ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

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From: Karen Noonan, Senior Vice President, Global Regulatory Policy
ACRO (Association of Clinical Research Organizations)

RE: ACRO Feedback on Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic Version 2 (27/03/2020)

Thank you very much for your email and for the opportunity to provide comments on the Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic Version 2 (27/03/2020).

ACRO's comments are included immediately below.

Please let me know if ACRO can provide any additional assistance or answer any questions at all.
The global CRO and technology company members of ACRO stand ready to be a resource to you.

Respectfully submitted,

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ACRO Recommendations			
Page and section number	**Current Text**	**Concern**	**ACRO recommendation–**
Page 3, bullet 4	There may be a need for critical laboratory tests, imaging or other diagnostic tests to be performed for trial participant safety. In case the trial participant cannot reach the site to have these performed, it is acceptable that laboratory, imaging or other diagnostic tests are done at a local laboratory (or relevant clinical facility for other tests) authorised/certified (as legally required nationally) to perform such tests routinely (e.g. blood cell count, liver function test, X-ray, ECG etc.), if this can be done within local restrictions on social distancing. The sites should inform the sponsor about such cases. Local analysis can be used for safety decisions. If this is a trial endpoint and the samples cannot be shipped to the central	We recommend clarifying that the sponsor/CRO will require access to local labs' normal ranges and certification information to stay in compliance should the data be used for safety and efficacy determinations.	Add in the following additional language: It is important that the sponsor/CRO is given access to the normal ranges and certification information of any additional laboratory used in order to support the use and evaluation of results.

	lab, analysis should be performed locally and then explained, assessed and reported in the clinical study report following ICH E3.		
Page 3, final sentence	Changes should be well balanced, taking into account in particular the legitimate interest of trial sites in avoiding further burden in terms of time and staffing during the COVID-19 pandemic.	We recommend adding clarity here to confirm that the rationale for such changes should be fully documented.	Add in the following additional language: Alternative arrangements, consistent with the protocol to the extent possible, should be fully documented with a well-reasoned rationale as to how they will ensure patient safety, data integrity and the protection of personal data.
Page 4; Section 4	4. Safety Reporting Sponsors are expected to continue safety reporting in adherence to EU and national legal frameworks (Directive 2001/205; CT-36). When per protocol physical visits are reduced or postponed, it is important that the investigator continue collecting adverse events from the participant through alternative means , e.g. by phone.	Capacity issues related to COVID-19 may prevent timely reporting.	Sponsors are expected to continue safety reporting in adherence to EU and national legal frameworks (Directive 2001/205; CT-36) where possible; if reporting is not possible within the timelines, it should be undertaken as soon as practicable. When per protocol physical visits are reduced or postponed, it is important that the investigator continue collecting adverse events from the participant through alternative means, e.g. by phone.
Page 9, lines 11-14	So-called remote source data verification (e.g. providing sponsor with copies of medical records or	With appropriate controls in place, trial participants' rights can be protected in accordance with data privacy	Change current text to the following text:

	remote access to electronic medical records) is currently not allowed in most Member States as it might infringe trial participants' rights. In addition, provision of redacted/ de-identified pdfs files will not be acceptable as it puts disproportionate burden on site staff.	requirements, and there are sites within the European Union that have the capacity to support the process of either providing redacted/de-identified (i.e., pseudonymized) records for remote data verification, or providing remote, read only access limited to trial participants electronic medical records. Below we outline (1) recommended controls that would protect EU participants' rights while permitting remote source data verification, and (2) considerations for permitting sites to make their own individual determinations of whether or not they are willing and able to support remote data verification. **(1) Protection of trial participants' rights** We consider that implementation of the following controls would appropriately protect EU trial participants' rights while permitting remote source data verification: • Conducting a trial risk assessment to establish the risk to the trial participants and the study if monitoring of source documents cannot continue in some form in the near term. • Consulting with the sponsor to verify their agreement to the process.	If permitted by relevant national authorities, clinical trial sites should make their own determination of whether or not their individual circumstances make the provision of redacted/de-identified (pseudonymized) remote data verification manageable at their site, or provide direct, suitably controlled remote access to electronic medical records, in a way that protects trial participants' rights and does not place a disproportionate burden on site staff.

		• Consulting with the principal investigator (PI) at each site to establish whether the provision of *copies of medical records or remote access to electronic medical records* is feasible and manageable for their site • If the sponsor and PI confirm their agreement to the conduct of remote source data verification in writing, inform the Ethics Committee and Regulatory Authority where required before proceeding, provided that the remote source data verification process is permitted by the relevant national authority. • Site staff and Monitors are trained on the remote source data verification process • Site staff obtain consent from each trial participant to permit the remote review of their records for study purposes If a trial participant does not consent to remote review of their records, no remote source data verification will occur for that participant. • Performance of remote source data verification by the Monitor may only occur in locations that prevent unauthorized third party viewing, and through a secure	

		internet connection (where applicable) • If the agreed remote source data verification technique involves site redaction/de-identification (pseudonymization) of source records: ○ The Monitors provides a request to the site for the specific participant's trial records required to verify the source documents to be reviewed ○ Site staff confirms study participant consent was obtained as outlined above ○ Site staff will create certified copies of the requested participant's records (per ICH-GCP E6 (R2) section 1.63), redact/de-identify (i.e., pseudonymise) the certified copies, maintaining a copy at site, and send the pseudonymized certified copies to the Monitor using a secure transfer mechanism. ○ The Monitor stores the records securely, completes the monitoring	

		task and then securely destroys the copies • If the agreed remote source data verification technique involves site providing the Monitor with remote access to the site electronic medical record (EMR) system: ○ Regional or national regulatory authority rules must permit this process. ○ Institutional rules must permit the remote read-only access of Monitors to the EMR system. ○ Site staff confirms study participant consent was obtained as outlined above. ○ The EMR system must have an audit trail. ○ There must be unique password-controlled access to the EMR system assigned to each member of site staff. ○ There is unique password-controlled, read-only access to the EMR system assigned to the Monitor. ○ EMR access is restricted only to trial participants' records and other patient	

		data will not be accessible to the Monitor. **(2) Disproportionate burden on site staff related to the provision of "*redacted/ de-identified pdfs*"** There are circumstances where remote verification of trial participant data through the use of redacted/de-identified (i.e., pseudonymized) copies of source documents may provide an efficient mechanism for confirmation that the trial data reported in Case Report Forms (CRFs) corresponds to the data included in the trial participant source documents. Indeed, ACRO member companies have found many sites (approximately 20% of sites globally) have reported they are willing and able to support remote data verification, subject to staff availability, through the provision of redacted/de-identified (pseudonymized) certified copies to Monitors. In addition, the COVID-19 pandemic will not impact all sites the same way, resulting in some sites having greater capacity to support remote data verification	

		through the provision of redacted/de-identified (pseudonymized) records to Monitors. Accordingly, we recommend a risk-based approach dependent on the actual circumstances affecting specific sites involved. We have identified that, without limitation, in the following circumstances sites may be more interested and able to support remote data verification during the COVID-19 pandemic: • geographical areas within countries where there is limited impact of the COVID-19 pandemic; • professional clinical research sites that do not experience significant increase in the level of patient care due to the COVID-19 pandemic; • sites with study coordinators who are not licensed to provide medical care and, therefore, can continue provision of clinical trial support. Based on the variance in site circumstances, we would recommend that sites be allowed to make their own determination	

		of whether or not they are willing and able to support the provision of redacted/de-identified (pseudonymized) certified copies of participant records for remote data verification.	
Page 9, point 12	**Changes to auditing** In the current situation, audits should in general be avoided or postponed. Audits should only be conducted if permitted under national, local and/or organizational social distancing restrictions. For critical trials, onsite visits as well as remote audits can be considered, after agreement with the investigator and if the audits are assessed as essential, e.g. triggered audits with the purpose of investigating serious noncompliance.	We recommend that the same provisions applied to auditing should also apply to regulatory inspections. We also recommend it is important to note that, as the disruption caused by the COVID-19 pandemic eases, audits and inspections of data and processes relating to the period of disruption will need to take account of the alternative arrangements put in place in response to the pandemic, and that there will be delays to the timeliness of trial master file completion.	Change current text to the following text: **Changes to Auditing and Inspections** In the current situation, audits and inspections should in general be avoided or postponed. Audits and inspections should only be conducted if permitted under national, local and/or organizational social distancing restrictions. For critical trials, onsite visits as well as remote audits and inspections can be considered, after agreement with the investigator and if the audits and inspections are assessed as essential, e.g. triggered with the purpose of investigating serious noncompliance. Inspections and audits of data and processes relating to the period of COVID-19 disruption should focus on compliance with the

			documented alternative arrangements that have been put in place. Inspectors and auditors should recognize that the disruption caused by COVID-19 is likely to result in delay to the collection of the required documentation and data in a timely manner. It is unlikely, therefore, that the Trial Master File will be updated contemporaneously as would normally be the case. A documented plan to update the trial master file and restore the timeliness of trial master file activities post-disruption should be developed.