the required frequency) - I assume this must be a file-neutral format - has the CRO had to devise ways to extract that from their LIMS - how is the study structure made available? - has PointCross assisted in that? I assume the CROs are charging for this data provision.

A1. PointCross: The CROs load the data (in whatever native format is allowed by their LIMS system) directly into the secured and encrypted Virtual Data Room (VDR), which is a space made for the CRO or the Sponsor customer. LIMS systems are computers with the ability to export selected data for a study in digital format including their native data model, columnar formats including CSV, XML , XPT, EXCEL or other; and human readable tabulations in PDF format.

Because interim study data comes from CROs as well as external labs or research facilities, the disparate data is characterised as raw, as-collected, and oftentimes unstructured and must be mapped sequentially – a process PointCross assists through our Data Concierge Service.

The first time a CRO is brought on line to provide a Sponsors' interim study data, a sample study data upload is made - so that the automated transformations to the Universal Data Model (UDM) of the interim and study repository - can be mapped for re-use in future uploads from that CRO. This takes a few hours, and the subsequent mapping and automation renders the raw data to be made available for visualization and analysis in near-real time.

CROs usually know how to generate the data exports. If their staff are unfamiliar with the controls, PointCross aids the data transfer process and can help enable CROs to automatically upload data from specific ongoing studies at a pre-defined frequency, and if or when necessary, automation scripts will be provided. The CRO and Sponsor are kept on the same lines of communication at all times.

By "Study Structure" we assume the question is referring to the way the Study Design is coded. Some LIMS systems attempt to generate SEND-like domains for Trial Design. These work most of the time for simple parallel studies. However, the automatically generated Trial Designs in some of the LIMS systems tend to be incorrect. Since the Sponsor is intimately aware of the Protocol, a simple tool for generating the Trial Design domains is provided to the sponsor and they will establish the trial design domain before the first load is obtained. Having an accurate Trial Design is key to being able to analyze data efficiently and with confidence.

Dessi: We haven't had any requests for additional fees from our CRO's for uploading interim data. Prior to PointCross, the CRO would send us data every few days for a study in excel or PDF format. When we brought PointCross on board, we established a weekly data upload using XPTs from their data collection system (which is typically Provantis or Pristima) and/or from LIMs. As such, the process for the CRO has become more efficient and less cumbersome in getting data to us for interim study monitoring. Additionally, they use the VDR for study documents (protocols, amendments, etc) which has also proven to be easier and more efficient for them. In general, the process has streamlined our communications and data transfers with the CRO reducing theirs and our overall workload.

Dragomir: We have different arrangements with our CRO partners. One of them is charging the same rate for daily and weekly extracts and since everything on our end is fully automated, we receive daily extracts from their test sites. Another CRO charges based on the number of extracts for a study, so unless required by the Project Team specifically, we go with weekly extracts from them. The timing of the [weekly] extracts

can be optimized, so that relevant data (e.g. lab findings) become available for review as soon as possible (typically two days after blood collection for the lab data).

Q2. Is it very cumbersome for the CRO to upload the data? Does it add much cost in your experience?

A2. PointCross: CROs and labs have a LIMS system for the digital data they collect. Data extracts from the LIMS systems can be directly loaded into the encrypted Virtual Data Room (VDR) of Xbiom™. In the past few years most of these LIMS systems have a machine readable column format in XPT, CSV, XML or even Excel. This data can be "dragged and dropped", or selected for upload into the secure VDR in the allocated folder structure organized by Study. Automated upload is configured for repeat customers, as this is simpler and less effort for the CRO.

When data is not sourced from a LIMS system, we accept printed (e.g. PDF, or hand-written) and annotated lab notes, and PointCross digitizes and enters the data into Xbiom on behalf of the Sponsor or CRO, as a Service.

This is not an expensive or cumbersome process. PointCross charges, for example, a fixed monthly subscription for supporting interim study monitoring on a fixed number of studies per month. Additionally, multiple studies that have come in in non-English language have successfully (and quickly) been loaded into Xbiom™.

Dessi: See my answer above, it can also apply to this question.

Dragomir: Once the data transfer process is tested and established (your first study upload[s]), typically there no issues afterwards. Nowadays, this is pretty routine practice for the major CROs (might be a different story for the small, niche CROs).

Q3. Does PointCross need to be involved in the interim data uploads, or is the CRO in direct contact with the Sponsor

A3. PointCross: The sponsor can engage with the CRO independent of PointCross. PointCross's Data Concierge Service is designed to "plug-in" with the Sponsors' CRO to ingest the interim data load, process and map the interim data, and render the data available in Xbiom™ for visualization and analysis.

This Data Concierge service is leveraged by sponsors with limited internal data science resources or Sponsors who prefers to have the CRO and PointCross deliver analyzable data. In such cases, a tri-partite collaboration is maintained with PointCross only involved in making sure that the arriving data and its integration is checked for completeness and integration; the sponsor is entirely responsible for the interaction with the CRO.

If the CRO data is in SEND .XPT format, it is seamless, and the CRO can directly load the data into Xbiom without any involvement by PointCross' data standardization team. However, non-SEND, unstructured, or alternative formatted LIMS extracts require data curation and conversion to a universal data model to enable the data to be visualized and analyzed in Xbiom, and this normally takes only a few hours upon receipt of the raw data.

Q4. What are the implications of using SEND data that is not considered GLP to interpret a study?

A4. PointCross: A study report in a GLP study is considered GLP because the data in the study report is traceable back to the LIMS system, and it is audited before signature. During interim monitoring, the only data that is used is what comes from the CRO using their LIMS system as the source.

SEND, on the other hand, is a separate process done by separate people who take the GLP LIMS data and reconstruct it according to the SENDIG model and CT to generate SEND. There is no traceability required, or possible, and it is entirely up to the SEND preparer to confirm that it is capable of regenerating the same summary data as reported in the GLP Study Report.

Because a 100% consistency check of thus prepared SEND against the Study Report is considered expensive by many SEND preparers – they resort to a spot-check. PointCross does a 100% check by comparing it against the SRR, which is a digital extraction of the Study Report.

The implication, in our perspective is that the user of SEND data must be "aware" of whether the data has been 100% checked against GLP or not before making interpretations or decisions based upon that data.

Dragomir: According to the GLP, the Study Director is responsible for all aspects of the study, including the study results interpretation. The individual and summary results as well as some statistical analyses as defined in the Study Protocol (Plan) are typically created within the validated LIMS at the Test Facility. SEND-like data (extracts from the LIMS) while study is ongoing and the SEND packages created by the CRO SEND teams or third party are not audited and there is no regulatory requirement for these to be GLP-compliant. This data is used by the Sponsors and FDA to generate their own opinion on the study outcomes.

Q5. It was mentioned that CRO uploads data to shared folder and that this data are accessed from there for integration. Has the VDR been used for this exchange? If not why?

A5. PointCross: If Xbiom is used, then the VDR (Virtual Data Room, a secure encrypted shared space) is used for automatic loading according to a schedule, or loaded on demand by the Lab personnel. We do not recommend sharing of study data using other messaging or email applications, and accordingly we maintain the encrypted Virtual Data Room as a controlled access environment defined by the primary Sponsor or CRO customer. The VDR is a shared space that allows authenticated users authorized by roles provides a streamlined and safe environment to share such confidential data.

Dragomir: I misspoke during the webinar. We have a secure site with very strict and limited access where each particular CRO uploads the data. There is a crawler set up to check these secure sites periodically and upload the data to our system. Once certain [automated] checks are performed to confirm the successful upload, the original files are removed from the site.

Q6. Are the CROs open to this link with PointCross Xbiom to upload the interim data? Are they charging sponsors significant more cost for interim data access through Xbiom?

A6. PointCross: PointCross establishes a dedicated, encrypted VDR site for each customer that is reserved only for them, whether a Sponsor or a CRO. The sponsor's system, in this case Xbiom, automatically picks up data that has arrived for ingestion and integration. CROs that serve Sponsors have individual, secured "instances" of the VDR where their folders are structured to load (often times automatically) interim data.

PointCross is not privy to the contractual arrangement and costs agreed between the Sponsors and CROs.

Q7. Are there examples where pathologist's have used SEND data to make their interpretation and perform the peer review?

A7. Dessi: I think this question is confusing SEND with Interim Study Monitoring. Although SEND is the basis for the Xbiom system, the data is not in SEND format when it is in an analyzable format (e.g., graphs, tabulations, etc) in Xbiom. With this in mind, pathologists can use Xbiom for their interpretations and peer reviews in relation to using clinical pathology, organ weight data, etc to determine target organs or adverse

effects. The actual analysis of the slides is not done in Xbiom, however the study data surrounding histopathology is used to support their interpretation and the story.

Dragomir: It appears to me that the question relates to histopathology data. During the in-life phase of the study, such data (MI domain) might become available for pre-maturely euthanized animals, animals found dead and/or for animals scheduled for interim sacrifice. If the peer-review is done internally, our pathologists have access to the available histopath data and may explore for any corroborating evidence from the other results in the system, as indicated by Dessi above. A potential advantage (and the most common use case) is to query the system for similar microscopic findings in other studies with the same or different compounds and/or in non-treated control animals.

Q8. Is this going to cause more deviations to the ongoing studies? Won't this impact the original intent of the study from the protocol?

A8. PointCross: Monitoring any study may cause for changes in the study through a formal protocol amendment. The intention of monitoring ongoing interim studies is to understand, analyze, and view the emerging data as soon as possible after it is collected. The intention is not to make protocol deviations but if the contemporaneous understanding of the study progress informs the sponsor about the importance, value or benefit of making a protocol change on the ongoing study; or of making study design changes on other studies being contemplated then that stands to the strategic benefit of the sponsor. Absent interim monitoring, the same conclusions would likely have been made after the study was completed and the Study Report published, and then later, after the SEND data arrives. At that point a significant amount of irrecoverable time would have been lost for the sponsor.

Q9. Is the sponsor required to have a repository for all study data to do cross-study analysis or does point cross offer this?

A9. PointCross: The Sponsor is not required to have their own repository, assuming that "repository" includes the ability to analyze any study, or any study against other studies of interest.

Where a sponsor does not have their own internal repository, PointCross offers to stand-up a Software as a Service site for Xbiom on the cloud with a secure encrypted private repository and analysis/visualization capability for the sponsor. Completed (legacy) studies can be loaded for cross-study analysis and visualization against the interim data set. Cross-study analysis is possible when the studies in question are loaded in Xbiom. These can be SEND, non-SEND, or indeed interim study data.

Q10. Can the VDR be configured differently for study monitoring vs submission datasets?

A10. PointCross: Yes, a separate track can be maintained for submittable datasets to be *designated for regulatory submission* versus *raw data for ongoing study and interim monitoring*. However the design and approach is exactly the same for both. One can consider the following cases:

1. The sponsor wishes to, at the end of the study, visualize and analyze the data. Once the study report is published, the sponsor wishes to have the SEND automatically generated from the last interim data set (comprising the final dataset), and reconciled against the study report. In this case, a single data flow stream that uses the same VDR and a streamlined process can be used.
2. The sponsor wishes for the submittable SEND to be generated by the CRO. In this case separate VDR spaces are allocated for the interim data and the final submission. There are two cases to be considered here:
    a. The sponsor wishes to validate the final SEND against the Study Report and the Interim Data last established. PointCross offers a service to generate an SRR, or digital extract of the actual

Study Report to be used with a Reconciler that the sponsor can run the SEND data against the SRR.

b. The sponsor wishes to maintain a validated environment for the regulatory submission data flow, for which the two data streams for interim versus submittable maintained separately.

For any questions, or would like to chat further, please contact us at ask@pointcross.com