25 July 2019
EMA/179292/2019

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

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	ACRO Association of Clinical Research Organizations
2	Bayer
3	Bristol-Myers Squibb
4	ClinBuild
5	Clinical Ink
6	DMB (French association of Data Management Biomedical)
7	EAHP European Association of Hospital Pharmacists
8	EFPIA
9	EUCROF Clinical Trials Legislation Working Group
10	Pfizer
11	Target Health Inc.

Note: As for all qualifications, the Opinion is given based on the characteristics of the proposal submitted by the Applicant. Some of the comments received highlighted that other solutions and settings may be possible. These comments are noted for future reference, but may not have resulted in changes to the Qualification Opinion, as they are not relevant to the submitted proposal. Details of technical standards are not covered, as their pace of development is high: the principles that need to be satisfied by the technical solution are the main focus of the opinion. The Qualification opinion does not constitute general guidance, however the general principles outlined could apply to different scenarios, while specific characteristics of different systems might require specific evaluation.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	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 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	

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	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 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 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	

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	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 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: The use of eSource DDC for collecting a subject's written informed consent is not addressed in the draft Opinion. ACRO recommends that appropriate guidance is	

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	included. 1. It is not clear if EMA expects any kind of standardization for eSource DDC from vendors/sponsors. 2. 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.	This was not specifically raised as part of the qualification advice request. Compliance with general requirements applies. Raised also further down by other stakeholders. Amendment to text introduced.
2	The esource DDC approach proposed by Novartis relies on the fact that the sites have continual access to the data they generate and can generate pdf copies for archiving/transfer to a site's EMR/paper MRs. It is not clear if the pdfs also contain the audit trail information. However, there is a lack of information around how data changes are managed (are the paper copies edited, or the source database?), who owns the source database and how the CRF data is checked for patient identifiers and redacted if necessary. With the advantage in elimination of paper source documentation comes the challenge of maintaining data integrity of eSource DDC tool and database. Suggest providing additional discussions and considerations for various operational processes of ***data lifecycle***, from the collection to retention of data (especially back-up and restore tests, BCP, and disaster recovery practices, in the absence of paper source data). It is stated that: The authorization, conduct and supervision of clinical trials and of clinical care (healthcare services) fall outside of the remit of the European Medicines Agency (EMA). How does the guidance ensure in practice that eSource DDC when it is implemented complies with these rules? If a clinical trial takes place in an EU member state where specifically a written	Raised also further down by other stakeholders. Amendment to text introduced.

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	informed consent is required for collection and processing of personal data from patient in compliance with all the applicable privacy regulations then we infer that **a mechanism must be specified as part of the opinion, for obtaining patients' informed consent through the eSource DDC**; that mechanism will need to comply with the National EU rules and the specific EU member states. Additionally if there is any intention to transfer personal data to third countries then that will need to be specified as well in eSource DDC. **Details:** In the eSource Direct Data Capture (DDC) qualification opinion, it is stated that the eSource DDC system allows for a **safe collection and processing of personal data from patients**, in compliance with all the applicable privacy regulations, while providing a more efficient and faster environment to the site personnel, the investigators and the institutions According to General Data Protection Regulation, processing personal data is generally prohibited, unless it is expressly allowed by law, or the data subject has consented to the processing as the consent is being one of the more well-known legal bases for processing personal data. GDPR gives individuals a right to be informed about the collection and use of their personal data, which leads to a variety of information obligations by the controller. The obligation to inform may be provided in writing (consent on a paper form bearing the patient's wet signature), orally at the request of the individual when identity of that person is proven by other means, or by electronic means where appropriate. The obligation to inform **includes the processing purposes and the legal basis**, any legitimate interests pursued, the recipients when transmitting personal data, and **any intention to transfer personal data to third countries outside the EU**. In addition, the right to be informed also includes information about the duration of storage, the rights of the data subject; the ability to withdraw consent, the right to lodge a complaint with the authorities and whether the provision of personal data is a statutory or contractual requirement. In addition, the data subject must be informed of any automated decision-making activities, including profiling. **EU**	

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	member states differ on accepting informed consent on a written form rather than electronic form. It is stated 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. Will the draft on the EMA guidance on Electronic Systems also be subject to an opinion for comments? The content of the guidance document on Electronic Systems and the content of the eSource Direct Data Capture (DDC) qualification opinion will need to be aligned. Include an opinion regarding the eDDC in different languages Include an opinion as to when information should be entered in the eDDC In sites/countries where an EMR is not used how will certified copies of the eDDC be provided to sites?	
3	Thank you for providing Bristol-Myers Squibb Company the opportunity to review and provide comments on the "eSource Direct Data Capture (DDC) qualification opinion" document. We welcome the opportunity and believe that eSource in general has the potential in many instances to improve data capture in clinical research. The document generally reads very well, and we have some general as well as specific comments. We believe that the EMA's opinion to have interoperability and integration between eSource, EDC and EMR is in the right direction. However, the requirement to integrate eSource DDC with the site's EMR system and the sponsor's EDC system may become a barrier to wider adoption of eSource DDC in the medium term (next 2-4 years). In the US, at least, there are hundreds of EMRs, and no robust standards adopted for interoperability for most of them. Added to the complexity is that sponsors use multiple sites per clinical trial, each of which may have a different EMR system, hence involving the need to integrate with multiple EMR systems for	Noted

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	one single study. The proposal of using a PDF export from the DDC system to upload in the EMR system seems to facilitate this requirement, but may not be deemed useful for sites, as it would not provide structured data into the EMR. Furthermore, the EMR IT Administrator may restrict or even prevent upload of PDFs from an external source into the EMR. We suggest the agency revises or relaxes this requirement, to further promote the adoption of eSource DDC where there is a fit. Additional comments are provided in the specific comments section below. Moreover, we believe that the adoption of eSource DDC may be facilitated by having the large EDC providers add a feature in their system to enable DDC. From a sponsor's perspective, using a third-party DDC tool and having to integrate it with its own EDC system may be too cumbersome to be deemed worth the investment, especially if it is done for a single study. The ideal scenario may be that EDC software contains a native DDC functionality directly available to be used by sites, without the need for additional integration. We believe that eSource DDC may be particularly useful for sites that currently don't have an EMR system, and therefore use paper as their primary source data capture solution. The use of DDC would alleviate the need for paper, and may entice such sites to move towards the adoption of EMR for healthcare documentation.	
4	It is good to see company initiatives aiming to improve data collection for clinical sites. The use of eSource could be a part of the solution. A more comprehensive solution should include direct communication between the Electronic Medical Records (EMRs) and the sponsor Electronic Data Capture (EDC) system. In order to achieve this, interoperable standards for both healthcare and clinical research will be needed. Clinical research standards are being addressed in the HMA-EMA Joint Big Data Taskforce. Some hospitals around Europe are working towards the goal of standardizing their EMRs. It should be coordinated on a European level with the aim of linking EMRs to clinical research data for the benefit of the patients. This will	Noted

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	require joint EMA and EU Healthcare policies. https://www.ema.europa.eu/en/about-us/how-we-work/big-data If interoperable standards are not in place the resource requirements for data integration between the EMR (and eSource) and EDC may be beyond the expected value. Data integration will be needed on a CRF by CRF, site by site and sponsor by sponsor basis. Study updates to CRFs could delay data entry at the site and require backup paper worksheets to be used. This topic is scheduled to be addressed in the HMA-EMA Joint Big Data Taskforce in the section "Observational Data Subgroup Recommendations (Electronic Health Records)". Efforts could also be taken to work with international regulatory agencies to ensure that there is scope for international alignment using standards like CDISC (CDASH and ODM V2) and HL7 FHIR (e.g. OHDSI OMOP or others).	
5	**Comment:** A definitions section should be created to aid the reader in understanding what is meant by varying terms/words used throughout the document. (example – mobile technology system, MAA, etc)	As this is not a guideline, a glossary is out of scope. The terms are defined by the submitted proposal's characteristics.
7	The guidance gives insights on the use of Direct Data Capture (DDC) which is generally welcomed since it eliminates paper in between and transcription of information. EAHP acknowledges however the data protection issues mentioned in the document and would like to underline specific points for consideration in relation to this topic (see point 2 below).	Noted
8	It is recommended that the Qualification Opinion (QO) be prefaced with a list of definitions to facilitate understanding.	As this is not a guideline, a glossary is out of scope. The terms are defined by the submitted proposal's characteristics.

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8	It would be extremely beneficial to have a table that summarizes the roles and responsibilities of eDDC Vendor, Sponsor and Sites.	The scope of this document is to provide advice on the submitted proposal.
8	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.	Noted
8	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?	This is out of scope for EMA.
8	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).	Noted and clarified
8	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	Amendment in the introduction

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	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.	
8	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.	Noted and amended where relevant
8	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".)	The document follows the usual format of Qualification opinions (question/answer/company position)
8	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?	Agreed
8	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.	Agreed
8	Question 8 – draft answer does not align clearly with question. Reference to Q5 not	Agreed

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	specific to topic of patient data privacy.	
8	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	Amendments introduced to text. CTR is out of scope in present request.
8	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	Noted

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	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.	
9	EUCROF welcomes the opportunity to submit comments on the eSource DDC topic as we think that the topic will gain importance in the near future. EMR will be used to greater and hopefully also to more harmonized extent and the idea to pull protocol mandated data from already existing EMR data into an eCRF (here via the eSource database) suggests itself and has been already addressed in the past. The concept of creating a trial specific repository of source data by pulling already existing EMR source data and to offer an interface (tablet) for data entry of those data that are not present in the "normal" source (or are only available on paper source), is supported by EUCROF. However, EUCROF felt that this document represents a "not so common" type of	Noted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	document and therefore needs better introductory explanation where this document is coming from. It is not obvious for the reader that this opinion represents answers to questions which were posed by one single company (Novartis). Only when reading through the Annex, this becomes clear. EUCROF suggests to include an introductory section to explain the background and the context of this opinion document.	
9	There are several cross references in the answers to the questions that may confuse the readers a bit. On the other hand, there are redundancies. Maybe it would be possible to streamline the answers, once the overall opinion towards the presented concept is outlined.	Noted
9	The document insists on sustainability of data access after completion of the trial at the sponsor as well as at the investigator site. As, in the meantime, the Guideline on TMF/eTMF has been published and will be in effect in June 2019, this Guideline should be taken into consideration when talking about sustainability, archiving periods and other elements which are required in the Guideline. That would make it easier for the reader and complete the picture from the collection of source data to archiving source and CRF data.	Reference made
9	Even though compliance with GDPR requirements is assured throughout the document, we propose to refer to the fact that patients' prior consent is required for the Collection, Processing and Transfer of Patient's Personal Data (up to the fact that the data might end up in Third Countries with lower data protection standards). The request for patients' consent in the given context should be clearly distinguishable from the other matters covered by the Informed Consent Form. Consideration should also be taken to the additional safeguards set by National Authorities in the EU on the compliance with GDPR. In Greece, for instance, a special statement is required for the Clinical Trial submissions to the National Ethics Committee.	Noted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
9	Terminology is not unambiguous at times. EUCROF suggests to strictly use eSource DDC when the suggested system is addressed and not switch between eSource, DDC and eSource DDC. Along this line, a definition of eSource DDC would be very welcome.	Noted and amended where relevant
9	**Punctuation and typos throughout the document:** Page 2, Line 19: there is an extra space after the "Qualification Opinion". Page 2, Line 53: the wording "CRA monitor" is deemed as a superfluous repetition (pleonasm). We can refer to either CRA or Monitor. Page 3, Line 101: a full stop is omitted at the end of the sentence. Page 3, Line 106: the letter t is omitted from the article the [..these cases the use of trial…]. Page 3, Line 110: there is an unnecessary full stop at the end of the sentence. Page 3, Line 132: there is an unnecessary semicolon at the end of the sentence. Page 5, Line 206: there is an unnecessary space at the beginning of the sentence. Page 6, Line 254: a full stop is omitted after the reference to General Data Protection Regulation.	Amended
10	The draft Opinion document does not address the use of eSource DDC for collection of clinical trial patients' written informed consent for participation in the clinical trial. For example: Should the clinical trial take place in a jurisdiction where patient's explicit written informed consent is the only accepted GDPR-compliant basis for the processing of personal health data, such consent could be obtained using the eSource DDC. If applicable, explicit written informed consent regarding the potential transfer of patients' personal health outside the EEA could also be collected through the	Noted – current framework applies

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	eSource DDC.	
11	As a company, we have been doing web-based DDC for 10 years with regulatory approvals. In our system, the eSource record is placed into a trusted 3rd party hosted environment, before the data enter the clinical trial database. Access to these eSource data is controlled by the clinical investigator. There many points made in this opinion that are very important and clarify the value, as well as legitimate concerns for all clinical trial stakeholders, when DDC is utilized. The only concern we have is to differentiate the requirement for data to be contemporaneously located in an EMR or EMR which tend to be commercial software packages. We suggest to change the wording to say that collected clinical trial data should be available in "real time" in a compliant Medical Record," and that the type of Medical Record that is maintained must be human readable and under control of the clinical trial Investigator. This will allow for different solutions to a common regulatory requirement. The following are some of the very positive attributes of DDC as highlighted in the opinion: 1. Eliminating the manual transcription step from paper worksheets, which can occur today, is desirable. 2. "eSource DDC" refers to an electronic application and/or device that allows direct entry of source data, and to directly identify some of these data as CRF (Case Report Form) data, for clinical trial purposes at the point of care by investigator site staff, for example via an electronic tablet. 3. An essential element of the eSource concept is that the clinical assessment data and other source data is entered during the clinical visit in an eSource DDC system. 4. To be acceptable, an eSource DDC system and application should be customized in line with legal requirements and ICH GCP, validated, secure	Noted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	and maintained. 5. GCP requires that all entries, changes and deletions in a system are fully audit-trailed. This would also apply to an eSource system. 6. EDC systems already allow for direct data entry when defined and approved in the trial protocol. In this respect, the presented eSource system, therefore, is already to a wide degree covered by existing guidance. 7. Protocol related data should be under the control of and directly accessible at any time site/healthcare institution staff involved in patient care. Direct investigator's access to eCRF data should not be precluded in any way. 8. An increase of the investigator staff's workload must be avoided. 9. Only protocol mandated source data should be recorded in the part of the eSource system which is accessible to the Sponsor. It is agreed that it is valuable to avoid specific transcription of data from one place to another and CRFs (and eCRFs) may already, where specified in the protocol, be the original point of recording specified information – rating scales are a typical example, where these are not used in normal clinical practice, or detailed recording of multiple blood sampling times, or other parameters. For such data the direct transcription into eSource rather than initial recording in a medical record and later transcription into an eCRF seems likely to improve data quality 10. It is important to perform this benefit/risk evaluation 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. 11. Missing continuous investigator control over eCRF data is a frequent GCP inspection finding. As long as sponsor-independent source data exist and an audit trail is possible, at least a verification of the eCRF data against the	

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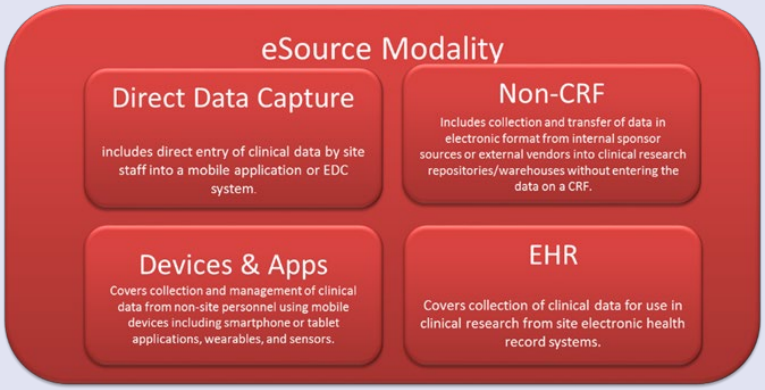
	sponsor-independent source data can be carried out in such cases. 12. The elimination of sponsor-independent source data would significantly affect data integrity and therefore change the classification of these results from major to critical.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
11	2	Proposed change (if any): CGP -> GCP	Agreed
19-21	6	It is clear that eSource DDC is developed by a sponsor but the context should be specified: does it have to be developed for each study or could it be developed more globally for the investigational site's own use (knowing of course that only data related to clinical trials will be transferred to the sponsor)?	Noted- clarified
Lines 19-21	10	**Comment:** The definition of eSource varies among stakeholders and this lack of consensus leads to unnecessary confusion. While the full scope of eSource may be theoretically accepted, often the conversation focuses on one aspect and does not reflect the full definition or architectural opportunities. The U.S. Food and Drug Administration, defines eSource as data captured initially into a permanent electronic record (eSource document) and is used for the construction and evaluation of a clinical study or a source data item included in an electronic case report form when direct entry is made. Note that the term "permanent" in the context of this definition implies that any changes made to the electronic data are recorded via an audit trail[1,2] and CDISC proposes several potential architectures[3]. However, with the rapid improvements and engagement of the stakeholder community, care must be taken not to imply limiting the definition of eSource to direct data capture into electronic data capture systems (EDC) as this reduces potential opportunities to capture data directly in other architectural designs such as: the electronic health record (dubbed as "fully integrated eSource" by the US FDA[4]), data capture into patient reported outcomes or new approaches that are in development. All methodologies of eSource should comply with the twelve requirements outlined by the eSource Data Interchange [5] and included in the EMA's guidance for field auditors[6]. TransCelerate BioPharma, Inc.'s definition of eSource (see Figure 1)[7] is robust and while it extends beyond the scope of these comments,	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		it is the most inclusive definition known and therefore that definition that is the basis of the Pfizer comments. (It is understood that this document does not refer to direct data input from mobile technology systems.)  Figure 1: TransCelerate Biopharma, Inc. definition of eSource	
22	10	**Comment**: It is generally accepted that the investigator or site research staff will collect research data contemporaneously, but it is equally possible that a patient could provide data for clinical research or clinical care data may be reused for clinical research. Limiting the expectation that eSource DDC represents data collection by the clinical trial purposes at the point of care by investigator site staff limits the other potential direct data capture workflows.	Advice based on submitted proposal
38-39	2	**Proposed change (if any):** suggest to state to "…customized in line with **local** legal requirements"	Accepted
39	8	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,	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		secure, tested for User Acceptability (UAT) and maintained.	
41- 48	10	**Comment:** Electronic Data Capture systems (EDC) are an example of an eSource system but are only one example of the current and future eSource systems.[8]	Advice based on submitted proposal
46-48	3	**EDC being the eSource** Comment: The agency states "*EDC systems already allow for direct data entry when defined and approved in the trial protocol. In this respect, the presented eSource system therefore is already to a wide degree covered by existing guidance*". Proposed change (if any): BMS requests clarification. By this definition, does the agency consider EDC systems (or IRT systems) allowing direct entry of data from investigator sites as e-source DDC systems? If yes, does the scope of the opinion paper then cover those EDC systems that are used in a DDC capacity?	Advice based on submitted proposal
50-54	2	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 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.	Advice based on submitted proposal

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
50-51	8	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 …	Accepted
lines 50, 146	8	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.	Noted
53-54	8	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).	Noted
56-57	1	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.	Accepted
56-58/ 76-82	10	**Comment:** The essential element of eSource is to gain improved patient safety, data quality and operational efficiencies for clinical research allowing for breakthrough therapies to reach patients faster.[9] This should not be limited to the manual entering of data directly into an EDC system; the outcomes metrics outlined in lines 542-546 seem to represent peer reviewed literature evaluating the secondary use of electronic medical record data for clinical research and not direct data. The TransCelerate Biopharma Inc. definition of eSource includes the secondary use of EMR data for clinical research which according to Kush & Nordo (2019) will "eliminate redundancy, improve data quality, realize learning health systems, improve research through real world evidence, inform patient choices, and realize	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		patient or personalized medicines".[10] Please see Table 1 detailing the current peer reviewed publications that pertain to the reuse of EMR data for research and is not reflective of any evaluative outcomes on manual direct data capture into an EDC. [11] Table 1: Peer Reviewed literature detailing secondary use of EMR data for clinical research projects [11]	

Source	Summary	Findings / Limitations
Gersing KR, et al. (2003)	Designed a behavioral health EMR that integrated research and care.	Evidence that clinical data can be captured once and subsequently used for patient care and clinical research.
Murphy EC, et al. (2007)	Demonstrated custom-built screens in an EHR system that included capturing research-related data, which were later extracted from the EHR database.	Evidence that clinical data can be captured once and subsequently used for patient care and clinical research.
Kush MG, et al. (2007)	STARBRITE Demonstration Project: demonstrated the feasibility of a single capture of clinical data with subsequent use in patient care and a clinical trial.	Due to the delayed finalization of clinical documentation at the institution, initial data capture occurred in the study CRF.
Kim D, et al. (2008)	Distilled 42 distinct ways (14 use case categories) in which direct use of EHR data might improve clinical trials.	Five use case categories involved the conduct of prospective clinical studies – the primary interest of this review is the clinical trial data collection use case.

Line no.	Stakeholder no.	Comment and rationale; proposed changes		Outcome
Kiechle M, et al. (2009)	The Munich Project: Leveraged HL7 messages from the EHR and, upon human review, data was transferred to the EDC system.	Demonstrated a statistically significant reduction in time for data collection activities; resulting in an almost five-hour reduction in data collection time.		
El Fadly A, et al. (2011)	RE-USE Project: leveraged a semantic mapping process to match EHR data to elements of the eCRF for research.	The RE-USE approach demonstrated a reduction in redundant data entry and improvement in data quality and processing speed.		
Laird-Maddox M, et al. (2014)	Cerner Discovere: demonstrated pre-population of diabetes eCRFs in a Cerner EHR extension of the IHE RFD standard.	The investigators claimed improved data quality and reduced data collection time, but the results were not quantified.		
Beresniak A, et al. (2014, 2016); Doods J, et al. (2014); De Moor G, et al. (2015); Dupont D, et	EHR4CR European Pilot: report on aspects of the collaborative EHR for Clinical Research (EHR4CR) initiative.	Estimated cost benefit of the EHR4CR platform for the three use cases using experts rating hypothetical studies as part of pre-commercialization assessment. The EHR4CR European Pilot went further than a single facility and demonstrated installation of the software in university hospitals in five European countries. However, the EHR4CR platform has not yet been tested in a randomized clinical trial.		

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
al. (2017)			
Lencioni A, et al. (2015)		AERS: EHR-to-Adverse Event Reporting System integration with the EHR to automate detection of detectable Adverse Events. The system uses MirthConnect's web service, HL7 messages, and the IHE RPE integration profile. Associated with a reduction in sponsor generated AE-related queries, and a staff-estimated 75% increase in lab-based AE reporting. Data quality was not assessed. Implemented at a single site and assessed only two endpoints based on staff perceptions.	
Ethier JF, et al. (2017)		European FP7 TRANSFoRm Project: developing eSource connectivity for randomized controlled trials. The TRANSFoRm eSource method and tools were formally evaluated using a mixed-methods study of TRANSFoRm as a nested cluster randomized trial embedded fully within an RCT. Although this study failed to detect a significant difference in overall or weekly recruitment rates, the secondary outcome of data completion rate did show a significant treatment-related difference. Unfortunately, data quality and site effort were not evaluated. Nonetheless, the TRANSFoRm project did demonstrate that implementation of EHR-to-EDC integration can occur within an RCT's start-up timeline.	
Nordo AH, et al. (2017)		Development, installation, and evaluation of standards-based EHR-to-eCRF software in an ongoing single site for an OB/GYN registry; based on the IHE RFD integration profile. The evaluation study compared eSource to non-eSource data capture. The overall average data capture time was reduced (difference, 151 sec. per case; eSource, 1603 sec.; non-eSource, 1754 sec.; p= 0.051). eSourced data field transcription errors were also reduced (eSource, 0%; non-eSource, 9%). However, the results lack generalizability due to implementation at only one site.	
59-61	4	Comment: Linking the EMR to the EDC would be most in line with the current	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		practices of the site and reduce data entry. eSource could be used where the EMR and EDC cannot be linked or for protocol specific data. Proposed change (if any):	
59	10	**Comment:** Clinician burn out is an unfortunate reality in the current healthcare field and great lengths are taken to ensure safety measures by reducing cognitive overload. While direct data capture into an EDC is appropriate for some use cases (i.e. dedicated research visits) this is not a viable workflow for other use cases. Simultaneously collecting data in an EDC and EHR for a patient who is receiving clinical care and participating in a clinical research study concurrently could require some data to be entered into the EDC system (Line 89- only protocol-mandated source data should be transferred and accessible to the sponsor) and some data into the EMR. Splitting data entry into two separate systems is not only error prone but may provide undue burden to the investigators reducing interest in conducting clinical trials and more importantly poses a patient safety risk.	Accepted
60	10	**Comment:** Not all hardware (i.e. tablets) allows for multiple applications to be used at all or at minimum simultaneously. Care needs to be taken to ensure that clinicians are not responsible for multiple devices (computer and tablet) to document data.	Accepted
61	10	**Comment:** Clinical research is a contributor to the development of an overall learning health system and as such, should fit into the workflow of a site without becoming burdensome or a one-off process that is unable to be scalable, reproducible or evaluated for outcomes. Best practices and lessons learned on the inclusion of clinical research into a learning health system are necessary for the community to advance. The interpretation of 'information should be recorded in line with the current practice at the study centre' should be better clarified.	Accepted in part- amendments in introduction

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
62	10	**Comment:** Variability amongst EDC, EMR and other electronic data collection vendors' standards is confounded by the variability amongst sites utilizing the same vendor. Location of where data is documented, semantic standards and terminologies differ amongst sites as well as between sites and sponsors. Standards Development Organizations have gathered key stakeholders to address the variability and representational data quality concerns, but the reality remains that mapping will need to occur for electronic data exchange. Patient care and safety is the hallmark of healthcare, "first do no harm", is the responsibility of all engaged in the care and treatment of patients. Documenting clinically relevant data into the EDC with the expectation of that data being "moved" into the EMR raises several areas of concern. 1. The data entry needs to not only be contemporaneous but simultaneous. Patient's completing a research visit must have their data available immediately in their EMR for patient care. This is a patient safety issue 2. Data moving from the EDC to the EMR must be documented in the location and format that the clinician at that specific site is accustomed to. The location within the EMR (unstructured note) of the documentation of an eboli outbreak in the US caused a lack of awareness by the clinician of this health risk is proof that this is a serious concern for patient and community health. (As referred to in lines 189-196)	Noted
67	2	**Comment:** First instance of reference to 'electronic patient reported outcomes'. **Proposed change (if any):** Revise to 'electronic patient reported outcomes (ePROs)' to include the acronym, which is introduced later (line 176)	Accepted
66-72	3	**<u>Scope of Opinion Paper on eSource</u>** Comment: The agency mentions eSource is also "*electronic patient reported outcomes, eCRFs, real-time monitoring of patient outcomes such as routine aspects,*	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		electronic capture of laboratory test results." Then the guidance states that "*direct data input from mobile technology systems*" is not in scope. It is not clear if the agency means to include all the cited modalities above in the term "mobile technology systems", or not. Proposed change (if any): BMS proposes the agency explicitly cite which of the eSource modalities listed in line 66 to 69 are in scope for this qualification opinion, as the term "mobile technology systems" is broad and may lead to confusion. We suggest a clear-cut definition of what is in scope and out of scope.	
71	2	**Comment:** 'This Qualification Opinion does not refer to direct data input from mobile technology systems, as this is out of scope.' This statement needs further clarification, since many references to mobile device data entry still exist throughout the document (e.g., line 66 'electronic patient reported outcomes', line 130 'battery life of a tablet', references to 'eSource DDC tablet' throughout). **Proposed change (if any):**	Accepted
Lines 71-72	5	Comment: "This qualification opinion does not refer to direct data input from mobile technology systems, as this is out of scope." What is a mobile technology system? Since this is an opinion on direct data capture using mobile systems (DDC), we are unclear as to why this would be out of scope. **Proposed change (if any):**	Accepted
81-85	1	Comment: While the first sentence notes the importance of 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	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
84-109	10	**Comment:** We agree with the CHMP especially on the importance to perform the benefit/risk evaluation both for data collected mainly for the clinical trial and for data that will also be a regular part of the medical record of the patient. Only protocol mandated source data should be recorded in the part of the eSource system which is accessible to the Sponsor. In addition to that, safety related data (e.g. adverse event; serious adverse event) is typically required as part of protocol mandated source data. Per our experience, this type of data could also be a regular part of the medical record for example a medical event that still exists after a trial participant gets enrolled into the study and the severity of the same event gets worse. The medical record could include hidden adverse events but often be missed or not recorded. It should be carefully reviewed during source data verification. Proposed change (if any): Propose to add recommendation/guidance on safety data review for data collected for the purpose of the clinical trial and for data that will also be a regular part of the medical record of the patient.	Accepted
85-87	9	"It is important to perform this benefit/risk evaluation 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." Comment: It should be emphasized that the benefit/risk assessment should be	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		documented. Proposed change (if any): "It is important to perform and document this benefit/risk evaluation 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."	
85-87	10	**Comment:** Could you please provide clarification on how a copy of the data electronically will be available within the Principal Investigator's control and behind the sites' fire wall.	Noted
89	4	Comment: Would eSource encourage the creation of unsolicited site comments that would be transferred to the sponsor? The current best practice in clinical data management is to avoid the collection of unsolicited comment. They can include information related to adverse events or other important clinical information that should be recorded in specific eCRF locations. Please see CDASHIG 2.0 section 7.2 CO - Comments - Solicited Comments versus Unsolicited Comments https://www.cdisc.org/standards/foundational/cdash/cdash-20#Bookmark24 Proposed change (if any):	Accepted
91-93	10	**Comment:** Site/healthcare institution staff are required to operate multiple lifesaving technologies and data collection systems. Clinically relevant data collected in an additional system (i.e. EDC) that is not available elsewhere will require training of all staff at the site and the infrequency of use in these systems will bear a cognitive overload to the clinicians as well as an unfair expectation of extensive technical support requirements leading to a concerning potential for error.	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
94-95	9	"As such, only protocol mandated source data should be recorded in the part of the eSource system which is accessible to the Sponsor." Comment: There might be additional data that should be collected outside of the scope of the trial protocol and required for safety reasons. Such data, in some cases have to be reported to the sponsor (e.g. to a DMC/DSMB) for correct decision making. Proposed change (if any): "Typically, only protocol mandated source data should be recorded in the part of the eSource system which is accessible to the Sponsor."	Accepted
95-98	9	"As such, only protocol mandated source data should be recorded in the part of the eSource system which is accessible to the Sponsor. It is agreed that it is valuable to avoid specific transcription of data from one place to another and CRFs (and eCRFs) may already, where specified in the protocol, be the original point of recording specified information …". Comment: It is EUCROF's understanding that the sponsor would have access to the clinical database (DB) only (eCRF/EDC DB), i.e. only to mapped data from the eSource DB. Please see figure on page 9 of the document and also lines 782-783: "Investigators have full access to all patient data (source data), whereas the sponsor's access is limited to the anonymized data contained in the system-generated CRFs (EUCROF note: anonymized should read pseudonymized). Also, using the eSource DDC, would not be equivalent to entry of source into the eCRF (as described above), it would rather mean to enter source into an eSource DB (via tablet interface) and from there data would be automatically mapped into the clinical DB (equivalent to eCRF database). The above sentences are misleading.	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
100-101	2	**Comment:** 'For such data the direct transcription into eSource rather than initial record and later transcription into an eCRF seems likely to improve data quality.' Not 'seems likely', use of direct entry in eSource to eliminate potential risk of inaccurate transcribed data **will** improve data quality. This is discussed in Q2 response (line 185). Suggest referencing Q2. **Proposed change (if any):** use of direct entry in eSource to eliminate potential risk of inaccurate transcribed data **will** improve data quality	Noted
100	8	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 …	Accepted
101	1	Comment: Typographical error. Proposed change (if any): Add a full stop (period) at the end of the sentence.	
100-101	10	**Comment:** The absence of quantifiable peer reviewed research to support the proposed efficiencies in the comments for manual direct data capture into an EDC system limits the ability to comment; however, there is quantifiable peer reviewed published research on the outcomes of secondary use of EMR data for clinical research demonstrating the positive benefit of this methodology that can be categorized into three areas: patient safety, data quality and operational efficiencies.	Noted

Table 2. Outcomes Reported in Relevant Studies[9]

Study & Standards	Measure: Operational Definition	Result

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
STARBRITE Kush et al. 2007		1. **Data availability**: Percent of study data elements available in EHR. 2. **Representational differences**: differences data representation between the study and the EHR e.g., units, synonyms, individual dose versus daily dose, and detail level 3. **Workflow**: Qualitative description of workflow steps and sequence 4. **Time**: Time required of the site study coordinator during start-up period	75% Qualitative description Qualitative description 20%
Munich Pilot Kiechle et al. 2009		1. **Data availability**: Percent of study data elements available in EHR. 2. **Time**: Reduction in screening visit data collection time (minutes per visit) 3. **Time**: Reduction in chemotherapy visit data collection time (minutes per visit) 4. **Data quality**: Number of data discrepancies, i.e., queries, identified through programmed data checking rules 5. **Timeliness**: Time between data availability in EDC system and data origination	48 – 69 % 53.1 15.5 Too few queries to assess ≤ 24 hrs
Florida Hospital Laird-Maddox et al. 2014		No quantitative outcome measures reported	
UAMS Automated AE detection Lencioni et al. 2015		1. **Detection rate**: Staff estimated number of lab-related Adverse Events (AEs) detected 2. **Data quality**: Number of rule-based data discrepancies detected in AEs	75% increase 42% decrease

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		3. **Time**: Statement of saved staff time	
			Qualitative description
		REUSE	**1. Data availability**: Percent of study data elements available in EHR.	13.4%
		El Fadly et al. 2011		
		TRANSFoRm,	1.**Recruitment rate**: number of study participants recruited per time period	10%-point difference
		Ethier et al. 2017	2.**Completeness**: Percent of subjects with a first clinical outcome measure for which there was also a second	14%-point difference
		RADaptor Pilot	1.**Time**: Data capture time measured by automated keystroke and click tracking	37% reduction
		Nordo et al. 2017	2.**Data quality**: Transcription error rate	9% difference
		Japan SS-MIX	No quantitative outcome measures reported	
		Kimura et al. 2011		
102	10	**Comment:** Technology solutions to complex clinical care and clinical research processes are defined by the details of the architecture and while broad stroke recommendations[13] provide direction they are not descriptive enough to determine success. Quantifiable evaluative outcomes for eSource must be accepted by all stakeholders and universally applied across modalities and regions in order to compare and contrast solutions.	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 102-103 and 202-213	5	**Comment:** Would the practice of reverse transcription into the site EMR be adequate to address the collection of source data in the DDC tool? In short, when initially capturing clinical trial protocol mandated data in the eSource DDC tool being used for the trial, is it acceptable to reverse transcribe any needed EMR data? **Proposed change (if any):**	Noted
102	8	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 …	Accepted
102-103	8	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'.)	Noted
103-108	8	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.	Noted
104-108	10	**Comment:** EMR vendors have demonstrated a desire and willingness to support the inclusion of clinical trials into the learning health systems, and as such have created flexible technological designs for the custom creation of trial specific data collection "papers or sheets". This enhanced functionality of EMR vendors provides flexibility in the development of electronic substitutions.	Noted
106	1,2,8	Comment: Typographical error.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "he" should read "the".	
110	1	Comment: Typographical error. Proposed change (if any): delete the full stop (period) after the colon at the end of the line.	Accepted
110	2	**Comment:** Given that the Novartis model also anticipates the transfer of study relevant data from existing sources such as paper and EMR systems into the eSource tool, the tool should be designed in a way to rapidly distinguish those data fields which are true source (ie the definitive record) and those that have been entered based on other sources (and thus may need additional verification activities by the sponsors monitoring team). **Proposed change (if any):** as above	Accepted
115-116	1	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. Proposed change (if any): The Qualification Opinion should describe the required functionality of DDC eSource to accommodate different national requirements.	Not possible to specify all cases- but must be compliant under sponsor Responsibility/validation
Lines 115-116; Lines 258-259	8	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.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed changes (if any): The sponsor should have may never have remote access to patient-identifying data.	
117-119 and 204-205	1	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.	Accepted
116	8	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.	Accepted
117-118	8	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?	Noted
117-119	8	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	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
117-119	10	**Comment:** Flexibility in the rendering of the documents should include, but not be limited to, paper as the upmost concern for patient information security is the driving force behind how to store and maintain documentation.	Accepted
124, 130	4	Comment: Would updates to the trial (EDC and eSource) while live either due to protocol amendments or quality issues in eSource/EDC design or eSource/EDC/EMR mapping cause the eSource system to be offline for a period of time? Would these updates be scheduled on the weekends and would backup paper worksheets be needed until fixes occur? Proposed change (if any): update line 130 temporary technical non-usability of the eSource DDC tools (e.g. updates to the eCRF/eSource, battery life of a tablet)	Accepted
Lines 124 to 144	7	Comment: Feasibility is an important point to consider. Overall, the idea behind the system is good. However, there should not be an automatic transfer of information. There should be validation, e.g. the system of DDC is from a pharmaceutical company, data on patients belong to the hospital. Proposed change (if any): Changes in the document should be made to reflect the above comment.	Accepted
Lines 124 to 144	7	Comment: It should be made clearer that the data are owned by the hospital until there is a formal release. This should be formalised in the contract between the hospital and trial sponsor. Proposed change (if any):	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Changes in the document should be made to reflect the above comment.	
125-132	10	**Comment: "**Increased data dispersion, depletion of medical records, increased workload for the site personnel that might potentially be in breach of national requirements for the upkeep of medical records" is a valid concern. The burden to the sites to maintain multiple eSource systems is a responsibility of all stakeholders and therefore collaboration among groups for shared solutions is key to the success of eSource. Expectations that sites will instantiate, train, monitor and maintain multiple systems for clinical research eSource in addition to the many other systems necessary for a learning health system is unreasonable. Stakeholder's alignment and development of open source products by the sites and consortiums hold great promise on the integration of clinical care and clinical research systems.	Accepted
Line 130	8	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).	Accepted
130	2	**Comment:** Temporary technical problems may also include no internet access (this may be more common). **Proposed change (if any):** include no internet access	Accepted
131	10	**Comment:** Clinically relevant data documented manually in any other system than the EMR must be available to appropriate clinicians for patient care at the time of collection. The lack of availability of this data is a patient safety concern. Expectation of data overlap for clinical care and clinical research is generally accepted to be dependent on the phase of the study (see Figure 2) [14]	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome

Figure 2: Overlap of data used in clinical research by phase (green circles) with data availability in the HER (blue circle).

Data overlap between clinical care and clinical research has been quoted to be between 48-75%. Pfizer eSource work demonstrates between 60- 80% of the data collected for clinical research is also collected in the patient medical record (see Table 3) and therefore available for reuse. This significant overlap of data between clinical care and clinical research increases the need to ensure that all clinically relevant data is available in the patient medical record in near real time in a way that supports its reuse.

Table 3: Evaluative Outcomes of Pfizer pilots based on methodology used in Nordo, et al, 2019 publication [9]

	Pfizer Pilot 1 Pfizer Study "A" CRF to Site EHR		**Pfizer Pilot 2** Pfizer Study "B" CRF to Site FHIR Server*	
Domain	**CRF-EHR Data Availability (approx.)**	**CRF-FHIR Data Availability (approx.)**	**CRF-EHR Data Availability (approx.)**	**CRF-FHIR Data Availability (approx.)**
Demog	80%	60%	Not evaluated	100%

Line no.	Stakeholder no.	Comment and rationale; proposed changes					Outcome
		Vitals	90%	85%	[redacted]	Not evaluated	
		Local Labs	70-90% depending on lab	60-90% depending on lab		60%	
		ConMeds	70%	60%		Not evaluated	
		Adverse Events	60%	0%		Not evaluated	
		Tumor Assessment	Not evaluated	Not evaluated		65%	
131-132, 186-196, 215-218 & 266-269	3	**<u>Interoperability requirement between DDC, EMR and EDC and mirroring of source data</u>** Comment: The agency states "*ideally, the system should allow automatic (real-time) transfer of the captured eSource DDC data to the respective sections of the EMR management systems*". Also, it is stated that "*It is the sponsor's responsibility to ensure the system performs as intended. The required quality control and validation of the capability of the system to ensure correct, complete and real-time transfer of eSource protocol-mandated data into the (E)MR needs to be performed under the responsibility of the sponsor."* We believe that the EMA's opinion to have interoperability and integration between eSource, EDC and EMR is in right the direction as a long-term ambition. However, a potential imposed requirement to integrate eSource DDC with the site's EMR system and the sponsor's EDC system may become a barrier to wider adoption of eSource					Accepted

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		DDC in the medium term (next 2-4 years). In the US, at least, there are hundreds of EMRs, and no robust standards adopted for interoperability for most of them. Added to the complexity is that sponsors use multiple sites per clinical trial, each of which may have a different EMR system, hence involving the need to integrate with multiple EMR systems for one single study. In line 266 to 269, the agency states: "When using an eSource tool to collect source data in a clinical trial, it must be ensured that the collected information and data is mirrored in the patients' medical record to minimize a duplicated collection effort and documentation of data at the risk of divergent information and data in both sources". As per our response above, varying EHR systems may make it challenging to "mirror" data. Patient data would need to be transformed until standards are widely in place and adopted. In addition, this may impose that eSource DDC systems replicate the medical records design such that data can flow in near real-time with minimal transformation and delay. Proposed change (if any): BMS proposes that the agency clarify that the automated transfer between eSource DDC and EMR is not made as a requirement for the use of DDC, as we believe this could become a deterrent and a barrier for sponsors to use and reap the benefits of eSource DDC. Additionally, if the agency deems this automated transfer to be required, we propose that the agency provides guidelines or expectations on the would-be requirements of an integration between DDC and EMR – for example on which data would have to be transferred, data standards to be used, the minimum expected delay in transmission of this data, etc...	
135-136	9	" • a site qualification procedure should be conducted before deploying the system in any given site (see Q7);" Comment: it should be mentioned that within the process of site qualification for a certain trial, the deployment of eSource DDC needs to be explicitly addressed and all aspects (even beyond what is addressed in Q7) need to be checked by appropriate	Accepted, CRA training is part of systems qualification

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		personnel (especially trained CRAs).	
135	10	**Comment:** A site qualification of the system is appropriate and necessary but indicates the need for a consortium of stakeholder groups to align on eSource solutions in an effort to reduce the number of products that each site will need to instantiate, validate and maintain.	Accepted This is a long term aim and is encouraged
138-139	1	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.	Accepted
140, 157	2	**Comment:** In consideration of 'security and traceability of the data' and various parties involved (including investigator), suggest discussion of 'role-based security with specific set of privileges per role' implementation in Q1 response (which is also referenced in Annex Q8 response). **Proposed change (if any):**	Noted
Lines 141-144	8	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.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is recommended that this paragraph be revised to provide more clarity on this topic.	
142	10	**Comment:** This bullet says, "each individual piece of information needs to be pseudonymised prior to transfer from the investigator/institution to the sponsor, and the hospital will need to be the sole holder of the link to the records." The sole holder of the records could also be medical practices or research units. **Proposed change (if any):** Propose using 'investigator site' instead of 'hospital'	Accepted
146	2	**Comment:** The sponsor may also choose to subcontract the DDC Tool to 3rd party vendor (e.g. EDC Software as a Service). As per ICH-GCP E6(R2) 4.2.6 'If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure integrity of the trial related duties and functions performed and any data generated.', the sponsor should have full access to the third party's DDC tool development / validation documentation (and any other relevant quality system documentation) to ensure quality oversight (also see line 215-216). **Proposed change (if any):**	Accepted
146-155	1	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	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Medical records held at outside parties • External laboratory records • Pharmacovigilance and medical coding activities (often 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.	
Figure between lines 146 and 147	9	EUCROF is of the opinion that this figure is not in line with what has been presented (and intended) by Novartis in the figure on page 9 of the document. There, it becomes clear that the eSource DB (the repository of all trial specific source data) is not accessible to the sponsor (other than by the CRAs who do on-site monitoring and therefore would have access to fully personalized source data). This is also described in lines 782-783 of the document. What is called eSource DB on page 9 is called "DDC tool database" on page 4. This database is NOT under sponsor control. Also, mapping takes place between the eSource DB and the clinical DB (eCRF DB) and not between the DDC tool on page 4 (which is the tablet and serves as a data entry device) and the DDC tool database (eSource DB on page 9). EUCROF sees some discrepancies between the Novartis position (intention) and what the authors of the opinion document might have perceived.	Noted- This figure was proposed by the CHMP as a possible alternative.
Line 149	8	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	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		record data from previous visit (e.g., tumor assessments)	
150- 151	9	"A faithful copy of the DDC tool data is mapped and filtered to ensure that only pseudonymised data and data defined per protocol is uploaded to the DDC tool database (red).." Comment: Please see comment above, pseudonymization in the eSource DB (DDC tool database) is not necessary.	Not accepted- no sponsor or provider access to personal data
157-159	10	**Comment:** Digital health and digital clinical trials is a rapidly growing field with many new disruptive innovations on the horizon that as long as they are compliant with all necessary regulations should be equally considered.	Accepted
157-161	9	"Different arrangements from the above might be envisaged, provided that (in addition to the other comments in this Opinion) the investigator can identify the individual patient entries at any time without having to consult the enrolment log. Also, it should be possible to distinguish at any time between the eSource version completed and held by the investigator and the version held by the sponsor or third party." First sentence is not entirely clear. The second sentence is not accurate according to EUCROF's understanding, as there is no eSource version held by the sponsor. The sponsor has access only to the data mapped from the eSource DB into the eCRF DB. Also, the eCRF DB could be held by a third party (e.g., CRO).	Accepted with amendment
159-161	8	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	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to simultaneously send data to 2 places.	
159	10	**Comment:** "Different arrangements from the above might be envisaged, provided that (in addition to the other comments in this Opinion) the investigator can identify the individual patient entries at any time without having to consult the enrolment log. Also, it should be possible to distinguish at any time between the eSource version completed and held by the investigator and the version held by the sponsor or third party." ICH E6 (R2)8.3.21: Subject Identification Code List is the respective log required to identify individual patients instead of enrolment log. **Proposed change (if any):** Propose using 'Subject Identification Code List' instead of 'enrolment log'	Accepted
line 159	8	Comment: line 159: misspelling: "enrolment" should be "enrollment"	Superseded by above
174	2	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.	Noted
185-189	6	As there should be a consistency of the data between eSource and EMR, must the sponsor perform an additional SDV between eSource and EMR or will the validation of the process of data transfer between eSource and EMR be sufficient (and no SDV needed)?	Noted
185-188	10	**Comment:** Reduction of manual data entry and removal of "swivel chair" [12] data transcription are necessary improvements to data collection for clinical research that will have a direct impact on patient safety, data quality and operational efficiencies. Accessibility of all clinical relevant research data in the EMR is a key factor in realizing learning health systems and broadening the knowledge that can be used to	Noted

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		improve health care and patient health outcomes.	
186	11	Comment: While we appreciate the noble goal of immediate transfer of data The statement about "long term ambition" to do automatic data transfers to the site's own EMR, this is only feasible in today's world if there were one global EMR and one global data collection system. Many EMR vendors would balk at this security risk. Proposed change (if any): Collected data should be available in "real time" within the Medical Record of the clinical site. The type of Medical Record that is maintained by the Investigator must be a compliant medical record and under control of the clinical trial Investigator.	Accepted- no change as text reflects current situation
187	8	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	Accepted
Lines 189, 222 & 304	8	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.	Noted
191 to 196	4	Comment: lines 526 to 528 mention that phase I sites were used as part of the pilot. Phase I studies are usually less complex and phase I units are usually staffed by professional site staff that primarily deal with clinical studies.	Noted, but the aim of Qualifications is also to start with earlier, simpler cases

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		A more detailed pilot would be needed to assess the challenges on multicenter phase III studies located in different European countries using site staff that are new to both EDC and eSource systems. It may not be currently feasible to roll eSource out past phase I units until there are more comprehensive clinical research and healthcare standards. Proposed change (if any):	
191-196	1	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 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.	Acknowledged. The comments relate to the current proposal and situation.
Line 195	8	Comments: Change management should address the impact of study/protocol configuration updates on data transmission accuracy, and completeness.	Change introduced line 205

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195	8	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.	Noted. A qualification can be requested for different proposals.
197-200	9	"If the data is initially collected in an EMR, worksheet or paper form (data flow 3 in Figure 1 as submitted by the Applicant), the proposed system data flow for protocol-mandated information would not be different from an eCRF, as currently existing, and would require monitoring by the study site monitor or CRA." Comments: The monitoring would only be required for transcriptions of paper source (routine paper source data or paper worksheets, if in use). It is assumed that protocol-mandated EMR data would be accessed and transcribed via the eSource Portal/ eSource DB (see figure on page 9) onto the eCRF DB by a validated process. If so, no source data verification would be necessary for the EMR data in the eCRF and the eCRF data would qualify as certified copies of EMR data. Paper source and EMR source data should be differentiated in the above paragraph.	Amended line 209-210
197-200	10	**Comment:** The expectation of eSource is that it will reduce on-site monitoring. If therefore, there is a requirement for monitoring of data entered into the EMR, this would remove a large benefit to eSource	Noted, See above
204	2	**Comment:** The statement*" This is only possible if the eSource only contains elements which can be adequately mirrored in a printout or pdf flat file."* Does this requirement include the audit trail elements of a record as well, or just the current data?	Noted The form is part of the EDC tool the meta info and context are reflected in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	the data available to the site
206	1	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.	Repeat comment- See above
215-218	1	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.	Accepted
215-218	10	**Comment:** "It is the sponsor's responsibility to ensure the system performs as intended. The required quality control and validation of the capability of the system to ensure correct, complete and real-time transfer of eSource protocol-mandated data into the (E)MR needs to be performed under the responsibility of the sponsor. An increase of the investigator staff's workload must be avoided." The control and validation process performed under the responsibility of the sponsor must also comply with the Data Protection Act and the GDPR. **Proposed change (if any):** Propose to add data protection requirements also for sponsor's responsibility.	Accepted
220-222	1	Comment: ACRO strongly supports this position.	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 224	8	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.	Noted, amended
Line 225	8	Comments: Clarifications would be needed regarding this statement "In case of eSource, 1-to-1 coding of data is expected". Could you clarify what "1-to-1 coding of data is expected" means?	Noted- Original must be reproducible
226	8	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?	Accepted
227	8	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).	See above
237-277	1	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.	Accepted and introduction clarified
Line 231-234	8	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?	Noted

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		Clarification will be helpful.	
Line 231	8	Comment: It is not clear why the "centralized monitoring" is described here. What actions could be done?	Noted
243	11	Comment: The statement about national requirements regarding the EMR maintenance should state Medical Record requirements in lieu of EMR. Proposed change (if any): The concept of [eSource] presents challenges but no theoretical obstacles: if it can be designed to meet all requirements for ICH source data and (national) requirements regarding the Medical Record maintenance, then it could be compliant	Amended
247-259	1	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.	EMA has no authority to seek the opinion of the EDPB. We could consult either formally or informally the EDPS, our DP supervising authority, but we could not trigger a discussion at the EDPB level directly. Also, we would probably have to inform the Commission in advance as we did for other instances (e.g. interplay between the CT Regulation and the GDPR).
247-253	10	**Comment:** Data ownership and data stewardship are separate but equally important concepts. Patients own data about themselves and therefore have the rights to use that data in accordance with all regulations without maleficence. "As technological advances encourage exponential growth in the amount of data produced, data has been referenced as "the world's most valuable resource" [15] and 'owning' data has been equated to power."[10] Patient's need to retain the rights and	Noted

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		power of their own data. Healthcare professionals are data stewards of a patient's data responsible for the security and use with the consent for patient to the benefit of humanity.	
254-259	9	"It has to be ensured that information in the eSource system is pseudonymized, however for the completeness of EMR the information needs also to be transferred to the patient record. Traceability and rigorous quality assurance and quality control should be ensured for these data transfers (pseudonymized in eSource and non-pseudonymized in EMR). The sponsor should have no remote access to patient-identifying data." Comments: As mentioned before, EUCROF's understanding differs in as such as the sponsor does not have control over the eSource DB and therefore pseudonymization of eSource DB data is not necessary. Only the on-site monitor would have to access the eSource DB to perform (limited) SDV (only for those data that had to be manually transcribed from site paper source). In a traditional process (transcription of source data into a eCRF/EDC DB), the monitor has access to non-pseudonymized data as well. The mapping from eSource DB into the eCRF/EDC DB does not have to be monitored as long as the mapping process has been validated.	Noted
254-259	10	**Comment:** Please clarify how the data from the EDC would be exchanged with the correct patient's medical record at the correct provider if the sponsor only maintains de-identified data and the sponsor "should have no remote access to patient-identifying data" which is understood and agreeable. Please provide further reflection on the mechanism for patient, patient provider and study identification mapping?	Out of scope as this is a technical requirement
266	11	Comment: One issue is to clarify the definition of the word "mirrored" and the definition of the word "Medical record." "Mirror" should mean that what is in the investigator's Medical Record is a certified copy of the patient data. The "Medical Record" should any record, no matter where it is located, which is under control of	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the clinical investigator for the specific trial. The Medical Record should not be defined as an EMR or EHR which are commercial products. Investigators may keep records in various media and we must not micro-manage investigator behaviour and record keeping as long as they can produce an acceptable patient Medical Record at the time of a regulatory inspection or at the request of a patient. Proposed change (if any): No change in wording	
271 to 275	4	Comment: in line 202 to 205 it is said that the system creates PDFs for archival. That is a useful feature but not very useful for importing the data into the EMR at a later stage. The CDISC Operational Data Model (ODM) standard is designed for transfer and archival of clinical trial data. Using ODM both importing into the EDC system and EMR could be facilitated. Proposed change (if any):	Noted- this Opinion does not endorse a single proprietary system
273	2	**Comment:** *"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."* Based on this statement would it be acceptable for the esource database to be held by a sponsor contracted third party that provides continual data access to the investigator? **Proposed change (if any):**	Noted Outsourcing DB is out of scope
274	8	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.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
288-292	1	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.	Accepted
Lines 288-292 and 364-368	5	**Comment:** What is recommended for validation as described in these sections? Is the conduct of study design, setup, study specific testing and user acceptance testing adequate? **Proposed change (if any):**	Accepted
289	2	**Comment:** *"…use of the eSource tool is not too complex and not limited to capture data only, but allows capturing of free text as well."* The use of free text fields increases the chance safety data or unreported events are not entered correctly (they should be captured in other data fields). Suggest limited use of free text; is it acceptable to limit their use to specific disease or diagnosis narrative sections? **Proposed change (if any):** "…but allows controlled and limited capturing of free text where necessary."	Accepted (part) should not impact from the freedom currently afforded to HCP in recording patient information
289-290	2	**Comment: Use of** eSource should not create more work for investigators. **Proposed change (if any):**	Accepted
290	8	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.	Accepted (part)

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Lines-290-292	8	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.'	Accepted-clarified
291-292	6	The Qualification Opinion calls for system validation by comparing data collection via eSource DDC versus collecting the same data without eSource DDC. We are concerned with the complexity of that process across so many sites using so many different systems. Would User Acceptance Testing not be enough to prove eSource reliability?	Accepted
296-301	9	"In order not to increase the workload on the investigator and the investigation sites staff, transcription requiring manual intervention, between eSource and EMR, should be avoided and systems should be in place to have automatic real-time transfer of the data that has to be captured in both. Using an eSource should definitely not result in a depletion (in terms of completeness of data and ease of accessibility by the physician- see also Q5 below) and/or disorder of the information available in patient records. Comments: EUCROF recommends to mention that formats of data might differ between eSource and EMR (or even paper source) and that this should be considered when transcribing data (automatic or via print-outs) from eSource DDC to the "original" source. For example, height and weight collected in most of the EU countries will be in	Noted-unchanged from current practice

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		meters (or cm) and kilograms; or blood pressure (mm vs cm) ... The conversion mechanism should be validated within the validation of data transcription.	
296-301	10	**Comment:** Manual transcription is an unfortunate reality of present day clinical research data collection. While a goal of electronic manual data exchange is shared, the realization that this new reality will come in phases must be appreciated. While the process, regulations, standards and products mature it is reasonable to expect some manual transcription to be required during the transition period.	Noted
Line 300	8	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.	Noted-unchanged from current practice
Lines 314-317	8	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.	Noted
314-316	1	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.	Noted
315-317	2	**Comment:** It may be difficult for a system to guarantee the continuous control of the investigators over the data? **Proposed change (if any):**	Noted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
322	8	Comment: Transfer of ownership and definition of what is the eSource after completion of the trial should be recommended.	Accepted
324-328	8	Comment: Clarification is required regarding the meaning of "Missing continuous investigator control over eCRF data", perhaps by providing an example.	Accepted
324-328	9	"Missing continuous investigator control over eCRF data is a frequent GCP inspection finding. As long as sponsor-independent source data exist and an audit trail is possible, at least a verification of the eCRF data against the sponsor-independent source data can be carried out in such cases. The elimination of sponsor-independent source data would significantly affect data integrity and therefore change the classification of these results from major to critical." Comments: It is the understanding of EUCROF that the eSource DB represents a sponsor independent repository for source data containing non- pseudonymized trial specific (protocol mandated) personal data. The sponsor does not have access to the eSource DB (DDC tool database). The EMA's concern is not shared by EUCROF.	Noted-clarified
324-328	10	**Comment:** It is not clear what the agency referred to for "sponsor-independent source data". **Proposed change (if any):** Propose clearly defining "sponsor-independent source data".	Accepted
324-328	1	Comment: This point is of huge significance for the acceptance 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.	Noted
324-328	3	<u>Ensuring Sponsor-independent source data</u> Comment: We agree with the agency's identified risk of DDC having clinical trial	Agreed in part

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		data no longer captured in the document management system of the investigator's site. We believe that eSource DDC brings some novelty and ambiguity around source data control, as it brings the addition of a third party involved in the source data (eSource technology vendor). As such, we believe that it may be required to enforce processes contractually between site, sponsor and the eSource technology vendor to ensure sponsor-independent source data. Additionally, clarity is required on the role and expectations from the eSource technology vendor. Proposed change (if any): BMS proposes specifying in the Opinion Paper that contractual language would have to be in place between all involved parties in an eSource DDC implementation contract, to ensure clear processes are in place for source data remaining available for investigator control, and remains sponsor-independent during the trial and after the trial is concluded. Additionally, we propose adding language in the Opinion Paper on the role and expectations from the eSource technology vendor's access level to eSource data. Finally, from a patient data privacy perspective, we ask that the agency provide clarity on whether there is a need to specify in the informed consent form (ICF) that a third party (eSource technology vendor) can see source data during and after trial in the eSource system. In general, EDC (eCRF) vendors are not mentioned in the ICF even though some source data may be entered directly into eCRF. However, eSource is a slightly different situation from eCRF because eSource technology vendors can see original (protocol-mandated) source data theoretically.	
330- 331	8	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.	Agreed
Lines 330-331	8	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.	Agreed
314-331	3	Investigator Approval & Safety Reporting for eCRFs	Agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: The section within these lines describes "*the need to develop and implement processes that ensure the continuous control of the investigators over these data during and after the trial.*" There is also a reference to ICH-GCP E6 [R2], chapter 8, to further solidify the agency's response. Similarly, ICH 4.9.3 (Records and Reports) and ICH 8.3.14, (Signed Dated and Completed Case Report Forms) indicate that the Investigator must endorse all changes to the data and that Signed, Dated and Completed CRFs must be retained at the Investigator site to confirm the observations recorded. We do not see any guidance or reference to requiring Investigator signed eCRFs in the DDC tool in the Opinion Paper. More specifically, we do not see any guidance regarding the Investigator's Signature on Serious Adverse Events (SAEs) in the eSource tool or the expected timeframe for the reporting of the SAEs to the Sponsor company. Proposed change (if any): BMS requests clarification. Does the EMA endorse the same requirements for Investigator Approval of data in the DDC system as they do for eCRF data collected in EDC systems? Is the EMA's opinion that electronic signature by the Investigator is required for any data entered or modified in an eSource system?	
342	6	For long-term archiving, could you please detail the expected requirements? Knowing that no actual system warrant access to the data for 25 years must the Sponsor to create copies of the data at regular intervals in alternative formats? In that case, which standards are we to use in order to certify those copies?	Agreed
345-351	1	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.	The guideline will override any advice, once into force

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		Proposed change (if any): Ensure alignment with the updated guideline.	
346	2	**Comment:** *"Back-up processes should be in place and migration of data and media should be planned, performed, and traceable."* Suggest adding, 'back-up and restore' process – periodic restore tests should be performed to ensure viability of the eSource back-up data. Suggest including back-up and restore test requirement as part of the sponsor's oversight responsibility in Q2 response to the operational consideration as well. **Proposed change (if any):** *"Back-up **and restore** processes should be in place….."*	Agreed
349	2, 8	misspelling: "wrights" should be "rights"	Agreed
349	8	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.	Agreed
350	2	**Comment:** **Proposed change (if any):** 'It should be ensured that eSource data is may be machine readable in the future, independent from specific software platforms and operating systems.	Section amended
350-51	~~8~~	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?	Agreed
Line 349-350	8	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	Agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		system log or journal describing the system access considered an "audit trail" ? what kind of information should be captured in this "audit trail"?	
350-351	9	"It should be ensured that eSource data is machine readable in the future (independent from specific software platforms and operating systems)." Comments: No matter in what format electronic data are stored, there will be a certain software/operating system environment necessary to access/read the data. Maybe it was meant that no "special" software platform and operating systems are required and the access of data is possible using a "commonly used" software/operating system. It should be better described what is meant with the text in brackets.	Agreed
Line 350	8	Should the sentence say "human"readable rather than "machine" readable?	Agreed
Line 350(also 138)	8	Comment: Could you clarify what is intended by "Machine Readable": is a static format such as PDF adequate, a full relational database,…?	Agreed
350-351	3	**Ensuring eSource data is machine readable in the future** Comment: "*It should be ensured that eSource data is machine readable in the future (independent from specific software platforms and operating systems)*". Due to a lack of standards across the industry, ensuring that eSource data remains readable across several platforms and operating systems may prove to be challenge for many applications to meet the stated requirement. Proposed change (if any): BMS requests clarification. To ensure that DDC applications are designed to meet non-proprietary standards, BMS proposes that the agency specify in the Opinion paper the need to use of standards recommended for eSource DDC data in the future.	Agreed
364-368	1	Comment: The current text does not differentiate between the empiric validation of	Agreed

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		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.	
364-368	9	"In case an eSource system is proposed to an investigator, the supplier of the eSource system and the sponsor must guarantee to the investigator/health care institution that this system is GCP compliant. It is the responsibility of the sponsor to ensure that the validation takes place. This has to also include the validation of data transfer from the eSource system to the investigator's/health care institution's EMR of the patient and should be done in a way that fulfils national legislation and standards." Comments: The above paragraph should be amended with: "In addition, the mapping from the eSource DB into the eCRF DB has to be performed via a validated process.	Agreed
Line 365	8	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.	Agreed
366-367	10	**Comment:** Clarification on the process of validating the data transfer from the eSource system to the investigator's/health care institution EMR without de-identification is appreciated.	

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377-379	1	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.	Agreed - Section amended
377-380	2	**Comment:** Suggest, not to limit the example to encryption technology and integrity of the data during data transfer only. In order to ensure data privacy, eSource data entry system must also consider full aspects of the industry standard security features, e.g., password complexity and expiry, role-based security, etc. **Proposed change (if any):**	Part agreed- technical solutions out of scope
377-378	8	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.	Agreed
378	10	**Comment:** What does "state of the art" encryption include?	Part agreed- technical solutions out of scope
434	2	**Comment:** Correct the number sequence	**From now on the comments refer to the Sponsor's proposal and as such**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): depending on the intention, suggest changing 2 a) to 2).	**the text has not been modified.**
418 & 488	2	**Comment:** Use of eSource DDC technology does not ensure the quality collection of accurate and complete data. It better facilitates contemporaneous collection / review of the data, granted (as with the non-eSource DDC technology), the requirement of adequate programmed data entry checks and queries is met. **Proposed change (if any):**	
422	8	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.	
465, 937-939	3	**EMA Requirements for eSource DDC data in the MAA** Comment: In Novartis's request in Question 9 line 465, the EMA responds that eSource collected "*data can be submitted in the support of a MAA provided that this data is sufficiently GCP compliant*". However, in Novartis's response in lines 938-939, they specify: "Novartis received feedback from EU Health Authorities, and following this feedback, the use of eSource DDC was discontinued in this trial." It is not clear from the text what caused the sponsor to renounce the use of eSource DDC after the feedback received from the EMA. Additionally, it is unclear what the EMA feedback was. Proposed change (if any): BMS requests clarification on the requirements needed for eSource DDC so as to avoid a similar situation described by Novartis. Does the EMA plan to provide clear recommended, specific requirements for eSource DDC systems to support an MAA submission? Until system requirements are defined, does the EMA recommend and would they be willing to proactively meet with Sponsor companies that wish to pilot eSource DDC systems to ensure the systems are	

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		meeting all requirements prior to study initiation and during the course of the study?	
496	2	**Comment:** The statement that SDV could be reduced or eliminated is clearly dependent on the extent to which the site is utilizing other existing source data types (paper records, EMR etc) which according to the model also need to be entered on the eSource tool) and thus require some level of verification activity by the sponsor. **Proposed change (if any):**	
Line 513	8	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?	
530	10	**Comment:** The feedback from the pilot trials are helpful. However, the data were from investigators' and sponsors' perspective but no feedback from patients or trial participants' perspective. For example, did the investigators and site personnel have 'quality time' or better 'quality time' provided to patients/trial participants once they use the eSource DDC, if they did, what was patients/trial participants perspective re satisfaction. **Proposed change (if any):** Propose to provide the data from patients/trial participants perspective for the trials utilizing eSource DDC technology, if possible and feasible.	
698-702	8	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 paper Proposed 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	

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		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	8	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	8	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.	
736-738	10	**Comment:** "The tool utilizes a tablet-based system, which provides portability and enables data collection from anywhere (physician office, hospital ward, on-the-move etc.), as well as a centralized dashboard which provides oversight of all collected source data/documents and management of data review and data cleaning activities." This advantage also comes with disadvantage in the case of inappropriate data disclosure if a tablet gets lost or misplaced from the investigators' site. Sponsors should plan and design the eSource DDC tool to support this type of situation or similar. **Proposed change (if any):** Propose to provide some recommendations/guidance in the case of inappropriate data disclosure such as loss of the tool utilised a tablet-cased system from investigators' sites. And/or advise sponsors to plan and design the eSource DDC tool to support this type of situation or similar.	

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Line 819	8	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.	
830-832	3	**Audit Trail on .PDF exports** Comment: "*Source data collected by the eSource DDC system can be readily stored due to its electronic format. Electronic format allows for easy generation of certified copies (PDF files) that can be maintained separately both in the short and long term and available at all times for inspection*". In the case that this export feature to .PDF is used instead of a direct integration with the EMR of the site, it is not clear what is required to be in the content of the exported .PDF. Specifically, does an audit trail from the eSource DDC need to be captured in the exported .PDF? Proposed change (if any): BMS requests clarification on the requirements for information needed to be on the exported .PDF for storage in the site's EMR. Specifically, can the agency specify if an audit trail needs to be exported into the .PDF for long term storage in the site's EMR?	

References cited in the comments

1. [Online] Food and Drug Administration. [Cited: June 30, 2018]. (https://www.fda.gov/downloads/training/guidancewebinars/ucm383657.pdf).
2. Guidance for Industry: Source Data in Clinical Investigations (eSource). September 2013. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf.

3. [Online] [Cited: February 18, 2018]. https://www.cdisc.org/system/files/members/standard/foundational/glossary/CDISC%20Glossary%20v11.pdf.
4. [Online] [Cited: December 6, 2018] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm625385.htm
5. [Online] [Cited: February 25, 2019] https://www.cdisc.org/esdi-document.
6. [Online] [Cited: February 25, 2019] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf.
7. Keller, E., *Optimizing the Use of Electronic Data Source in Clinical Trials: The Landscape, Part 1.* Therapeutic Innovation and Regulatory: 2016, Vo. 50 (6) 682-696Nordo, A., et al., *Use of EHRs Data for Clinical Research: Historical Progress and Current Applications.* Learning Health Systems, 2018.
8. Nordo,A., eta al., *Evaluative Outcomes in Direct Extraction and Use of EHR Data in Clinical Trials.* International conference addressing Information Technology and Communications in Health (ITCH): February 14-17, 2019, Victoria, BC, Canada.
9. Kush, R**.**, Nordo, A. "Re-use of Electronic Health Record Data for Clinical Research". In: Richesson RL & Andrews JE (ed). Clinical Research Informatics, 2nd edition. Springer-Verlag: London. 2019.
10. Garza, M., et al., *eSource for Standardized Health Information Exchange in Clinical Research: A Systematic Review*. International conference addressing Information Technology and Communications in Health (ITCH): February 14-17, 2019, Victoria, BC, Canada.
11. [Cited: February 6, 2016] Bain, L.
12. [Online] [Cited: February 26, 2019] https://www.cdisc.org/system/files/all/reference_material_category/application/pdf/esdi.pdf
13. [Cited: March, 2018] Zozus, M.
14. *The Data Economy .* 9039, London : s.n., 6-12 May 2017, The Economist, Vol. 423.