EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 March 2019

Submission of comments on eSource Direct Data Capture (DDC) qualification opinion (EMA/282576/2018)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our 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 and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all biopharmaceutical-sponsored clinical investigations worldwide. With more than 130,000 employees, including 57,000 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 welcomes the opportunity to comment on the draft Qualification Opinion on eSource Direct Data Capture (DDC). We have restricted our comments to the main text of the draft Opinion and have not commented on the Annex, which contains information as submitted by the applicant (Novartis). We note, however, that the applicant specifically requested advice on the use in clinical trials of eSource DDC, which was defined by the	

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	applicant as any technology that allows the capture of clinical study source data electronically by investigator site staff at the point of care, into an electronic form that has been specifically validated to capture clinical data. Inevitably, this means that the Opinion has a relatively narrow focus and does not cover important topics such as direct data capture using mobile technologies and the automated extraction of data from electronic medical/health records (EMRs/EHRs). While recognizing that this is outside the scope of the current Qualification Opinion, we strongly recommend that the EMA should take steps as a matter of urgency to facilitate the seamless integration of digital technology in clinical trials, and to ensure the integrity of data that is captured and processed for multiple purposes by multiple applications, in order to maintain the EU's global lead in clinical research. The relationship of the Qualification Opinion to the current Reflection Paper and the planned EMA Guideline on Electronic Systems and Electronic Data in Clinical Trials is not addressed and should be clarified within the final Opinion. Further, it is not clear in the draft Opinion to what extent, if any, the Good Clinical Practice Inspectors Working Group (GCPIWG) has been involved in its development. There are several instances where the draft sets out a general requirement on which the	

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	GCPIWG may have a view on the detail of how this requirement should be satisfied. In order to maximise the value of the Qualification Opinion for both industry and regulators, ACRO recommends that it should provide detailed and fully integrated guidance on the expectations for regulatory compliance. Additionally, while we recognize and appreciate the EMA's foresight and concern that "eSource systems might come into existence which allow an automatic real-time transfer of the captured eSource data to the respective sections of the EMR management systems" (lines 208-209), we believe that the features and implications of such systems are sufficiently significant to require much more detailed and specific guidance, and strongly recommend that the current Qualification Opinion should focus on the current state of the art as described in the original Novartis briefing document. ACRO agrees with the EMA's concerns in lines 125-129 that investigators may have to use different eSource systems for the various clinical trials conducted by different sponsors/vendors in parallel and that, if the systems are not compatible for data transfer into the medical records, this would increase data dispersion, deplete medical records, increase workload for the site personnel and might potentially be in breach of national	

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	requirements for the upkeep of medical records. The Novartis briefing paper addresses this by recommending (lines 798-799) that the site can produce a certified copy of the data in the form of a PDF file generated by the system upon data save at any time. The PDF file can either be downloaded to an EMR or printed and incorporated in a paper-based medical record according to the site's routine practice. The draft Qualification Opinion, however, with a view to future developments, gives the impression that greater electronic integration of data in eSource with the site's EMR may be necessary. Given the diversity of EMR systems currently in use and the corresponding lack of data standardization in such systems, we do not believe that this is feasible at this time. Further, while we strongly support the EMA's view that an increase of the investigator staff's workload must be avoided (line 218), this does not seem possible in the case of fully integrated systems where the site institution's IT department would almost certainly expect to be involved in any testing or validation of a third party's eSource system's interoperation with the institution's IT system (indeed, the institution might well bar any such testing/validation in the absence of such collaboration). Also, with regard to data mapping between eSource DDC and the site EMR, in addition to the obstacles of	

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	institutional multiple terminologies and variable quality of the EMRs, other country-specific regulatory and language constraints (i.e. specific legal requirements, EMR in languages other than English) can be expected. It is not clear how the automated transfer between databases would be appropriately validated in this scenario or if these constraints would mean that eSource DDC would be predominantly used for clinical trials in English-speaking countries only. Even though advanced technologies for translation exist, such data mapping would be time consuming and expensive, and data quality could not be guaranteed. In view of the above, we strongly recommend that the current Qualification Opinion should focus on providing guidance for current state of the art systems, and that a joint working group of EMA and appropriate interested parties be established to develop practical principles applicable to future developments. Additionally, ACRO recommends that the following topics should be addressed in the final text of the Qualification Opinion: 1. The use of eSource DDC for collecting a subject's written informed consent is not addressed in the draft Opinion. ACRO recommends that	

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	appropriate guidance is included. 2. It is not clear if EMA expects any kind of standardization for eSource DDC from vendors/sponsors. 3. The use of eSource DDC for multiple trials and/or sponsors at the same investigational site may require additional controls to ensure that data transfer from eSource to Sponsor (eCRF) comprises data relating to the correct subject. ACRO recommends that the final Opinion should describe the controls needed to ensure appropriate data transfer in this regard.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
28-29		Comment: The statement "The authorisation, conduct and supervision of clinical trials and of clinical care (healthcare services) fall outside of the remit of the European Medicines Agency (EMA)" is not entirely accurate. The EMA is responsible for the development and maintenance of the clinical trials portal and database required by Regulation (EU) No. 536/2014, which, when implemented, will be an essential component of the authorisation and supervision processes for clinical trials in the EU. Further, the EMA is responsible for the authorisation of medicinal products for the EU market and has a responsibility to ensure that the data included in clinical trials supporting marketing authorisation applications are sufficiently robust that they can be relied upon for regulatory decision-making. Proposed change (if any): Revise the statement to reflect the role of the EMA more accurately.	
50-54		Comment: "Edit checks" are performed not just with regard to data being entered at field-level but can also compare against other fields within a form and from data captured by non-human-entry means such as previously captured data and data from other sources. Further, sophisticated edit checks have the ability to "learn" and modify their logic/behaviour based upon previous activities. Additionally, it is no longer	

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		necessary for a CRA monitor to perform source data verification (SDV). Current technologies and approaches mean that SDV in this fashion can be virtually eradicated in favour of real-time data analytics within a centralized and automated monitoring function. Proposed change (if any): The Qualification Opinion should describe modern approaches that take into account technological advances. We recommend EMA to convene a stakeholder workshop for a full discussion of the capabilities of current technology before finalising the Qualification Opinion.	
56-57		Comment: Clinical data are not necessarily entered during a clinical visit. For instance, direct data capture can be used to record laboratory test values after a clinical visit, following analysis of samples which may have been taken during the visit or at some other time as defined in the trial protocol. Proposed change (if any): Modify the text accordingly.	
59-61		Comment: We recommend the inclusion of an additional bullet point. Proposed change (if any): Add "recording of data should be contemporaneous with the measurement/assessment."	
81-85		Comment: While the first sentence notes the importance of	

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		weighing the advantages and disadvantages of each system against each other, the text goes on to describe potential disadvantages only whereas we recommend that the potential advantages are also described. Further, we recommend that reference to existing guidance, especially relating to ensuring data integrity, is included. We also recommend the EMA to take a more holistic approach and to discourage thinking that data associated with clinical trials should be siloed from wider healthcare data management. Proposed change (if any): Revise this section to include the potential advantages of direct data capture in the introductory paragraphs, to include reference to existing guidance relating to ensuring data integrity, and to discourage the concept that data associated with clinical trials should be siloed from wider healthcare data management.	
85-87		Comment: ACRO agrees that it is important to perform a benefit/risk evaluation of the advantages and disadvantages of the proposed system, both for data collected mainly for the purpose of the clinical trial and for data that will also be a regular part of the medical record of the patient. However, the expectation that an increase of the investigator staff's workload must be avoided is clear throughout the draft Qualification Opinion but it is difficult to see how such an evaluation can be undertaken without the involvement of the investigator, who is responsible for the medical record.	

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		Proposed change (if any): Define more clearly the respective roles and responsibilities of the sponsor and investigator in this benefit/risk evaluation.	
101		Comment: Typographical error. Proposed change (if any): Add a full stop (period) at the end of the sentence.	
106		Comment: Typographical error. Proposed change (if any): "he" should read "the".	
110		Comment: Typographical error. Proposed change (if any): delete the full stop (period) after the colon at the end of the line.	
115-116		Comment: ACRO concurs that only pseudonymised information should reach the sponsor and the sponsor should have no remote access to patient-identifying data. However, data protection concerns have led to different national requirements for collection of different data elements, e.g. date of birth may be collected in some member states whereas in others only age may be collected, and in others a fictitious date of birth is required.	

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		Proposed change (if any): The Qualification Opinion should describe the required functionality of DDC eSource to accommodate different national requirements.	
117-119 and 204-205		Comment: The draft Qualification Opinion is clear that generation of worksheets (lines 117-119) and other certified copies from eSource (lines 204-205) should be possible only if the eSource contains only elements which can be adequately mirrored in a printout or pdf flat file. While this guidance is appropriate for the data content that will be subject to data analysis and reporting for the clinical trial, it does not address the metadata that will be associated with eSource data entries and the use/review of the metadata to provide assurance of data integrity. Proposed change (if any): Provide additional guidance on the maintenance of metadata to provide assurance of data integrity.	
124-132		Comment: ACRO recommends that this section should include text to encourage all stakeholders to work towards greater DDC/EHR integration, and provide encouragement for leveraging unified platforms to streamline and integrate systems and reduce site burden (e.g., greater standardisation of data definitions, terminologies and messaging formats to allow for interoperability of data between systems). We also	

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		recommend making clear that broader non-availability scenarios should be catered for (e.g., non-availability of supporting technology infrastructure). Proposed change (if any): Modify to provide encouragement for EDC/EHR integration and development of unified platforms, and highlight that broader non-availability scenarios must be catered for.	
135-136		Comment: We agree that a site qualification procedure prior to implementation is important but the guidance lacks any detail of what this should entail; also, as per comment on lines 85-87, the expectation that an increase of the investigator staff's workload must be avoided is clear throughout the draft Qualification Opinion but it is difficult to see how such site qualification can be undertaken without the involvement of the investigator. Proposed change (if any): Provide additional guidance on what should be included in a site qualification procedure and define more clearly the roles and responsibilities of the sponsor vs. the site in this process.	
137		Comment: Further detail is required on the functionality of the IT Help Desk and levels of access of its staff, e.g. will they have access to subject data and how will this be controlled?	

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		Proposed change (if any): Provide further details on the required functionality of the IT Help Desk and access controls for its staff.	
138-139		Comment: Consistent with GCP requirements, continued access to the trial data will vary (in mode and means) with time based upon contractual provisions (e.g. with the sponsor and/or with CROs/service providers). Proposed change (if any): The wider aspects of continued access to data should be addressed in alignment with emerging EMA guidance around data retention and accessibility.	
146-155		Comment: The figure and accompanying text describe a possible acceptable workflow for ensuring the collected information is mirrored in the patient's medical record. However, source data may be queried and updated as part of the cleaning tasks in the clinical database. This is not addressed in the draft Opinion. Further, the diagram represents a major simplification of a very complex process and as such is in danger of being misleading. For example, the diagram does not include: • Multi-functional participation by one or more CROs • Medical records held at outside parties • External laboratory records • Pharmacovigilance and medical coding activities (often	

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		conducted closely with other sponsor or site activities). Proposed change (if any): The figure should be more representative of real-world situations and include an appropriate workflow for handling data corrections, and the text should provide guidance on ensuring that corrections to data in the DDC database are also captured in the EMR.	
157-161		Comment: The notion of "version" is outdated. The concept should be modified to a model whereby there is a single source of overall truth held within controlled repositories but with controllable accessibility determined by role. Proposed change (if any): Modify the text accordingly.	
174-189		Comment: ACRO strongly supports the ambitions and intentions of these paragraphs. Indeed, in order to facilitate change (especially at clinical sites), we would encourage a greater level of mandate from EMA. The long-term ambition as stated is laudable and requires encouragement, but has many technical and institutional obstacles to be overcome. Proposed change (if any): Consider strengthening - and admitting challenges - via additional EMA guidance. In particular, we recommend that higher levels of automation, incorporating machine learning, should be promoted.	

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206		Comment: We recommend that this sentence is expanded to provide guidance around the provision of pdf files back into medical records. Proposed change (if any): Add guidance around the provision of pdf files back into medical records.	
191-196		Comment: These paragraphs are the first to focus upon the practical issues associated with (bi-directional) interfacing of an EMR app and eSource DDC. As noted in our General Comments, we believe that the inclusion of this discussion in the draft Qualification Opinion is premature at this time. We fully recognize and appreciate the limitations and challenges associated with these developments, but at the same time, in the same way that various solutions have become pre-eminent in the clinical trial space, we believe that a new generation of EMR solutions will emerge to serve the other side of the equation. When, how and commercially this happens are key unanswered questions but it is more likely to occur within territories that have more uniform and integrated healthcare approaches, such as the EU. Proposed change (if any): We recommend that EMA should continue to encourage the interoperability of EHR systems and should consider leveraging the SPOR program for creating standard terminologies and definitions for use in EHR. We further recommend that the current Qualification Opinion	

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		should focus on providing guidance for current state of the art DDC eSource, and that a joint working group of EMA and appropriate interested parties be established to develop practical principles applicable to future developments.	
202-205		Comment: While recognising that not all investigator sites have sophisticated IT systems, we recommend that the notion of printing materials containing complex data should be discouraged in clinical site environments where continued paper use is already high. Proposed change (if any): Modify the text accordingly.	
215-218		Comment: As in our comments on lines 85-87 and 135-136, while we agree that the ultimate responsibility for ensuring eSource DDC performs as intended is the responsibility of the sponsor, we cannot see how verification of the transfer of data into the EMR can be achieved without the input and involvement of the investigational site staff. Further, while we agree that the sponsor is responsible for ensuring the intended performance, the investigator is responsible for ensuring the EMR is complete and accurate. Proposed change (if any): Define more clearly the roles and responsibilities of the sponsor vs. the site in this process.	
220-222		Comment: ACRO strongly supports this position.	

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		Proposed change (if any):	
237-277		Comment: The ICH E6R2 guideline on Good Clinical Practice specifies in section 6.4.9 that the trial protocol should identify any data to be recorded directly into the CRFs as source data. Proposed change (if any): ACRO recommends that this requirement of ICH E6R2 should be specifically stated in the final Qualification Opinion.	
247-259		Comment: This section briefly summarises data privacy issues but does not address fully the complexity associated with eSource DDC. This complexity has potential to generate considerable confusion among stakeholders and possible lack of harmonisation between member states. Proposed change (if any): ACRO recommends that the EMA should seek the opinion of the European Data Protection Board and provide guidance on acceptable procedures for eSource DDC.	
254		Comment: Typographical error. Proposed change (if any): Add a full stop (period) after "Regulation".	

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271-275		Comment: We recommend that this section should also highlight the ongoing availability of eSource DDC over time (as provisioned by a trial sponsor and/or third-party). Proposed change (if any): Modify the text accordingly.	
288-292		Comment: The proposed validation method may assess performance in the collection of information, but does not measure the impact on the interaction between the investigator and the patient, which is a subjective measure and open to interpretation. Proposed change: The text should be expanded to describe the desired attributes that should be demonstrated for eSource DDC before implementation.	
314-316		Comment: The draft Qualification Opinion on the impact of the eSource DDC concept on access and control of data during and after a clinical trial, and its compliance with ICH GCP standards, does not address the proposed data transfer to sites following trial completion (lines 797-802). Proposed change (if any): Provide additional guidance for an acceptable standard of continuous control following the end of the trial.	
324-328		Comment: This point is of huge significance for the acceptance	

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		of DDC eSource in clinical trials. Consequently, we recommend that the final Qualification Opinion should describe the measures that have been agreed between the GCPIWG and stakeholders to ensure satisfactory investigator control of the original subject data. Proposed change (if any): Modify the text accordingly.	
345-351		Comment: This section should be reflective of the updated EMA guideline, currently in preparation, on Electronic Systems and Electronic Data in Clinical Trials. In this context, there should be no need for different or specific provisions relative to eSource DDC. Proposed change (if any): Ensure alignment with the updated guideline.	
364-368		Comment: The current text does not differentiate between the empiric validation of a system and the validation of the use of that system. Commercial app providers generally cater for the former. The sponsor (or delegate) of a clinical trial typically caters for the latter (including the interfacing with EMRs). We recommend that the final Qualification Opinion should reflect this. Proposed change (if any): Modify the text accordingly.	

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377-379		Comment: The draft Qualification Opinion currently states "Data is intended to be transferred off site, and personal information may be contaminated with identifiers (free text). All data transfer must be encrypted by state of the art encryption procedures. Source data transferred must be protected from alteration, access and duplication in transfer." It is not clear how the measures stated will prevent transfer of contaminating identifiers in free text. Proposed change (if any): Provide more detail on acceptable measures to prevent the transfer of contaminating identifiers in free text.	
		ACRO thanks the Agency for the opportunity to provide comments on this public consultation. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.	

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