

September 15, 2020

To the Attention Of:

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cc: Linda Malaguti, Public and Stakeholders Engagement, Department Assistant, EMA

In response to the EMA request for feedback on:

The use of rSDV and the recent guidance on the management of clinical trials during the COVID-19 pandemic.

Introduction:

The Association of Clinical Research Organizations (ACRO) (www.acrohealth.org) represents the world's leading clinical research and technology organizations. Our fourteen member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support the majority of all biopharmaceutical sponsored clinical investigations worldwide. With more than 200,000 employees, including over 60,000 in Europe, engaged in research activities in 114 countries the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO's committee of Risk-Based Monitoring and Quality Assurance subject matter experts contributed to the responses below, providing answers to the specific questions posed around remote access for the purpose of source document verification (SDV) or source document review (SDR). The committee welcomes future discussions with the European Medicines Agency (EMA) on this topic, and greatly appreciates the opportunity to provide our insights.

General Comment:

ACRO members have interpreted the reference to SDV as inclusive of both SDV and SDR. We believe this is a common interpretation from within the industry. If the intention is to decouple SDV from SDR, we suggest clearly distinguishing the two in future guidance iterations.

The types of remote SDV used, including details of the methods used to ensure the rights, safety and wellbeing of trial participants, as well as data integrity are safeguarded:

Sponsors, CROs, technology providers, and clinical research sites around the world have created and adopted software systems specifically designed to safely and securely provide access to electronic versions of clinical trial subjects' medical records in order to conduct remote source document review (SDR) and source document verification (SDV).

Remote SDV (rSDV) can be done safely, securely, and in a compliant manner using one of the following approaches:

- Direct access to electronic medical records (EMR)
- Video (e.g., WebEx, Zoom) is useful for reviewing certain types of documents that need to be seen unredacted (e.g., ensuring the ICF is signed)

- Third party file transfer platform
 - Using sponsor-owned or -managed systems that enable sites to control document redaction and document upload
 - Using site-owned or -managed systems that enable sites to control access to source documents, technologically limit reproduction or download of documents, audit access to documents (including views, changes and deletion)
- Electronic messaging* (e.g., fax or email)

These methods are available and, in most cases, free to use for sites. With these types of systems, sites are able to ensure the protection of their patients' rights by contracting directly with providers, managing workflows specially designed for rSDV. This eliminates duplication and errors resulting from other forms of document exchange. Sites can also ensure compliance with GDPR and other health data protections when the servers, systems and reviewers are all located within the EU. Across member companies, when CRAs are utilizing the video option, they are instructed to be in a secure location without any screenshots or photographs allowed.

*Typically, across ACRO member companies, the CRA requests the data to be sent/viewed remotely. The site staff are given instructions to copy and redact the data appropriately for the method being utilized (except for ICF reviews over video). In some situations, the site staff must also retain a copy of the redacted source data. Emailed documents must be encrypted with an agreed password specific to the site. rSDV is completed in a timely fashion and any received documents should be deleted from both the individual CRA's computer and the mail server through the internal IT department.

The context of use: short descriptions of the clinical trial and which data were verified by rSDV:

ACRO member companies have reported use of rSDV globally on over 100 clinical trials across countries including United States of America, United Kingdom, Canada, Australia, New Zealand, Germany, Tonga, Turkey and Bulgaria as a result of the COVID-19 pandemic.

For sites limited to more burdensome approaches, ACRO member companies have intentionally focused on critical documents. Documents for review have been determined based upon central monitoring findings related to primary efficacy and safety data, and/or study-specific assessments. Documents that are most commonly reviewed for rSDV include concomitant medications, adverse events, serious adverse events, select medical history, general case history notes, informed consent, EMR records, radiography reports, laboratory reports, ECG reports and investigational product reports/logs. Primary emphasis has been placed on screening, baseline and randomization to confirm inclusion/exclusion criteria.

In general, review of data is performed at a subject visit or procedure level as opposed to an individual data point level (e.g., visit 2 or blood pressure collection vs. systolic blood pressure value). An individual data point does not provide the supported context to perform adequate SDR whereas a visit or procedure level document better supports SDR and protocol adherence practices.

How the introduction of remote SDV was communicated to trial participants, investigator sites, Independent Ethics Committees and regulatory agencies:

Given the limitations established by the COVID-19 guidance, very few studies could apply for the use of rSDV within the EU. It was only possible for 1) clinical trials involving COVID-19 treatment or prevention, or 2) pivotal trials in the final data cleaning steps before database lock that were investigating serious or life-threatening conditions with no current satisfactory treatment.

In the case when the above criteria were met, submissions following country requirements were completed and only upon approval, was rSDV then implemented. We've outlined examples from our member companies below of how the introduction of rSDV was communicated to each relevant group.

Communication to trial participants:

- Monitors instructed site staff to communicate the use of rSDV to trial participants, if/as required in each country.
- Study participants were informed through an updated ICF when the country guidelines required it.
- Country-specific example:
 - Turkey: the possibility of remote SDV/SDR was added in the ICFs in order to inform the participants.

Communication to investigator sites:

- Typically, monitors or sponsors had direct contact with the sites to explain why rSDV was required and discussed what method could be implemented for their sites. Depending on local legislation and practices, it was not always possible to use the same methodology across all sites globally.
- Some ACRO member companies reported the use of signed data review agreements and provided training on the process to ensure compliance with applicable regulations/laws.
- Sites were engaged to identify the options that each institution had to proceed with rSDV. Given the lack of consistency between systems and processes of each site, the approach was very much targeted to each site.
- Sites and CRAs agreed that no patient data shared during video calls would be recorded, photographed, or saved as screen shots.

Communication to Independent Ethics Committees:

- Engagements with IECs occurred about consent, re-consent and substantial amendments.
- Clinical operations teams were guided to follow their local regulations, as well as project-specific guidance before implementing rSDV. Examples do vary by study and country. An example of what was communicated to the IRB is 1) an updated protocol to explain the introduction of rSDV, 2) an updated ICF so that patients could re-consent and 3) Substantial Amendments submitted to the IEC/RAs.

Communication to Regulatory Authorities:

- Occurred primarily via substantial amendments to protocols and monitoring plans although these cases have been rare due to the uncertainty regarding country specific regulatory reporting requirements.

EU Member States where remote SDV was implemented:

ACRO member companies have reported use of rSDV at a small number of sites within the EU, which stands in contrast to what we're seeing on a global level. One ACRO member company reported that the only EU member state where they were able to implement rSDV was Bulgaria. Another ACRO member company reported limited requests for rSDV only in Italy and France. A third ACRO member company reported that only one request was submitted and approved across all of the EU. Collectively, ACRO members have seen that implementation in EU member states is extremely limited, especially in comparison to non-EU countries.

There is a reticence to apply for rSDV, due to the extensive caveats mandated by the guidance coupled with the concerns around potential missteps resulting in penalties.

The failure to expressly permit safe and secure electronic alternatives to SDV has had a negative impact on:

- The validity and accuracy of study data
- Data base lock and study completion

- Site staff workload and burden
- The placement of new clinical trials/sites in EU countries, particularly those for COVID-19

Limitations/challenges, impact of the various national restrictions on the options used, time to implement the type of remote SDV chosen:

Uncertainty and national-level restrictions have delayed or limited the adoption of safe, secure and reliable methods of conducting SDV. We do not believe the restrictions have had a meaningful additional benefit to the health, safety or privacy of clinical trial participants.

One ACRO member company reported that the following EU Member states did grant *some* level of rSDV approval: Spain, France, Italy, Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Hungary, Latvia, Netherlands, Poland, Portugal, Romania, Spain, Turkey and Bulgaria. However, rSDV was not performed on all projects or in all the countries where approval was eventually granted. In several of these cases, by the time all requirements were identified as “met”, travel to the site had started to resume.

As site and non-essential site personnel were moved to remote work, sites were unable to benefit from re-use opportunities as other documents and materials were shifted to electronic systems.

There have been more limitations than would have been desirable given that the situation forced industry to opt for rSDV to ensure the clinical trial’s data and patient safety was maintained during COVID-19.

Specific challenges and limitations reported by ACRO member companies:

- EMA guidelines with specific instructions about rSDV came late. Some steps towards implementation had been started when the EMA guidelines were released, which were contradictory to the processes already put into place.
- Countries were issuing their guidelines for clinical trials that helped explain what was required in each country, however, the content was inconsistent from one country to the next. Some local guidelines had a specific mention of rSDV while others did not. In addition, after EMA released the updated guidelines on 28 April, which resulted in some countries changing their previous approaches. This series of communications/guidelines put some CROs and sponsors in a position of non-compliance, which had to be quickly resolved.
- The lack of consistency between countries in terms of requirements as to what is potentially “approvable” criteria for rSDV. This makes the strategy for each clinical trial especially difficult. Especially in situations where in-person visits were cancelled and the administrative burden to have rSDV submitted and approved required lengthy timelines. The alternatives to ensure the clinical trial data was kept accurate and CT procedures were followed correctly were very limited and required a complete change of the previously agreed upon clinical management plan.
- Lack of availability and consistency of technologies used to share source documents for review. While certain sites have EMR and were already allowed to perform on-site SDV using technology and well managed usernames/passwords for the CRA role, other sites with paper source did not allow for an efficient rSDV process.
- Concerns from the Spanish agency. Even if they wanted to accept the use of EMR, they were concerned about the data visible to us beyond the data that we should be able to review for a specific study.

- Increased and excessive burden on site staff was a challenge. Early on, there were some complaints from sites about alternative strategies. Redaction and transmission are extra work for the site. From the sponsor perspective, the monitoring time is increased and the SDV cannot be marked complete based on redacted data verification (since the data cannot be cleaned). This is not an issue with non-redacted, electronic methods, to which sites responded favorably after the initial set up.

New terminology and processes introduced for remote SDV in the EU:

As stated earlier, terminology and lack of global consistency has limited wider adoption of rSDV thus impacting subject safety and data quality during the COVID-19 pandemic.

Examples of area where further information would be valuable:

- Aligned global terminology to ensure consistent and aligned global understanding as variance has been noted. E.g., SDV, SDR, rSDV, redacted source, etc.
- Global consistency regarding re-monitoring of data review via rSDV. I.e., FDA does not require this, EMA does at times.
- Review and consider adjustments to relevant privacy guidance.
- Introduction of a CRA CDA, per EMA Guidance v.3.
- Additional perspective or guidelines regarding the destruction of certified copies.

Additional comments, feedback and challenges encountered with the implementation of remote SDV:

The current pandemic has highlighted the consequential impacts of requiring 100% SDR/SDV and the undue and unnecessary burden that that obligation imposes on site personnel. **ACRO believes that a risk-based approach to SDR/SDV best serves the interest of sites, patients and the whole of the clinical research community.** We suggest that the EMA should discourage the use of 100% SDR or SDR in every case.

In addition, EMA should evaluate the recommendation to re-monitor pseudonymised data, since data reviewed remotely can accurately reflect source documentation. We believe the re-monitoring process to be redundant, especially when the focus should instead be on more critical and real-time data.

In addition, we suggest removing the requirement that remote SDV should be considered a substantial amendment.

Many challenges have arisen as a result of the lack of cohesiveness across EU member states. ACRO would welcome an EU-wide position that expands the approach beyond the limited case situations listed in the current COVID-19 related guidance. E.g., permitting remote access to electronic medical records (EMRs) for any study, not just those for COVID-19 Rx or prevention studies, or not solely limited to the final data cleaning for a very small subset of projects.

ACRO asks the EMA to consider allowing the use of secure viewing portals to upload unredacted source (as is currently allowed and done in the US). Currently, the use of redacted data review is permitted, but that low-value activity cannot be considered true source.

Challenges:

- Regulatory: Ensuring rSDV is implemented in line with regulations and guidance. This is due to:
 - Lack of a clear and globally aligned definition of rSDV
 - Lack of clear regulation/guidance for rSDV in many countries/regions
 - Discrepant, sometimes contradictory, adoption of the EMA guidance at the country-level
 - In some cases, conflicting guidance from different authorities
 - Frequent changes of EMA and country-level guidance/regulations.

- Restricted technology options:
 - New technology vendor and platform options for rSDV are limited due to the EMA guidance implying a data localization obligation.
- Company-level:
 - Sponsor company requests for secure methods to allow non-redacted source data uploads, or to remove or minimize the need for on-site re-SDV.

Lessons learned and views on the use of remote SDV:

ACRO believes that rSDV is a steppingstone in a transition to enhanced virtual/remote monitoring activities. The benefits of enhanced virtual monitoring activities include earlier identification of risk to subject safety and data quality while supporting more efficient clinical trial development processes.

Some lessons learned regarding data include:

- Enhanced engagement with sites/clinical investigators to ensure the technology support site activities. Examples of technology enhancements to support sites include:
 - Technology to improve site document capture techniques
 - Focus on remote access to EMR
 - Technology that auto redacts PHI and PII
- Aligned communication with regulatory authorities, consistency in reporting expectations will help the industry immensely.
- Sites are much more receptive to these practices as a result of COVID-19 than they were historically. Many sites have said they actually prefer rSDV over onsite monitoring as it frees time, supports more prompt responses to issues ensuring better and more timely corrective actions.

In Conclusion & ACRO Point of Contact:

ACRO believes action should be taken to create an environment within the EU that enables prompt implementation procedures for rSDV. This will serve as a risk mitigation mechanism as the global pandemic continues over the next coming months.

We would like to reiterate how much we appreciate the opportunity to provide EMA with this feedback. We hope to continue this discussion and stand ready and available to meet with the Agency, if this would be helpful. Should you have any follow up questions, please reach to the EMA's point of contact within ACRO, Karen Noonan (knoonan@acrohealth.org).

Respectfully Submitted,



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