

26 April 2021

To: Fergus Sweeney
Head of Clinical Studies and Manufacturing, EMA
Agnès Mathieu-Mendes
Deputy Head of Unit B4 – Medical products: quality, safety, innovation, European Commission

From: Karen Noonan, Senior Vice President, Global Regulatory Policy, ACRO

RE: EMA [Draft Guideline on Electronic Systems and Electronic Data in Clinical Trials](#):
Request for Timely Release of Guidance and ACRO Policy Recommendations for Inclusion

Dear Fergus and Agnès,

The Association of Clinical Research Organizations (ACRO) (www.acrohealth.org) represents the world's leading clinical research and technology organizations. ACRO member companies include full-service global CROs that manage a majority of commercially-sponsored trials, and the technology/data companies whose software and analytics support a preponderance of trials across Europe. 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. 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.

We are writing to both of you because of your leadership in European clinical trial regulatory policy and ACRO's position that eSystems guidance is a necessary element of a successful EU Pharmaceutical Strategy.

The stakeholder community has been waiting for the long-expected release of EMA's [Guideline on Electronic Systems and Electronic Data in Clinical Trials](#). On 25 July 2019, the EMA issued its "[Qualification opinion on eSource Direct Data Capture \(DDC\) \(EMA/CHMP/SAWP/483349/2019\)](#)." The Agency notes on page 2 of this document that "*a guideline on Electronic Systems and Electronic Data in Clinical Trials is currently under development at EMA, and once into force it would constitute the definitive guidance.*" More recently, we note that on 08 May 2020, the Agency issued the "[Work plan 2020 of the Good Clinical Practice Inspectors' Working Group \(EMA/INS/GCP/637644 /2019\)](#)". On page 3, this document notes the plan to publish the Guideline on Electronic Systems and Electronic Data in Clinical Trials during 2020 for public consultation. Further, during 2020, EMA issued its *Notice to sponsors on validation and qualification of computerized systems used in clinical trials*, and the Q&A: Good clinical practice (GCP) website has incorporated additional Q&A's. However, this content appears to represent incremental changes in the EMA's expectations but without consultative input being sought beforehand.

Timely release of Electronic Systems Guidance even more important due to COVID-19 pandemic

The disruption caused by the COVID-19 pandemic highlights the increased urgency for the release of this Guidance. Specifically, the pandemic has compelled stakeholders within clinical research to consider new, innovative approaches to trial design and conduct that increasingly leverage electronic systems. The digitization of clinical trials began well before the COVID-19 pandemic – from recruitment and retention to electronic consent, and the use of mobile technologies such as sensors and wearables. The disruption caused by the pandemic is expediting and necessitating the embracing of digital innovations and solutions including but not limited to decentralized clinical trials; utilization within trials of Patient Devices (sensors, wearables); [remote] eConsent; and remote and centralized monitoring (including source data review / verification and remote review of investigator site files). Release of this new Guidance will provide stakeholders with assurance and confidence that innovative approaches being developed and adopted during these times will have longer-term applicability. Moreover, the release of the Guidance will help to ensure that EU/EEA is viewed globally as a region that constructively and innovatively promotes and supports the wider utilization of advanced technology-based solutions for clinical research. Now, more than ever, it is important for guidance to keep pace with technological innovation. For example, there is a need to update computer system validation (CSV) guidance in order encourage the adoption of modern cloud-based solutions.

Opportunity to incorporate key policy issues into Electronic Systems Guidance

The delay in the release of this Guidance has created an opportunity to take account of lessons learned from the increased use of technological approaches during the COVID-19 pandemic. The delay also provides an opportunity to review a handful of topics related to electronic systems where an absence of clarity has negatively impacted clinical research. The following five topics are within the scope of the expected Electronic Systems Guidance. The Guidance would be an efficient vehicle for addressing and providing clarity on these topics.

- I. Remote SDR and remote SDV
- II. TMF issues: Draft Documents; Quality Issue Reports; and Secondary Locations
- III. Site Concerns: Investigator Site Files and Validation of site processes and facilities
- IV. Bring Your Own Device (BYOD) for eCOA
- V. Refinement of EMA website page “Q&A: Good clinical practice (GCP)”

In addition to these five issues, there is an additional topic that ACRO would like to highlight: eConsent and eSignatures. We realize that this topic may possibly be outside of the scope of the Electronic Systems Guidance. So, we have not included this issue within the body of this letter. However, because eConsent and eSignatures are vital components of modernized, 21st century clinical trials, we have attached a brief Appendix to this letter which outlines ACRO’s request to you on the topic of eConsent and eSignatures.

I. Enabling risk-proportionate, remote SDR and remote SDV in Europe

Concern:

European data protection laws may be interpreted as precluding remote source data review (rSDR) and remote source data verification (rSDV) in the EU, even under exigent circumstances. ACRO emphasizes that it is important to distinguish between source data *review* and source data *verification*. While SDV focuses on identification of transcription errors, SDR is in many ways the more significant value-added activity because it enables verification of subject eligibility, safety and protocol compliance. Source data review is crucial because of the history in patient notes, which is so important.

ACRO thanks the EMA GCP IWG and the DG Sante CTEG for collaborating to gather information from national DPAs about the position of the different Member States to rSDR/SDV in the context of GDPR and data protection. In addition, ACRO thanks the EMA for the most recent update to its key clinical trial management guidance. Although Version #4 (dated 04 February 2021) of the EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic contains helpful updates on remote SDV, the guidance does not go far enough and does not specifically make reference to being inclusive of remote source data review. Additionally, the proposed option of utilizing review of pseudonymized data cannot be considered true SDV as it does not meet the full ALCOA+ principles of enabling the recipient to confirm the data is 'attributable' or 'complete.' Consequently, there is a need, per the EMA guidance, to undertake at least some degree of re-monitoring on-site, rendering the activity inefficient and placing a duplicate burden on site staff. In addition to site burden, this slows down research -- and therefore the speed at which new medicines can be brought to patients.

Proposed Solution and Request:

In order to facilitate the use of rSDR and rSDV in Europe – encourage a risk-proportionate approach to monitoring that focuses on *critical study site documentation and source data* as a best practice, while discouraging 100 percent remote SDV. ACRO asks you to consider issuing new guidance that does the following—

- assures stakeholders that “processing operations related to reliability and safety purposes” enables remote review of unredacted data for purposes of source data review or source data verification (SDR/SDV) on the grounds of compliance with a legal obligation to which the controllers (sponsors and/or clinic-institution of the investigators/investigators) are subject under the requirements of GCP
- encourages EU/EEA-wide agreement to the use of common/EEA monitoring and risk management plans incorporating rSDR and rSDV across all Member States
- stresses that remote monitoring and rSDR/rSDV must not result in confidential patient information being sent to the sponsor/CRO or being stored by the sponsor/CRO if this has not already been addressed in the participant information sheet. For example, unredacted copies of medical notes, from which individuals may be identified, should not be emailed or posted to the sponsor. Source data verification may be done remotely by electronic means if the necessary security arrangements

can be put in place. For example, this could be done by using video calls, via controlled access to relevant electronic health records, or certified copies thereof (e.g., the use of a secure document sharing platform), but sponsors/CROs must not retain any screenshots or electronic records.

- states that the following four conditions shall adequately satisfy requirements for Electronic Health Record systems:
 - read only access
 - audit trail to enable site to confirm that monitor only reviewed trial subject notes
 - requirement for CRA to view in a secure location. For example, from their (home) office, rather than a public area
 - confirmation from the CRA that they will not download, screenshot or screen-print

II. Trial Master Files: Draft Documents and Secondary Locations

TMF: Draft Documents

Concern

Section 3.5.2 of the EMA Guidance on Content, Management and Archiving of the TMF indicates that documentation to demonstrate the review process of key documents should be present in the TMF. However, there is a lack of clarity regarding scope (which documents this applies to) and adequacy (the expected level of documentation that is required).

Proposed solution and request

ACRO believes that the planned Electronic Systems Guidance is an ideal opportunity for you to provide vital clarification on this topic. This clarification could be achieved via the inclusion of brief, circumscribed language such as the following—

- *It is recommended that a risk-proportionate approach is taken to the retention of draft documentation*
- *Retention should be limited to core documents such as the Protocol, IB, ICF, CSR, and Key Project Plans such as CMP, SAP*
- *Include a discussion on the retention of “core” system development documentation and “trial Specific” documentation*
- *Retention should be limited to review comments on drafts of these core documents which have a potential impact on critical data/processes, subject safety and/or data integrity*

TMF: Secondary Locations

Concern

EMA TMF Guidance 2018 requires the archiving of any system that contains ‘dynamic files’ of PDF files and also that ‘any electronic system that holds trial data and metadata (e.g., audit trails) required for reconstruction’ should be archived so these can be retrieved as usable datasets. It is impractical for

companies to maintain multiple systems for 25 years. Moreover, it is unclear what would constitute an adequate solution (e.g., a visit report generated in a CTMS system where the PDF report is filed in TMF and there is need to retain the original dynamic file in CTMS).

Proposed solution and request

ACRO believes that the planned Electronic Systems Guidance is an ideal opportunity for you to provide vital clarification on this topic. This clarification could be achieved via the inclusion of brief, circumscribed language such as the following—

- *Stakeholders should ensure a risk-proportionate approach is taken to the storage of systems/data based on the criticality of the metadata/ audit trail which is relevant to retain to reconstruct study management and document their rationale for the approach taken.*
- *We recommend that the guidance should recognize that what is needed over 25 years is to access key data generated by the systems and details of how it was configured*
- *Also, there is a perception that windows or other event logs created during routine system operation should be retained as part of the TMF – these should be maintained for forensic purposes only for a limited period*

III. Site Concerns: Investigator Site Files (ISFs) and Validation of Processes and Facilities

Sites: Investigator Site Files (ISFs)

Concern

The EMA TMF Guidance document 2018 provides guidance on expectations for an e-ISF. However, there is a lack of clarity in 2 areas: (1) Acceptable e-ISF formats & (2) Level of expected Sponsor due diligence.

Proposed solution and request

ACRO believes that the planned Electronic Systems Guidance is an ideal opportunity for you to provide vital clarification on this topic. This clarification could be achieved via the inclusion of brief, circumscribed language such as the following—

- *While this remains an Investigator responsibility, researchers will have adequately satisfied requirements for an e-ISF system/repository if they have established (1) controlled access available to Sponsor/CRO and site staff and (2) the ability to segregate blinded /unblinded information. Responsibility for the system compliance lies with the site and not with the Sponsor/CRO.*

Sites: Validation of Processes and Facilities

Concern

We see variations in expectations from inspectors and auditors across the EU region with respect to the extent to which they expect monitoring staff to evaluate site SOPs and facilities. For example, some expect monitoring staff not only to check that sites have relevant SOPs for their activities in place but to have also

reviewed those SOPs for content appropriateness. This can run into many hours to review and the Sponsor/CRO really has little or no influence over the site's responsiveness to change anything.

Proposed solution and request

ACRO believes that the planned Electronic Systems Guidance is an ideal opportunity for you to provide vital clarification on this topic. This clarification could be achieved via the inclusion of brief, circumscribed language such as the following—

- *It is appropriate to take a risk-proportionate approach to check if the site has SOPs in place and to ask the site to describe their process. Moreover, only if the site seems unclear on the process or it appears non-compliant with GCP should the CRO/Sponsor scrutinize the SOPs themselves in any detail.*

IV. Bring Your Own Device (BYOD)

Concern

The number of projects utilizing direct patient feedback via ePRO is growing exponentially. Legacy processes require the provision of devices to patients to minimize the variation in responses from patients. However, new research indicates that patient compliance and retention are increased by allowing patients to use their own device (BYOD).

With BYOD, sponsors and CROs do not control the overall look and feel of the device and hence there is concern that the device variability introduces variability to the responses by patients. Confirmation of equivalence can be achieved via lengthy and complex equivalence studies. However, this current standard approach does not work with a BYOD approach as it is not possible to test all variations of mobile devices. Recent publications show that it is possible to migrate instruments onto new variable devices and still achieve equivalence across the BYOD device landscape.¹

Proposed solution and request

New research shows that most instruments only consist of 3-4 scale types (or widgets). These are Verbal Rating Scale, Numeric Rating Scale and Visual Analog Scale. Scientific evidence shows that equivalence can be

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[Standards for Instrument Migration When Implementing Paper Patient-Reported Outcome Instruments Electronically: Recommendations from a Qualitative Synthesis of Cognitive Interview and Usability Studies Jan2018](#)

[Measurement Equivalence of Patient-Reported Outcome Measure Response Scale Types Collected Using Bring Your Own Device Compared to Paper and a Provisioned Device: Results of a Randomized Equivalence Trial May 2018](#)

Measurement Equivalence of Patient-Reported Outcome Measures Migrated to Electronic Formats: A Review of Evidence and Recommendations for Clinical Trials and Bring Your Own Device. Dec 2019.
(<https://link.springer.com/article/10.1177/2168479018793369>)

shown on widget level and therefore there is no need to test equivalence of instruments that utilize the three standard widgets. The literature shows that this applies independently of screen size and operating system for the standard widgets.

ACRO believes that the planned Electronic Systems Guidance is an ideal opportunity for you to provide vital clarification on this topic. This clarification could be achieved via the inclusion of brief, circumscribed language such as the following—

- *In order to allow for more efficient and faster implementation of ePRO systems in both standard randomized clinical trials and in decentralized clinical trials with BYOD, EMA supports the new process of Expert Screen Review for PROMs that are composed of well understood response scale types, whereby competent experts review screen layout and assure that the measure's items and response scale types have been implemented in line with C-Path recommendations.² Allowing patients to choose to use their own device already shows benefits for patients and increases compliance and retention within a clinical trial.*

V. Refinement of EMA website page “Q&A: Good clinical practice (GCP)”

Concern

Updates to the EMA website page “Q&A: Good Clinical Practice (GCP)” are often extremely helpful to stakeholders but may also lead to concerns as these updates appear with no prior notification, communication, nor consultation with stakeholders.

<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp>

Proposed solution and request

ACRO asks you to consider two improvements to the Q&A GCP website page:

Notification and Brief Consultation for New Content

It would be very helpful if EMA could implement a mechanism to notify stakeholders of draft content for updates to this page and provide a brief consultation period for input and feedback from stakeholders before finalization of the content.

Opportunity for Stakeholders to Propose New Content

Moreover, as stakeholders move increasingly from the original, pen-and-paper model of GCP towards modernized, digital, remote approaches in clinical trials, this will raise new questions surrounding GCP. Because of this it would be helpful to offer stakeholders a mechanism to propose specific new topics for inclusion on this Q&A page.

2

Best Practices for Participant Registration in Clinical Trials Using Bring Your Own Device (BYOD) Technology for Data Collection, Critical Path Institute, Best Practices Documents

<https://c-path.org/wp-content/uploads/2021/04/BestPractices5.pdf>

APPENDIX

Enabling eConsent and eSignatures throughout Europe in the Interest of Clinical Trial Modernization

Concern

ACRO notes that the proposed guidance on Electronic Systems and Electronic Data in Clinical Trials may not address e-consent and e-signatures, as this topic may be excluded from the scope of the guideline. However, clinical trial modernization in the 21st century and a focus on patient-centeredness means that trials need to incorporate digital and remote solutions and the lack of harmonization and standardization in Member States' acceptance of eConsent and eSignatures is a key barrier to optimized, 21st century clinical trials that utilize digital, remote solutions to meet the needs of participants, and adds to the cost and complexity of clinical research in Europe. The use of eConsent facilitates and supports ongoing initiatives to make the consent process more comprehensive and inclusive. By facilitating a consent discussion with a participant who is not physically at the site, eConsent expands participation to populations traditionally not afforded clinical research opportunities.

ACRO notes that this topic is even more timely, given the release of the ICH E6(R3) Draft Principles on 19 April 2021. The [Draft Principles](#) highlight the importance of technology and their specific potential for the informed consent process (emphasis added):

*The principles are intended to support improved and more efficient approaches to trial design and conduct. For example, **innovative digital health technologies may expand the possible approaches to trial conduct**. Such technologies can be incorporated in existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials. **This will aid in keeping clinical trial conduct in line with advancing science and technological developments**. The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the particular trial design. The use of innovative technologies may help enable those designing and conducting a trial to include relevant patient populations. (page 2)*

3.2

*The process and information provided should be designed to achieve the primary objective of enabling trial participants to make an informed decision on whether or not to participate in the trial. The informed consent process should take into consideration relevant aspects of the trial such as characteristics of the participants, the trial design, anticipated benefit and risk of medical intervention(s), setting and 19 April 2021 4 context in which the trial will be conducted (e.g., trials in emergency situations), **and the potential use of technology to inform participants and obtain informed consent**. (page 3)*

Proposed solution and request

ACRO acknowledges that the varied approaches to eConsent and eSignatures are based on national Member State regulations. However, ACRO asks you to encourage Member States to review their regulations that prevent use of eConsent and eSignatures, in order to promote patient centricity and access to clinical research; reduce the complexity and associated costs of managing clinical trials in multiple Member States; and enhance the perception of the EU as a supporter of innovation in clinical research.

Additionally, although several Member States permit e-consent and e-signature, there is currently little consensus on the standards that should be applied. Consequently, it would be helpful for new EMA guidance to recommend a standard approach in those Member States allowing e-consent and e-signature which:

- states that an acceptable e-signature for clinical trial purposes should be linked to the respective record and include details of the date and time at which the signature was applied.
- states that an e-Signature is acceptable for all clinical trial documents listed in the ICH list of essential documents for which a signature is required.
- describes the following requirements as adequately satisfying an e-consent system:
 - Participants must be informed of the nature, significance, implications and risks of the trial in an interview with the investigator, or another member of the investigating team
 - The interview should involve two-way communication in real time and allow confirmation of the participant's identity
 - Information about the trial does not have to be in writing and can be provided to potential participants using electronic methods. However, special attention should be paid to the information needs of specific patient populations and those of individual participants
 - Informed consent must be recorded 'in writing'. Electronic methods for documenting consent can be considered to be in writing
 - A copy (physical or electronic) of the signed consent form should be provided to the participant
- if consent and signature are both remote, the investigator/designee must implement a method to ensure the identity of the participant (e.g., verification of state identification or other identifying documents or use of personal questions or visual methods).

Thank you, in advance, for considering ACRO's recommendations.
Please contact ACRO if we can answer any questions or provide additional details.

Respectfully submitted,



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