13 March 2019

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

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA  |

*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).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
|  | Thank you for the opportunity to provide feedback on the eSource DDC qualification opinion.  |  |
|  | It is recommended that the Qualification Opinion (QO) be prefaced with a list of definitions to facilitate understanding.  |  |
|  | It would be extremely beneficial to have a table that summarizes the roles and responsibilities of eDDC Vendor, Sponsor and Sites. |  |
|  | There are several references to transferring/allowing access by the sponsor for “protocol mandated source” e.g. Line 89. It is suggested that a different approach or language be used that allows for appropriate patient/study oversight.As eSource would encompass/capture both “source notes and CRF data” – including commentary, assessments and other data that would not typically be collected on CRF, it would not be prudent or plausible to pre-define and limit access to the Sponsor. As part of trial oversight and monitoring, the Sponsor would require access to review patient progress during the study i.e. “typical source” and the eCRF data. |  |
|  | While we perceive the implementation of the eSource Data Capture approach very encouraging and promising, we also acknowledge that not all the countries/sites will be ready for the implementation of this technology in the short term. We would suggest a staggered approach for the implementation of such technology. Could the EMA share its views as to how and when this could be implemented in practice in the various EU Member States?  |  |
|  | From the scope and context of use of the technology section, and to confirm our understanding, this opinion holds true for any sponsor provided tool that the site would use to capture source data electronically. This includes direct data capture into systems designed to be only eSource for all data or a subset of data (i.e., eSource EDC, eCOA, labs) or systems designed to enter transcribed data from paper or EHRs but can be also repurposed to do direct data entry by the site if defined in the protocol as such (i.e., traditional EDC used for full or partial eSource).  |  |
|  | In addition, it would also be helpful to state what is and is not in scope within QO e.g. tablets, smartphones, wearable sensors, mobile apps, other devices, etc. While it appears that the type of eSource system, that is the subject of the QO, is ‘tablet’ based (and is provided to site(s) by the sponsor’s vendor), it is recommended that this be clarified.  |  |
|  | The concept of DDC as described in this document implies a shift from data entry-point from EDC to DDC system. It remains unclear whether there is a shift in other EDC functionality. E.g. medical monitor/DM data queries, PI CRF signature.(The scheme on page 9 does not show any PI/site interaction at eCRF)The document is on Direct Data Capture, but leaves open the option of transcribing data from other sources; which might be outside the scope of Direct Data Capture. It opens the floor to the DDC system becoming an alternative CRF entry option additional to eCRF.We would advocate a clear separation direct entry via DDC; any data which is not directly entered but 'delayed' entered (requiring source) via eCRF system.As a result DDC systems should not allow data entry outside subject visits. |  |
|  | We would suggest for the qualification opinion paper to be restructured. The Q&A format can create some overlap and redundancy and it can be difficult to interpret key information due to too many cross-references. (e.g.: Line 277 "See also the answer to Q2, Q4 and Q5".)  |  |
|  | Lines 220-222 are repeated on lines 303-305. Seems a better fit to question 2, which is about “operations”, rather than Q4 which is about “role as a health care provider”. Similar observation for lines 296-301. Is there an opinion on whether DDC can help health care providers provide more time per patient?  |  |
|  | Redundancy: lines 271-275 with lines 314-317 – information seems better placed in Q5, where there is good further description of opinion on the subject. |  |
|  | Question 8 – draft answer does not align clearly with question. Reference to Q5 not specific to topic of patient data privacy. |  |
|  | Additional topics for consideration: * Potential failure of eSource DDC tools (please refer to comment on line 130).
* The format of eSource data. eSource data that comes to the sponsor should be in a standardised format, and the format we are working to is SDTM so it is submission ready.
* There is no specific mention of regulatory needs if any exist (in terms of document or process flow, if such direct data capture approach will be used by the sponsors) for the CTA submissions to the regulators and/or Ethics bodies.
* Clarity on if some additional information would be needed in part I or Part II existing documents or any new document.
* Explanation on how this will be/could be managed when new CTR will become effective
 |  |
|  | With regard to the necessity to add the patients’ responses to questionnaires or diaries not used in normal clinical practice (e.g. eCOA) to the patient chart in the EHR, we agree that the illustration X (line 149) is one possible workflow. We respectfully offer another example workflow that meets ICH E6 R2 guidelines for eCOA and for eCRFs. (SHOULD WE DRAW ANOTHER PICTURE?) eCOA responses can be viewed contemporaneous to collection on a vendor hosted portal 24/7 during the conduct of the trial thus fulfilling ICH E6 R2 section 8 guidelines. Also the site has control and oversight of patient and site data; they can make changes if there is documented evidence at the site and the changes are not biased by recall (as defined by protocol). The sponsor can view the data only. At the conclusion of the trial, the site receives a complete certified copy of all patient and site reported outcomes via a CD (or hosted in a third party cloud) which can be downloaded and added to the patients’ medical records thus meeting the need to be able to reconstruct the trial and for archival. Sponsors will only receive pseudoymized data in periodic data transfers for the purposes of analysis and reporting. A final copy of the patients’ and sites’ data and audit trails will be archived at the Sponsor as well.Similiarly we offer an alternative dataflow for all eCRF data or partial eCRF data that is captured directly into an EDC tool. EDC responses can be viewed contemporaneous to collection on a vendor hosted database server 24/7 throughout the conduct of the trial meeting ICH E6 R2 section 8 requirements. The site controls the data, oversees the data and can make changes based on documented evidence. The sponsor can view the data, send queries and can do MedDRA coding. At the conclusion of the trial, the site receives a complete certified copy of all patient and site reported eCRFs via a CD (or hosted in a third party cloud) which can be downloaded and added to the patients’ medical records thus meeting the need to be able to reconstruct the trial and for archival. (Additionally in most systems, sites can also download the eCRF data at any time during the conduct of the trial and at the conclusion of the trial.) Sponsors will only periodically receive pseudoymized data in data transfers for the purposes of analysis and reporting. A final copy of the patients’ and sites’ eCRF data and audit trails will be archived at the Sponsor as well. |  |

1. 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)* |
| --- | --- | --- | --- |
| 19-22 |  | Comment: Clarification of the text is recommended to facilitate comprehension. Furthermore, it should be clarified that the electronic tablet to be used is that which has been issued to the site specifically for use in the clinical trial.Proposed change (if any): In the context of this Qualification Opinion, the general term “eSource DDC” refers to an electronic application and/or device that allows direct entry of source data, and **that** directly **identifies** some of these data as **required entries in the** CRF (Case Report Form), for clinical trial purposes at the point of care by investigator site staff, for example via an electronic tablet **issued to the site specifically for this purpose**. |  |
| 39 |  | Comment: In order to be acceptable, we consider that eSource DDC systems should also be tested for user acceptability. Proposed change (if any): To be acceptable, an eSource DDC system and application should be customized in line with legal requirements and ICH GCP, validated, secure, **tested for User Acceptability (UAT)** and maintained. |  |
| 43-44 |  | Comment: Clarification is required regarding whether this referring to existing (historic) data that might already exist or newly captured 'Source' data relating to a specific protocol. Also, there are no alternatives available for capturing data other than on paper or electronic media.Proposed change (if any): Data from clinical assessments is ~~usually~~ initially captured on paper or electronic media, i.e. Electronic Medical Records (EMR), ... |  |
| 50-51 |  | Comment: Edit checks would normally be taken after data entry and not concurrently (as could be inferred by use if the word “when”). Proposed change (if any): Sponsor-programmed edit checks, or queries, for the protocol-mandated collected data take place **after** ~~when that~~ data is entered in the system … |  |
| lines 50, 146  |  | Comment: Would it be possible for complex Queries to come from the Sponsor to the attention of the Investigator? It is actually believed that automatic queries are required.  |  |
| 53-54 |  | With today’s Risk Based Monitoring, the CRA monitor does not perform Source Data Verification (SDV) on all transcribed data, but rather conducts targeted SDV and Source Data Review (SDR). |  |
| Line 61 |  | Comments: Suggest addition of: "and current approved study protocol version" -since the system study configuration must be consistent with the current EC approved protocol.Proposed changes (if any):*[…] such information should be recorded in line with the current practice at the study center* ***and with the current approved study protocol version****.* |  |
| Lines 63-64 |  | Comment: The term “pseudonymised” is used in regard to personal data. Standard practice in clinical trial conduct is to use anonymised personal data instead. Please, indicate whether the use of pseudonymised personal data would involve different implications or risks compared to anonymized personal data. In addition, could EMA specify what is meant to be covered in this statement? We believe it should not include protocol mandated data such as age and dates. Sponsors should always receive exact, accurate data from the sites to be able to produce accurate analyses. |  |
| 66-69 |  | Comment: It is recommended that reference to the use of Clinician Reported Outcomes is also included. We also propose including specific examples of patient outcome.Proposed change (if any): In some types of trials, electronic technology is already in use, as, for example, electronic patient reported outcomes, eCRFs, **Clinical Outcome Assessments (COA, such as** **Clinician Reported Outcome, CRO) such as** real-time monitoring of patient outcomes such as routine aspects, electronic capture of laboratory test results, **reporting quality of life or episodes of pain.** |  |
| 66-73 |  | Comment: Given that “mobile technology systems” are often used in eSource direct data capture, it would be preferred to see them in scope of this qualification opinion. It is therefore proposed that the sentence, which suggests they are out of scope, is removed.Proposed change (if any):“In some types of trials, electronic technology is already in use, as, for example, electronic patient reported outcomes, eCRFs, real-time monitoring of patient outcomes such as routine aspects, electronic capture of laboratory test results. These types of trials could be a possible initial testing ground for an eSource system.  ~~This Qualification Opinion does not refer to direct data input from mobile technology systems, as this is out of scope.”~~ |  |
| 100 |  | Comment: Transcription relates to copying existing text, it is assumed this should read 'recording'Proposed change (if any): For such data the direct ~~transcription~~ **recording** into eSource … |  |
| 102-103 |  | In our alternative dataflow, the site has flexibility in how the data is incorporated into their site-specific dataflow and archival system. The site receives the eSource data as certified copies and can either upload the data into their EHRs or keep a copy in the patient paper chart. Each site is different so sponsors should not dictate how sites upload their data into their systems. (As stated in line 112-Flexible uploads align with requirement… ‘in accordance with the practice, degree of detail and accessibility in force at the study centre’.) |  |
| 102 |  | Comment: Recommend clarifying the meaning of the text.Proposed change (if any): The Company’s proposal is not sufficiently detailed on if (and if **it is**, how) incorporation … |  |
| 103-108 |  | Comment: It is assumed that the aim is to ensure that the protocol required data is transferred from EMR to EDC. It is recommended that a simpler process be used. It also should be clarified how an electronic worksheet differs from EDC. |  |
| line 106 |  | Comment: Misspelling: “he” should be “the” |  |
| Lines 115-116; Lines 258-259 |  | Comments:There is no reason for the sponsor to have remote access to patient-identifying data. The current language reads as if this is a recommendation rather than a requirement. For this reason, we would recommend that the language be strengthened as described below.Proposed changes (if any):*The sponsor ~~should have no~~* ***may never have*** *remote access to patient-identifying data.* |  |
| 116 |  | Comment: The sponsor’s CRA would be expected to have remote access to patient identifying data, as part of their role.Proposed change (if any**): With the exception of the CRA,** the sponsor should have no remote access to patient-identifying data. |  |
| 117-118 |  | In the alternative scenario, the CD or cloud archival has the ability to print out the forms with audit trail if needed. How do you see a printout being used and why? |  |
| 117-119 |  | Comment: There should be acknowledgment that machine learning reading of unstructured EMR fields (beyond the structured database content) has commenced (and will be an increasing feature in clinical trials feasibility in years ahead), and therefore data should be in a format that can be easily extractable.Proposed change (if any): The structure/content/context of the electronic worksheet should be transferable into a printout/pdf file without loss of information. Therefore the worksheet should only contain elements that can be adequately mirrored in a printout or pdf flat file. Given that machine learning reading of unstructured EMR fields (beyond the structured database content) has commenced (and will be an increasing feature in clinical trials feasibility in years ahead), data should be in a format that can be easily extractable. |  |
| 126-127 |  | Data transfer into EHRs with multiple systems are dependent on standards to lessen the burden; however, initial HL7 standard work has mainly focused to date on extraction (one way)- in the interim, appending the .pdfs representing the clinical trial data can be added to the EHRs. Is this acceptable? |  |
| Line 130 |  | Comments: No comments are made as to the situation if DDC fails (e.g. power failure of the DDC device, DDC device is lost, etc.). It would be helpful for EMA to comment on the acceptability of a backup process in such cases (e.g. paper CRF with manual data entry). |  |
| Lines 141-144 |  | Comments: The language describing the steps that need to be taken to pseudonymize data should be more precise and clear. For example, to say that “each individual piece of information needs to be pseudonymized” is not an accurate depiction of how to pseudonymize data as it is more about pseudonymizing a *set* of data rather by replacing all identifiers in such data sets with pseudonyms than individual pieces of information. Additionally, this section does not contain any information about what type of coding is required and how such coding should be applied. For example, does the data have to be double-coded or is it sufficient to use the subject ID number? Finally, the language is not clear about whether the data must be pseudonymized prior to any access to the data. It is recommended that this paragraph be revised to provide more clarity on this topic. |  |
| Line 146 |  | Comment: It is not clear if some Data in eSource must come from EMR (double ways: EMR => eSource => EMR)Where would the Investigator sign the eSource?Would this also cover CRF signature requirements? |  |
| Line 149 |  | Comments: It appears there is a gap between site EMR system and the eSource DDC system (line 149). It appears a one-way direction from DDC tool to EMR (workflow on page 4). It could introduce inefficiency because investigator will need to access 2 systems (DDC tool and EMR) system during a patient visit. Investigator use the DDC tool to enter standard health care data and clinical trial data but will likely need to access other data in the EMR such as lab results or relevant medical record data from previous visit (e.g., tumor assessments) |  |
| 159-161 |  | In the alternative dataflow, the 3rd party holds the eSource and provides certified copies back to the sites and sponsors separately at the end of the trial (or in the case of EDC, may be manually downloaded by the site at any time). We suggest that in Illustration X creating a separate dataflow back to the EHRs at the beginning creates a redundant step and opens up the possibility of inconsistency when trying to simultaneously send data to 2 places. |  |
| line 159-161 |  | Comment: diagram on line 146 – suggest to somehow incorporate visually in this diagram, the capability outlined in lines 202-206. |  |
| line 159 |  | Comment: line 159: misspelling: “enrolment” should be “enrollment” |  |
| 186-187 |  | We agree that the long term plan is to have 2 way communication between EHRs and sponsors using HL7 FHIR standards (or similar); however, while standards mature and implementation pilots play out, there is a need to have an interim process to help reduce site burden and improve quality/ data integrity. There are organizations such as Society for Clinical Data Management (SCDM) eSource Implementation Consortium w/ sites, sponsors, SDOs, technology companies etc working together to define and implement short term and long term solutions in real world settings and would welcome partnership w/ the EMA on defining solutions |  |
| 187 |  | The automatic transfer or capture should limit the ability to change data. In other words, if data is e.g. automatically captured from site's EMR, changing data in the DDC system should be locked; any change to automatic captured data should be at the source instead of an intermediate step. The same applies the other way round. (to ensure data remaining being mirrored)Changing of data should force synchronization between systems |  |
| Lines 189, 222 & 304 |  | Comment: Standardization is highly desirable and likely a key factor in a successful deployment of such eSource. However more specific guidance should be given with regards to how standardization can be achieved. The diversity of platforms, databases and data environments across the industry (CRO vs sponsors) needs to be taken into consideration. The nomination of a responsible party could also be an action point.  |  |
| Line 195 |  | Comments: Change management should address the impact of study/protocol configuration updates on data transmission accuracy, and completeness. |  |
| 195 |  | The Sponsors alone cannot define mapping or validation of data appended or inserted into the sites’ EHRs. All parties (sponsors, sites, technology vendors and SDOs) together can provide industry level implementation guidance and mapping based on established standards such as FHIR resources and CDISC. The implementation guidance though will not be point to point solutions as that is not scalable. HL7 BR&R team along with other organizations (like SCDM eSource Implementation Consortium and TransCelerate) are working on implementation guides using HL7 FHIR standards. We suggest to use this approach to drive eSource adoption and consistency. |  |
| 218 |  | Comment: It needs to be clearly defined how changes in the eSource after the initial upload into the eMR will be managed. |  |
| Line 224 |  | Comments:While DDC has the audit trials (line 224), it is unclear if audit trial information would transfer to EMR along with data. There appears no connection between the EMR and the DDC tool database. It is unclear about the mechanism of data change in the EMR after initial DDC data transfer. How would data update in EMR get reflected in the DDC tool database? Or any change must be done in the DDC tool so the EMR and DDC database are refreshed accordingly.  |  |
| Line 225 |  | Comments: Clarifications would be needed regarding this statement "In case of eSource, 1-to-1 coding of data is expected".  |  |
| Line 225 |  | Comment: Could you clarify what “1-to-1 coding of data is expected” means? |  |
| 226 |  | Does this imply that an audit trail is no longer per individual save, but should be per data-item. In other words if a form consists of multiple fields, and is saved at completion, the audit trail should have captured the entry/change to the individual fields already? |  |
| 227 |  | Please clarify if this statement means that the audit trail should start before submitting the data to the server or it means that each item has an audit trail (An audit trail at the item level is currently being done in most systems).  |  |
| Line 231-234 |  | Comments: Will there be any difference if the sponsor is using a combination of on-site monitoring versus remote monitoring in terms of e-source Direct Data Capture? May be same process will be applicable independent of the monitoring pathway? Clarification will be helpful. |  |
| Line 231 |  | Comment: It is not clear why the “centralized monitoring” is described here. What actions could be done? |  |
| 274 |  | Comment: After the trial the eSource should be handed over to the investigator.Proposed change (if any): This creates the need to develop and implement processes that ensure the continuous control of the investigators over these data during and after the trial. **After the trial the eSource should be handed over to the investigator.** |  |
| 290 |  | Comment: This free text will be screened by the monitor for any relevant information that should be captured per the protocol requirements.Proposed Change (if any): e.g. making sure that the use of the eSource tool is not too complex and not limited to capture data only, but allows capturing of free text as well. **This free text should not be shared with the sponsor.** |  |
| Lines-290-292 |  | Comment: The sentence may be interpreted as if a systematic comparison of eSource vs no eSource for each study and each site should be included in the feasibility phase of a new study. Is this really the objective? If so, this would prove very burdensome to sponsors. We would suggest retrieving a confirmation from the site that using the eSource system would not be a burden to them, without performing in use testing systematically. Proposed change (if any): ‘This aspect should be validated by **the sponsor in seeking for confirmation from the investigator that** using the eSource system **is not burdensome to them**.’ |  |
| 298 |  | Comment: Real time might be hard to establish and since eSource system needs to guarantee access 24/7 for the investigational staff the need for real time should be clarified. |  |
| Line 300 |  | Comments: In the case of multiple study configurations accessed on one eSource tool, the system design should ensure (e.g. through logical controls and checks) that subject data is not inadvertently entered into the wrong study database by the investigator or site staff.  |  |
| Lines 314-317 |  | Comment: If eSource data is automatically transferred into Electronic Medical Records (EMR), then it may occur that such data is modified in EMR and requires subsequent modification in the Case Report Form. It should be specified whether the eSource system should be required to detect such modifications in the EMR. |  |
| 322 |  | Comment: Transfer of ownership and definition of what is the eSource after completion of the trial should be recommended. |  |
| 324-328 |  | Comment: Clarification is required regarding the meaning of “Missing continuous investigator control over eCRF data”, perhaps by providing an example. |  |
| 327 |  | Please confirm that sponsor-independent, site source can be held in a hosted database by a 3rd party and subsequently, for archival, a certified copy of the database provided to the site directly from the 3rd party. |  |
| 330- 331 |  | Comment: In the case of eCOA, the sponsor provides the site with clinical trial data on a disk for archive at end of study. Clarification is requested regarding whether this is also in scope, with respect to direct investigator access to eCRF data. |  |
| Lines 330-331 |  | Reference to Q3 after the sentence about Investigator’s direct access to eCRF is not clear. There is no obvious reference to this topic in Q3.  |  |
| 349 |  | There is a practical hurdle, also frequently observed in the paper world. In case both e.g. study nurse and investigator are conducting a subject visit, and both are entering data: this would require switching of account to generate an integer audit trail. Like In the paper world we often see both SN and I making entries, and only I signing of the data. |  |
| Line 349 |  | misspelling: “wrights” should be “rights” |  |
| Line 349-350 |  | Question about the application of the term “fully audit-trailed” to “system access”. Usually the term audit trailed applies to changes in data or system configurations and not to system access logs. These should not be changeable in any way. Is a system log or journal describing the system access considered an “audit trail” ? what kind of information should be captured in this “audit trail”? |  |
| 350-51 |  | To ensure machine readability in the future which is independent from specific software platforms and operating systems, we suggest cloud based storage. Do you agree? |  |
| Line 350 |  | Should the sentence say “human”readable rather than “machine” readable? |  |
| Line 350(also 138) |  | Comment: Could you clarify what is intended by “Machine Readable”: is a static format such as PDF adequate, a full relational database,…? |  |
| Line 365 |  | Comments: Clarification to address validation of all processes between interoperable systems would be needed. Also, the provision for study-specific configuration validation of integrated EMR/eSource systems solutions should be anticipated. |  |
| 367 |  | See previous comments for line 195. |  |
| 377-378 |  | Comment: As indicated under the comment on line 290, free text fields as part of the eSource should not be shared with the sponsor but screened by CRA to ensure adequate information is captured elsewhere for protocol required information that is going to the sponsor.Proposed change (if any): Data is intended to be transferred off site, and personal information may be contaminated with identifiers (free text). **Free text should not be shared with the sponsor.** |  |
| 422 |  | This would imply that data validation (automatic query) moves from EDC to DDC system, but is also to be continued in EDC as manual entry to EDC remains. |  |
| Line 513 |  | Comment: With the eSource Data Capture approach, we don´t see an opportunity to reduce protocol deviations since patient charts are populated after procedures/decisions have taken place. Could the EMA please further clarify how it is to be expected that such technology would result in a reduction of protocol deviations? |  |
| 698-702 |  | Comment: The site must be careful to know that only the table must be used for the duration of the trial. There should not be a hybrid of eSource and paperProposed change (if any): If pre-existing source records exist (in EMR or paper source), the site staff should indicate in the eSource form that the source data is transcribed, then transcribe the data into the eSource form. **The site must be careful to know that only the table must be used for the duration of the trial. There should not be a hybrid of eSource and paper.** |  |
| 700 |  | This appears to be a right case scenario; could imagine that regulators would like to see the other end of the spectrum being covered, i.e. statement by investigator that data is entered directly (and that there is no 'hidden' source, from where the data has been transcribed) |  |
| 713 |  | It is unclear whether or not the use of DDC and documented specification of the system may waive the GCP requirement 6.4.9. In other words: would a DDC specification document prevent including the reference of applicable DDC data points in the clinical study protocol?6.4.9 : The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data. |  |
| Line 819 |  | Comments:eDDC vendor will also collect non-trial patient data that will be transferred in a validated manner (certified copy) to the site EMR. Once the study is closed out, is there a possibility to delete the non-trial data in the eDDC system based on an agreed and validated process and that the single source of truth would be in the EMR? There should be only one trusted source of electronic records that in this case would be the site EMR? Could you please confirm if this approach would be acceptable? This would reduce the amount of electronic records to be managed by eDDC and would avoid availability of duplicate eRecords.  |  |

Please add more rows if needed.