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eSource Direct Data Capture (DDC) qualification opinion

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Context of use of the technology

This Qualification Opinion is intended to give information about the regulatory acceptability to use an eSource Direct Data Capture (DDC, or simply eSource in this document) in clinical trials conducted to support a Marketing Authorisation Application for a medicine.

In the context of this Qualification Opinion , the general term “eSource DDC” refers to an electronic application and/or device that allows direct entry of source data, and 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. It is not intended to identify or support a specific, proprietary system, but to discuss some of the characteristics a system for direct data entry should present. It should also be noted 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.

The authorisation, conduct and supervision of clinical trials and of clinical care (healthcare services) fall outside of the remit of the European Medicines Agency (EMA). This Qualification Opinion is, therefore, without prejudice to applicable national (or EU level) requirements governing various aspects related to the above-mentioned activities under other frameworks that also have to be met, e.g. processing of clinical trial subjects’ personal data and documentation and record keeping requirements. While it is not in the remit of EMA to provide interpretation of or guidance concerning such legal requirements, the need to follow these requirements is, nevertheless, highlighted throughout this advice. When designing and implementing a system, national legislation, GDPR (including data controller requirements) should be complied with.

To be acceptable, an eSource DDC system and application should be customized in line with legal requirements and ICH GCP, validated, secure and maintained.

An eSource system can be considered as an EDC (Electronic Data Capture) system. EDC is the current technology used by research institutions, sponsors and CROs to manage clinical trial data when using electronic trial data handling and/or remote electronic trial data systems. Data from clinical assessments is usually initially captured on paper or electronic media, i.e. Electronic Medical Records (EMR), and then transcribed into eCRFs (Electronic Case Report Forms) at a later time but in a timely manner, as required by ICH-GCP; however, 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.

Sponsor-programmed edit checks, or queries, for the protocol-mandated collected data take place when that data is entered in the system and may potentially be helpful to reduce or identify missing or erroneous entries; however, any changes to data should be visible in the audit trail (see Q2). Additionally, the CRA monitor performs source data verification checks on data entered from an EMR, worksheet or paper form.

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. When designing the system there are some fundamental aspects to be respected:

- The ability of the physician to record clinical information in the patient medical record should not be limited or constrained;
- such information should be recorded in line with the current practice at the study center.
- The integrity of the medical records shouldn’t be compromised.
- The sponsor should have access only to pseudonymised information mandated by the protocol.

In some types of trials, electronic technology is already in use, as, for example, electronic patient reported outcomes, eCRFs, real-time monitoring of patient outcomes such as routine aspects, electronic capture of laboratory test results. These types of trials could be a possible initial testing ground for an eSource system.

This Qualification Opinion does not refer to direct data input from mobile technology systems, as this is out of scope.

Question 1 Benefits of the technology

We propose the use of eSource will improve the quality of the data collected. What is EMA's view on this concept, and are there any comments on the characteristics that a system to implement it should possess?

Draft CHMP answer:
In order to improve the quality of the data collected in clinical trials it is imperative that all advantages and disadvantages of the proposed system are weighed against each other.

Potential disadvantages that could have a negative impact on quality, traceability and accountability of data collected should be carefully evaluated beforehand. 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.

Only protocol-mandated source data should be transferred and accessible to the sponsor. Additionally, the system must not impoverish clinical care by depleting the medical records or limiting the capability of the healthcare professional to record, maintain and trace non-protocol mandated information. Protocol related data should be under the control of and directly accessible at any time to site/healthcare institution staff involved in patient care.

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 – 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
The Company's proposal is not sufficiently detailed on if (and if, how) incorporation into EMRs of any data collected primarily in the eSource DDC is possible.
Some clinical trials require data, which due to its protocol-related peculiarities cannot be integrated in existing patient medical file or electronic medical records, except by adding a separate sheet/page. In these cases he use of trial-specific worksheets may be suitable and investigators often create their own trial related worksheet to amend their routine documentation in the patient health records.
Those clinical trials may benefit from replacing such worksheets that require transcription by investigator staff into the eCRF by sponsor-provided electronic worksheets (eSource).
In these cases a pre-developed electronic worksheet (eSource) should:.

- add promptly the data entered into the electronic worksheet to the patient medical records in accordance with the practice, degree of detail and accessibility in force at the study centre.
- any patient identifiable information should be kept at the investigator's site for seamless integration in the patient medical record (see also answer to Q3 concerning data protection). Only pseudonymised information should reach the sponsor. The sponsor should have no remote access to patient-identifying data.

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.

Reference is also made to the EMA questions and answers on the Records of study subject data relating to clinical trials (link).

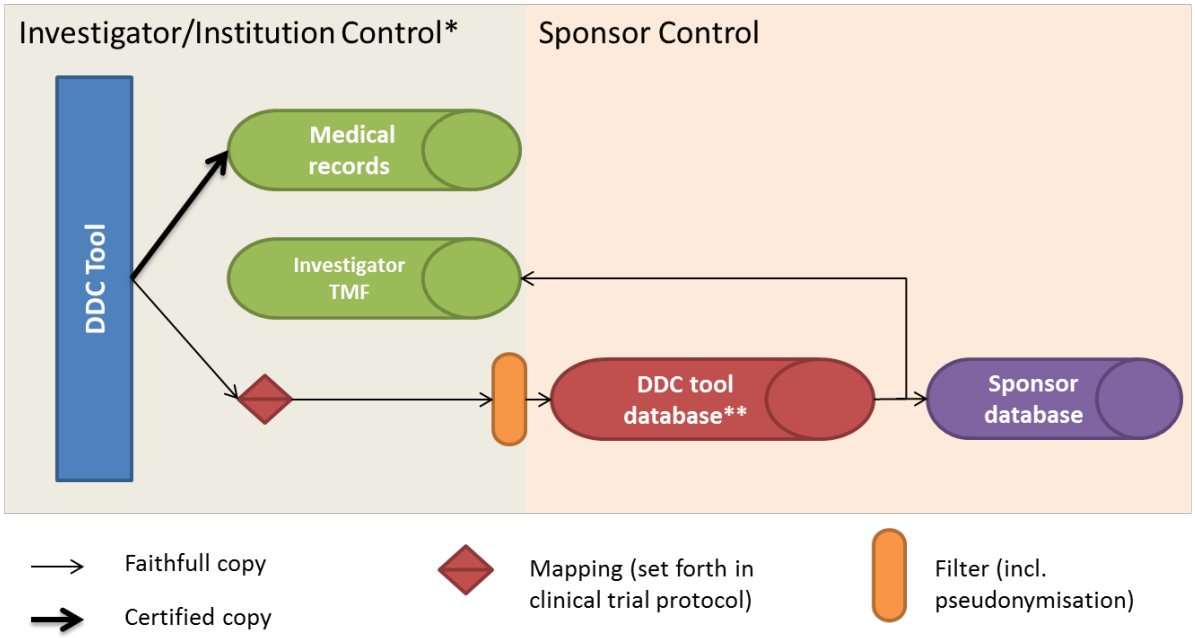
Aspects for consideration include:

- investigators having to use different eSource systems for the various clinical trials conducted by different sponsors/vendors in parallel: 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;
- temporary technical non-usability of the eSource DDC tools (e.g. battery life of a tablet);
- ideally, the system should allow automatic (real-time) transfer of the captured eSource DDC data to the respective sections of the EMR management systems (see answer to Q2). ;

The system should also fulfil the following requirements:

- a site qualification procedure should be conducted before deploying the system in any given site (see Q7);
- IT help desk support, accessibility (eg. 24/7);
- continuous accessibility and control of the eSource data by the investigator/its institution during and after completion of the study;
- security and traceability of the data;
- 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. National legislation, GDPR and data controller requirements would need to be complied to.

One possible acceptable workflow example would be:



*Based on ICH-GCP E6 (R2) 8.1, 8.3.13 in connection with 4.9.0 and 4.2.5 & 4.2.6 source data/documents belong to the investigator/institution and should be under the control of the investigator/institution.
** The sponsor might choose to subcontract the DDC tool database to a 3rd party vendor

Illustration X: Study data is captured by DDC Tool (blue) and directly transferred to the EMR (green); data is source data (ICH-GCP E6 (R2) 4.9.0 and 8.3.13). 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). Site specific data is transferred to the sponsor (violet) and to the investigators TMF (green) to enable verification of accuracy, completeness, legibility, and timeliness of data reported to the sponsor, analogues to the requirement of a CRF copy (ICH-GCP E6 (R2) 4.9.1, 8.1, 8.3.14 and 8.3.15). It is the sponsors responsibility to ensure all data transfers take place and are sufficiently validated and all audit trail information is kept throughout all transfers (ICH GCP E6 (R2) 5.5.3).

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.

Question 2: Site impact

Does the EMA have a position on the logistics and operational considerations at the investigator sites resulting from the use of the proposed eSource tool?

Draft CHMP answer:

The situation exists today where sites collect source data on paper and later transcribe it manually into EDC, and, if required by local process, transcribe it manually into the site EMR as well. In a tool like the submitted system proposal and eCRFs or other ePRO tools already implemented for some trials, data is not manually transcribed into EDC, but is either entered directly during trial visits or automatically transferred into EDC via a validated electronic process, with the aim of eliminating a manual transcription step into EDC for the sites.

In order to decrease the workload on the investigator and the investigation sites staff and to avoid transcription errors, transcription requiring manual intervention, between eSource and (E)MR, should be avoided.

Eliminating the manual transcription step from paper worksheets, which can occur today, is desirable. Therefore, unless immediately feasible, the long-term ambition should be that the collected data could be transferred automatically into a Site's own EMR, or captured automatically from the site's own EMR, taking into account national law and research governance requirements. Therefore, cooperation to achieve standardization of data interoperability should be supported.

There is no detailed description or Company question on the data mapping approach utilised by proposed eSource DDC to allow data mapping from the eSource DDC to the site EMR. Given the multiple terminologies employed by institutions and the variable quality of the EMR especially in the secondary care setting, it is expected that the automated transfer between databases would be appropriately validated. The Sponsor is responsible to ensure that such validation is carried out according to written, auditable procedures.
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.

The proposed eSource DDC tool allows a site to print certified copies of their eSource for paper filing or to upload an electronic certified copy of the source into an EMR without requiring transcription.
This is only possible if the eSource only contains elements which can be adequately mirrored in a printout or pdf flat file.
The data in the EMR uploaded from the eSource should be readily available and easy to trace.

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 for those data that has to be captured in both systems according to national legal requirements (ie. the maintenance of complete medical records according to national requirements), medical practice, or (national) established standards for EMR. Using an eSource must not result in a depletion and/or disorder of the information available in the patients' medical records.

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.

eSource systems should be sufficiently user-friendly to avoid the need for too much training of the investigator sites staff, especially in view of the potential emergence of multiple eSource systems. Standardization is highly encouraged.

GCP requires that all entries, changes and deletions in a system are fully audit-trailed. This would also apply to an eSource system. In case of eSource, 1-to-1 coding of data is expected. Any changes to data, including those resulting from automated data entry checks should be visible: consequently, the audit trail should be per field and it is not sufficient to have audit trail at the end of a submitted form. In addition user rights need to be defined, managed and documented, during the trial and after completion.

In their briefing document, the Company uses the term "centralized monitoring": of note, the definition of centralized monitoring is clearly outlined in ICH GCP E6[R2], and is a different process from remote

monitoring, which is assumed to be what is intended by the Company with the term in their briefing document.

Question 3: Source data collection in eSource

What is the EMA's view of the concept of eSource direct data entry in clinical trials and its compliance with ICH GCP guidelines?

Draft answer:
The concept presents challenges but no theoretical obstacles: if it can be designed to meet all requirements for ICH source data and (national) requirements regarding the EMR maintenance, then it could be compliant.

Data privacy is one of the main GCP principles. According to the Declaration of Helsinki, it is the duty of physicians who are involved in medical research to protect the privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects including their privacy must always rest with these physicians or other health care professionals and never with the research subjects, even though they have given consent. It is imperative that any eSource system should be fully compliant with the provisions of applicable data protection legislation In this context, it must be flagged that specific obligations are laid down for the processing of personal data in Regulation (EU) No 679/2016 the General Data Protection Regulation 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.

The developed eSource forms need to be consistent with the approved protocol. This means that they enable the collection of all the information and data necessary to evaluate the clinical trial, and allow the traceability and interpretation of the data, while avoiding that data and information that is not required for trial purpose, and thus falls within the scope of the subject's privacy protection and is to be considered as confidential, can be accessed by the sponsor.
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.

The proposed eSource DDC concept implies that source data is primarily no longer captured in the document management system of the investigator's site. 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. Increase of workload and complexity of data input/retrieval at investigator site must be avoided.

See also the answer to Q2, Q4 and Q5.

Question 4: Investigator's role as health care provider

Does the EMA have a position on the concept that eSource direct data entry does not negatively interfere with the physician/patient interaction and that this process is equivalent to that of entering data into an electronic medical record.

Draft answer:
It will have to be ensured that the use of eSource DDC doesn't negatively impact on the interaction between the investigator and the patient, by 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 aspect should be validated by performing in use testing of eSource versus collecting the same data not using the eSource system.

See also answer to Q2.

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.

eSource systems should be sufficiently user-friendly to avoid too much training of investigation sites staff, especially in view of the potential emergence of multiple eSource systems. Standardization is to be encouraged.

Question 5: Custody and control of patient data

What is the EMA's view on the impact of the eSource direct data entry concept on access and control of data during and after a clinical trial, and its compliance with ICH-GCP standards?

Draft answer:

The proposed eSource DDC concept implies that source data is primarily no longer captured in the document management system of the investigator's site. 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.

According to ICH-GCP E6 [R2], chapter 8:*The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data. The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.*

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.

Direct investigator's access to eCRF data should not be precluded in any way. See also the answer to Q3.

Question 6: Long term data custody / data permanence

What is EMA's view that, under ICH GCP, source data collected by an eSource data entry system can be as securely maintained, both short and long term, as paper-based source data?

Draft answer:

It needs to be ensured that data is sufficiently safeguarded from calamities (bankruptcy, data center calamities...). Data should at all times be available for inspection, both short term and long term. This access should be controlled by the investigator and independent of the sponsor.

It should be well documented how this data availability, accessibility and readability will be ensured, in accordance with all applicable laws and guidelines. Back-up processes should be in place and migration of data and media should be planned, performed and traceable. It should also be clearly described (contracts, SOPs, manuals etc.) and documented who has access to the data at what times and how (password-protected, administrator rights, writing rights, read-only wrights etc.) All data and system access should be fully audit-trailed. It should be ensured that eSource data is machine readable in the future (independent from specific software platforms and operating systems).

Question 7: Investigator validation of trial tools

Does the EMA have any comments on the proposal that the investigator does not need to directly validate the system, but GCP requirements will be met by ensuring that this validation takes place?

Draft answer:
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 fulfills national legislation and standards.

Question 8: Patient data privacy according to ICH-GCP E6 R2

Does the EMA have any comments on the compliance with privacy rules as required per ICH GCP E6 R2, in regard to the use of an electronic source direct data entry system?

Draft answer:
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.
For further details, see answer to Q5.

Question 9: Use of existing eSource data

Does the EMA have any comments on the regulatory adequacy to submit, in support of a marketing authorisation application, eSource data collected in a clinical trial utilizing a specific eSource direct data entry system?

Draft answer:
In case in the conduct of a clinical trial the eSource DDC system has been used, this data can be submitted in the support of a MAA provided that this data is sufficiently GCP compliant i.e. all above-mentioned requirements mentioned in this qualification Opinion are fulfilled, and is available for inspection.

ANNEX

Background information as submitted by the applicant

Executive summary

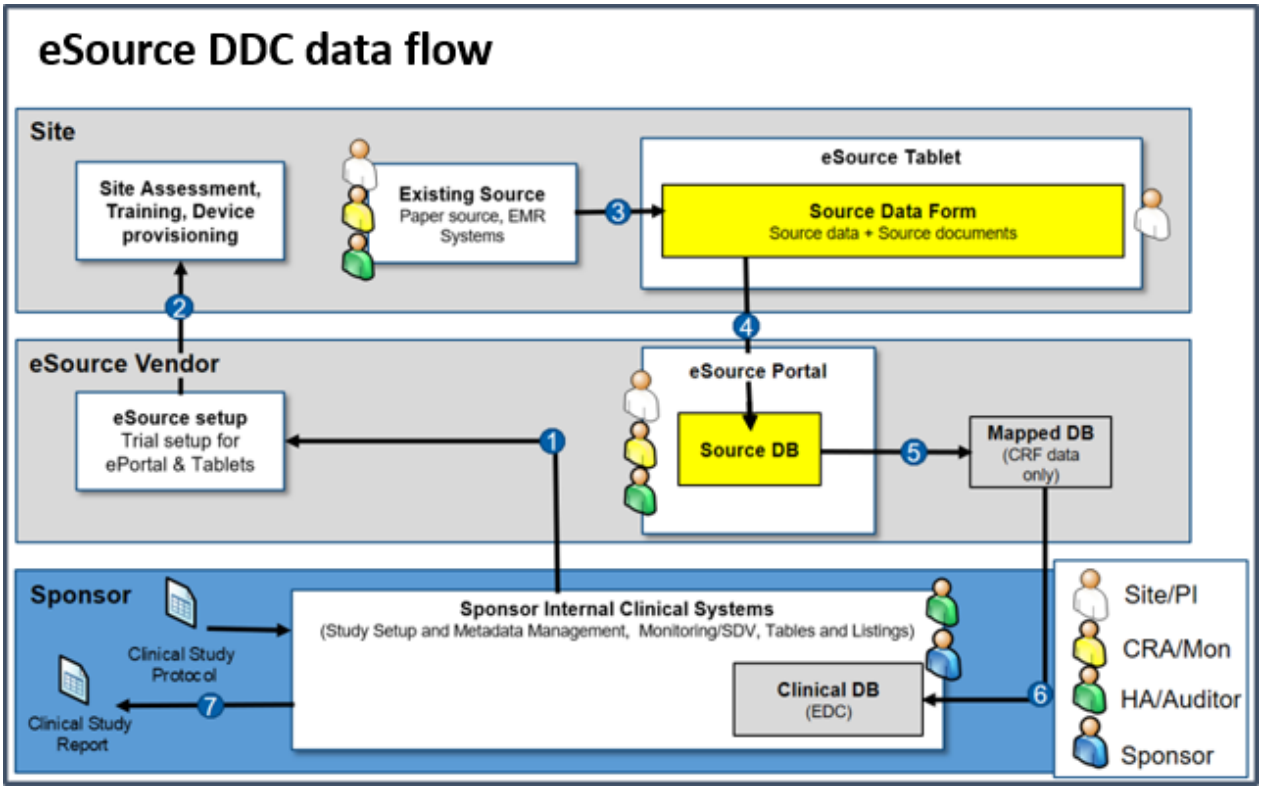
Digital Technology has the potential to streamline the conduct and improve the quality of data obtained in clinical trials. Novartis has piloted the use of Electronic Source Direct Data Capture to allow the capture of clinical study source data electronically in several clinical trials. It became clear that opinions on its acceptability varied globally. Based on this, Novartis sought the European Medicines Agency (EMA) Scientific Advice Working Party (SAWP)'s views on the use of eSource DDC in clinical trials and agreement that eSource DDC meets ICH-GCP guidelines.

eSource Direct Data Capture is 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. While historically "eSource" is a term often used to describe capture of eSource data at the point of care, Novartis has aligned with the TransCelerate[i] definition of "eSource Direct Data Capture" for consistency. From this point forward, "eSource Direct Data Capture" will also be referred to as "eSource DDC" throughout this document.

eSource DDC is an evolution of EDC (Electronic Data Capture). EDC is the current technology used by research institutions, sponsors and CROs to manage clinical trial data. With EDC, data from clinical assessments is initially captured on paper or in the Electronic Medical Record, and then transcribed at a later time into eCRFs (Electronic Case Report Forms) built within EDC. Validations, or queries, for that collected data surface only when that data is entered in the eCRF, after the clinical visit.

With eSource DDC, the clinical assessment data is entered during the clinical visit, eliminating the need to manually transcribe it into EDC, allowing validations for the data entered to occur at the same time. The data is more legible, accurate, and timely with an eSource DDC system. The eSource DDC system also allows the investigator more time to dedicate to the patient.

Presented below is an example of an eSource DDC data flow diagram showing accessibility to the data. Further explanations for each step in the process follow the diagram.



1) From the Protocol, Novartis designs and build its Clinical DB (database), usually referred to as EDC. Simultaneously, the eSource Vendor begins their eSource setup.
2)
   a) This includes the Source Data Form design (for collecting the Protocol required data), as well as the "Back-end" Source database, including the mapping specifications.

3) The eSource vendor configures tablets and provides them to the investigator site. Training is also provided prior to the start of the trial.

4) During the trial, the investigator site enters data into Source Data Forms in the eSource tablet, including the entry of any data to be transcribed from existing medical records, and data, which is entered directly into the eSource Tablet during a patient visit.

5) Following a data entry session, most likely during a patient visit, the site user *(manually)* or eSource application *(automatically)* uploads the Source Data Forms to the Source Database. The eSource portal is the interface that allows approved users of the system access to the eSource documents/data, which are stored in the Source Database.

6) Source data from the Source Database, automatically flows into the mapping utility to create a Mapping Database. During this process the system separates out and "stages" only the Clinical Trial Database required data.

7) At pre-defined time points, i.e. daily in the case of Novartis's pilot trials, the new (*or updated data*) is automatically transferred into the Sponsor's Clinical Trial Database. (Again, only the data required for the Clinical Trial Database is transferred to the Sponsor via a validated integration tool).

8) Upon database lock, the data from the Clinical Trial Database is analyzed and included in the Clinical Study Report.

Steps 3 to 6 presented in the above diagram will continue throughout the life of a clinical trial, as defined by the study protocol and dependent upon a site's standard practices. In addition, and based on a likely defined standard, sites will maintain a patient's "general" medical record. At any time point, sites are able to download certified copies of source documents/data and attach these to the patients' medical record, whether that be on paper or electronically within an EMR.

Question 1 Benefits of the technology

We propose the use of eSource will improve the quality of the data collected. What is EMA's view on this concept, and are there any comments on the characteristics that a system to implement it should possess?

Company position

eSource DDC technology has the potential to improve data quality in clinical trials. Like many technology platforms, eSource DDC faces a challenge to validate anticipated benefits during early stages of adoption.

Among various stakeholders including regulators[ii], it is acknowledged that the anticipated benefits of an eSource DDC technology are comprised of the following:

- Eliminate unnecessary duplication of data (recorded on paper once, then re-typed into Electronic Data Capture web interface)
- Reduce the possibility for transcription errors
- Encourage entering source data during a subject's visit, where appropriate
- Eliminate transcription of source data prior to entry into an eCRF
- Facilitate remote monitoring of data
- Promote real-time access for data review, which could help in ensuring the safety of the patient recruited into the trial.
- Facilitate the collection of accurate and complete data

Several peer-reviewed industry white papers[iii] also highlight the anticipated benefits from the perspective of the patient and the clinical data custodians:

- The **Patient** has more quality time with clinical site staff and potential for a better interaction with the investigator. They receive better patient oversight, with improved safety.
- The **Site** gains the key efficiency of one-time data entry. Their data is validated at the time of capture, using a familiar document-based solution. The patient interaction is improved overall.
- Site **Monitors** can shift their focus from Source Data Verification (which is reduced or eliminated) to source data review. They are better prepared for site visits given their access to a portal, and all audit trail information is available to them in the system.
- The **Sponsor** gains operational efficiencies by reducing Source Data Verification, Data Queries and Protocol Deviations. Data Quality is enhanced with the availability of real time data that can be monitored remotely.

These areas in particular present great potential opportunities for improved data quality, data integrity and a more integrated, streamlined workflow:

- During a conventional study visit, a patient's data is entered directly into his or her medical record, which could be either paper or electronic. Later, study relevant data is transcribed into the patient's case report form (CRF) in EDC and provided to the sponsor for analysis. Study monitors review data periodically for errors and omissions and the site is asked to resolve these issues, often long after the data was initially collected. With eSource DDC, data is entered only once and can be expected to be more complete due to "alert" functionality in the technology that flags missing data to the investigator. Alerts also inform site personnel when entries are out of the expected range, allowing them to make any necessary corrections in real time. This should result in a reduction in the number of data queries and protocol deviations.
- eSource DDC allows for remote data review, virtually in real time. This feature not only facilitates the work of study monitors, but also has the potential to simplify GCP audits. It should also be noted that the eSource DDC system has an audit trail, which is ALCOA+ compliant (ALCOA stands for Attributable/Legible/Contemporaneous/Original/Accurate), unlike many electronic health record systems.
- eSource DDC has the potential to increase patient safety. Protocol deviations are not uncommon and this technology allows study monitors to detect potential safety risks, which may result from the deviations. For example, a patient may be entered into a trial while on a medication that is disallowed because of known or anticipated drug-drug interactions. Due to the nearly real-time monitoring enabled by eSource DDC, this deviation can be caught prior to an adverse event occurring, bringing significant value to the patient, investigator and sponsor.

Early phase clinical trials utilizing eSource DDC technology were managed on behalf of Novartis by a CRO. While limited to a small sample of site and study team users (35 respondents), some preliminary metrics and feedback were collected and are listed in Table 1.

Table 1 Pilot trial metrics from trials managed on behalf of Novartis

Type of Feedback	Evidence from Pilot Trials
Site User Feedback	• 89% found the system easy to use • 85% say the system was as easy to use as the normal paper process • 70% say the system caught errors that would have been missed on paper • 74% would enjoy working on another eSource (DDC) trial
Data Management Efficiencies	• Study Setup time was observed to be the same as a typical EDC trial • Data available for cleaning activities to begin 14 days sooner than an EDC trial
Site and DM Efficiencies	• 45% reduction in manual queries, compared to comparable EDC trial
Monitoring Efficiencies	• Estimated 38% reduction in monitoring time for Source Data Verification allowing Monitors time to look at other documents on site and spend more time with the study team

Recent internally managed Novartis pilot trials collected useful and quantifiable metrics on the benefits of eSource DDC, which are presented in Table 2. The following statements can be made with some certainty, asserting an indication of how eSource DDC can positively improve over traditional data collection methods.

Table 2 Novartis internally managed pilot trial metrics

Metric Description	Evidence from Pilot Trials
Time to data availability within the Clinical Database is significantly reduced with eSource DDC	This has reduced 6-fold compared to EDC data availability metrics. i.e. data is on average, across the entire clinical database, available in only days instead of several weeks
The percentage (%) of "first time right data" has increased with eSource DDC	The number of data points which were not changed since initial data entry increased by over 7%, meaning that less data is being changed as a result of queries and data review/data monitoring activities
The time taken to action Queries has reduced by more than 50%	The number of days between queries being initially created to the time of them being closed down, presumably following an adequate response by site, has reduced by more than half, suggesting that sites are more proactively managing workload with eSource DDC or that eSource DDC is facilitating their clinical trial activities

While the early learnings from Novartis trials reflect the aspirational, anticipated benefits described in industry white papers, there is a scarcity of scholarly articles that empirically or specifically support eSource adoption with any quantifiable metrics. The available scholarly articles focus on data quality and operational efficiency:

- A comparative effectiveness study of eSource used for data capture for a clinical research registry[iv], eSource produced a 37% time savings, 0% data quality issues compared to a 9% error rate for manual transcription, and eliminated the need for a full-time employee at the investigational site.
- A pilot study conducted in Japan[v] explored a clinical trial model that used EMR data directly in clinical trials and developed a system to follow this model. The pilot study revealed many advantages over a conventional clinical trial process, eliminating the requirements to: transfer information from medical records to the CRF, perform source data verification at the participating site, transmit the CRF from the participating site to the coordinating center, and re-enter data into the CDMS from the paper-based CRF.
- The Journal of American Medical Informatics Association concluded in 2013 "there is currently little consistency or potential generalizability in the methods used to assess Electronic Medical Record data quality. If the reuse of Electronic Health Record data for clinical research is to become accepted, researchers should adopt validated, systematic methods of EMR data quality assessment"[vi].

From the small number of articles available, eSource DDC has the potential to improve quality of data and lead to operational efficiencies. This tool would not cause any changes in the control and pseudonymisation of data. Patients' identities would still only be known at the trial site with the subject identification log being the tool to link the patient number to the patient. Data, which is provided to the sponsor, is pseudonymised. Patient numbers are used as an identifier throughout the process and are maintained in the Clinical Trial Database. It would also not impact the ability to record non-protocol information.

The sponsor does not have sole control of the eSource data. In fact, much like EDC, eSource DDC is a model where the sponsor only receives a copy of specific data required by the protocol. Any source data entered into the eSource DDC system as the first point of entry is hosted by the supplier and made available to the site. The eSource DDC system also supports the entry of additional narrative notes via digitally captured handwritten notes (these can be applied alongside the protocol-required assessment data, or in readily available "notes" sections). Throughout the course of a trial all the collected source data, which includes the contextual notes, should be uploaded to the patient's record, following a site's standard practice, similar to how sites today manage their paper source documents. For more detailed information, please see Novartis' responses to question 3 (pseudonymised data), and questions 5 and 6 (custody and control of patient data/data permanence).

The major advantages of eSource DDC are simplification of data capture and review leading to greater efficiencies. While there are disadvantages to eSource DDC including the time spent to train the site staff by the sponsor and/or vendor, and acceptance of the system by the site, once the training is

completed, eSource DDC should streamline operational work at the clinical site and potentially facilitate oversight of patient care.

Question 2: Site impact

Does the EMA have a position on the logistics and operational considerations at the investigator sites resulting from the use of the proposed eSource tool?

Company position

The use of eSource DDC should streamline operational work at the clinical site. It introduces a different way to operationalize data entry and flow, which requires training of site staff by the sponsor and/or vendor. Once the training is completed, the use of the technology facilitates the conduct of the study, simplifying the work of investigators, site personnel, study monitors and auditors.

According to CentreWatch's[vii], providing clinical trial resources for professionals, "The need for...and barriers to...adopting eSource" survey[viii] 90% of research sites create study specific source documents" for each clinical trial in which they enlist. Of the 90% of sites, "96% still use paper-based approaches" for creating these source CRF templates. It is therefore clear that even though EMR adoption is on the increase, these systems are not yet widely used to collect clinical trial data directly, at the point of care. eSource DDC technology therefore has the potential to support the site workflow by providing electronic Source forms, which negate the need for each individual site to generate their own.

Investigators and site personnel also benefit from several other features of the eSource DDC tool. The tool includes the aforementioned source templates, as well as prompts for the capture of all required patient data, not just those data required for completion of the Case Report Form (CRF). This reduces the amount of omitted or missing values collected during the trial. The system flags values that are outside the normal range so that site staff can check the value in real time, ensuring that the data point was entered correctly. Protocol deviations (and related data queries) for example, can be alleviated where patients do not meet inclusion or exclusion criteria, since these items can be flagged immediately upon data entry, rather than at a later time when the data is transcribed (into EDC). This means that potential safety issues for the patient from including an ineligible patient in the trial is picked up before the patient is entered into the trial. Investigators and site personnel also benefit from having access to patient data in real time during the study and have continued access to the study data following the completion of a trial.

Study monitors using eSource DDC can query data in real time remotely, allowing omissions and inconsistencies to be addressed quickly. In addition, because many activities can be carried out remotely, site monitors need only visit sites to perform value added activities such as quality control, site training, saving both the monitor and the site valuable time. eSource DDC offers true centralized monitoring for study monitors given their access to a portal, and all audit trail information is available to them in the system.

Auditors could utilize this same approach to review clinical trials/systems far more efficiently by employing remote data access for much of their work, once again being able only to see CRF data.

The eSource DDC tool complies with all of the GCP requirements concerning the collection and maintenance of data. The eSource DDC system has an audit trail, which is ALCOA+ compliant. During the trial, data access in the tool is strictly controlled by user names and passwords, which are only obtained following successful completion of mandatory training and as authorized by the clinical trial team. After completion of the trial, similar to the archive provided in a traditional EDC trial, sites are provided with a comprehensive study archive including all of the data and contextual notes that have been entered, summaries of all modifications to data as reflected in the audit trail, and a full listing of all queries with their responses. Until a site receives and acknowledges receipt of their archive, access to the eSource DDC tool remains to ensure continued access to the source.

The major advantages of eSource DDC for the investigator, site personnel, study monitor and auditor are the simplification of data capture and review leading to greater efficiencies. If clinical sites do not find the system to be user friendly, the problem will be self-limiting: either sponsors would need to provide additional resources for training or site support, or investigators will object to eSource DDC use, and the technology will be improved or abandoned. eSource DDC is sufficiently flexible and can be individually set up to comply with local legal requirements, medical practice, and established standards to allow captured data being available in the site EMR.

Novartis, along with other companies, learned societies and in the frame of public private partnerships such as IMI EHR4CR, welcomes the standardization of data fields within EMRs to facilitate cross boarder healthcare systems. This would facilitate the pull of data from such systems into EDC systems to provide the same rapid data entry, which is seen with an eSource DDC system.

In relation to the associated action plan (eHealth Action Plan 2012-2020 – Innovation healthcare for the 21st century) and Directive 2011/24/EU, the Connecting Europe Facility will facilitate this process of pulling from EMRs, which will help improve data quality, facilitate the management of clinical trials and overall streamline clinical research.

Further information on the validation on the system can be found in Novartis' position to question 7.

Question 3: Source data collection in eSource

What is the EMA's view of the concept of eSource direct data entry in clinical trials and its compliance with ICH GCP guidelines?

Company position

The *Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6 (R2)* requires that all data gathered in the course of a clinical trial be captured in original records or certified copies, such as to allow the evaluation and reconstruction of the clinical trial. These records are required to be maintained by the clinical site for a period of time that varies depending on the country. Although historically, clinical trial data has been recorded in a patient's health record first, and then transcribed to the CRF as appropriate there is no guidance nor regulation requiring this or any specific order of entry be followed. Even if the utilization of the eSource DDC tool is a relatively new approach to the initial collection of source data, its use complies with all of the GCP requirements concerning the collection and maintenance of this data.

The eSource DDC tool is customized for each clinical trial based on the protocol and allows access to patient information strictly on the basis of trial roles, which guarantees patients´ privacy rights. Patient data collection/storage can be configured on a per-site basis to ensure only the permitted information is collected. Personal identifiable information is not collected or displayed on the source forms themselves. Patient clinical assessment (prescribed in the protocol) data is collected, processed and stored after having informed the patient about the necessary facts, as per the applicable privacy regulations (purpose of collection and processing, rights, etc.), as it would be done in a traditional paper-based trial. Sponsors have access to pseudonymised data only, complying with data privacy regulations such as GDPR. Investigators have full access to all patient data (source data) during and after the trial (PDF formatted data or directly from the vendor) and are ultimately responsible for the protection of this data. This is no different from the relationship a patient has with their physician. Per principle 5 of the European Charter of Medical Ethics[ix], the physician is to be a patient's confidant in order to ensure privacy of the patient's health.[x]

When using eSource DDC, data is first entered into the tool by the investigator on an eSource DDC tablet at the point of care. Once data is saved, a PDF file is generated, which meets the requirements for a certified copy of the source data. The PDF can be printed or stored electronically as an attachment in the EMR of the patient. Patient data is, now therefore, available for review at the site, both on the tablet and the portal, as well as in the patient's health record. The use of eSource DDC should simplify operational work at the clinical site. The electronic source forms on the tool allow for simple data input by clinical site staff, and access to the data is available in real time during the study on the eSource DDC tablet or via the eSource portal and also following completion of a trial (PDF formatted data or directly from the vendor). Based on Novartis' experience, sites are more proactively managing workload with eSource DDC or eSource DDC is facilitating their clinical trial activities (see Table 2).

With the Novartis eSource DDC approach, the eSource system (whenever possible) should be used as the primary data entry point during a clinical visit. 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.

Where sites have a documented process that dictates that the EMR or paper source must be the primary data entry point (even for clinical trials), the EMR system or paper source should be used as the primary data entry point during a clinical visit. The site staff should indicate in the eSource form that the source data is transcribed, and then transcribe the data from the EMR or paper source into the eSource form or EDC system.

This approach to documenting patient data in a trial is compliant with section 1.51 of ICH GCP E6 R2 on source data, which states 'all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial'. Novartis trial-level documents describe the specific data collection and data access requirements. The approach is compliant with ICH GCP E6 R2 sections 6.4.9 and 6.10, which stipulate trial design documentation and data access requirements, respectively.

Finally, the eSource DDC tool is compliant with section 1.52 of ICH GCP E6 R2, which states that source documents can include 'copies or transcriptions certified after verification as being accurate copies' if they are generated through a validated system or with a dated signature. Section 8.1 of ICH E6 R2 also states that 'when a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.'

Data privacy requirements of GDPR are ensured by data environment controls such as logical separation of personally identifiable information from other data, use of strong encryption to encrypt data both at rest and during transit, use of two or three factor authentication for all users and administrators of the system, and maintenance of user logs and audit trails.

Question 4: Investigator's role as health care provider

Does the EMA have a position on the concept that eSource direct data entry does not negatively interfere with the physician/patient interaction and that this process is equivalent to that of entering data into an electronic medical record.

Company position

The eSource DDC tool allows for the simplification of data capture via a platform which is similar to traditional EDC, but which is more comprehensive in functionality and features. 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.

The eSource DDC tool is also compliant with section 4.9.0 of ICH GCP E6 R2, as it provides the institution with the ability to "maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects." The system has been validated to create source data that is "attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data [are] traceable, [do] not obscure the original entry, and [can] be explained if necessary (e.g., *via* an audit trail)."

The eSource DDC tool does not negatively interfere with the physician/patient interaction as the eSource DDC case report forms are built to collect data in the order that is required by the study protocol. Unlike in a traditional EDC model where data are more commonly entered, grouped by a common theme or topic such as Vital Signs or Blood Collection, eSource DDC data are entered in the order in which the data were required to be generated per Protocol, regardless of the topic. Therefore, the visit with the patient can be more efficient in the eSource DDC model, as the investigator and site staff do not need to refer back to the protocol to ensure that all required data is collected in the manner to which it is expected, as the eSource DDC entry screens are designed to include all required data collection (Source and EDC required fields), in addition to useful reminders and prompts to ensure nothing is missed.

eSource DDC does not result in a depletion and/or disorder of the information in the patient's medical record. It is well known that often investigator sites utilize worksheets to capture protocol specific data, however, often these do not make it into the patients' medical record. With eSource DDC this is not the case. eSource DDC has the potential to improve the consistency and accuracy of the information that will be transferred into the medical record.

Novartis expects that the use of eSource DDC will enable better patient oversight and enhanced patient safety as all data, including adverse event data that is entered into the eSource DDC tool, is available immediately for local or remote review. It is expected that the eSource DDC tool will allow for better physician/patient interaction because the patient has more quality time with the clinical staff. Finally, it is Novartis's wish to standardize data collection forms and tools as far as is possible across its clinical trials and we currently collaborate with trade associations and industry consortia to drive standardization across industry.

Question 5: Custody and control of patient data

What is the EMA's view on the impact of the eSource direct data entry concept on access and control of data during and after a clinical trial, and its compliance with ICH-GCP standards?

Company position

Features of the eSource DDC technology allow appropriate access and control of data during and after a clinical trial in compliance with GCP regulations. The eSource DDC tool is customized for each clinical trial based on the protocol and allows access to patient information strictly on the basis of trial roles. 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.

Data access in the tool is strictly controlled by user names and passwords, which are only obtained following successful completion of mandatory training (which includes clear procedural instructions to prevent the sharing of user accounts at the site). The system is validated and the vendor manages user accounts, ensuring the separation of roles as required by section 5.1 and 5.5.3 of ICH GCP E6 R2. During the conduct of a Novartis eSource DDC trial, the investigator site staff is the only party that has "write" access to the data entered into eSource DDC forms. Sponsor monitors can view the source data as well as the protocol-defined CRF data, but can only add queries to forms during monitor data review. Similarly, sponsor or CRO data managers can only add queries to the protocol-defined CRF data; they cannot write or modify any data entered by the site.

Per section 8.1 of ICH GCP E6 R2, 'the investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the trial.' As such, full access to data will be available to clinical sites at all times. During the trial, investigators can access data from the eSource tablet, via the eSource portal, or from the PDF file generated by the system upon data save. Following completion of the study, PDF formatted data is provided to the site, and investigators can also access data from the vendor at any time without the involvement of the sponsor. This meets the requirements of section 8.1 of ICH GCP E6 R2, which states that 'the sponsor should not have exclusive control of those data'.

In the unlikely event of a complete system failure or vendor insolvency during trial conduct, a transition to traditional EDC can be made. Contractual controls are in place to safeguard data stewardship in the event of vendor insolvency. Due diligence to ensure the financial viability of suppliers is performed before technical due diligence is applied. Technical due diligence by Novartis ensures that appropriate disaster recovery and business continuity processes are in place with verifiable evidence of these processes at the vendor.

Finally, it should be noted that source data collected by the eSource DDC system can be more readily and safely stored compared to those data collected in paper systems. The electronic format itself is easily maintained and can be backed-up both in paper format and electronically as certified copies to ensure availability. The major risks to paper files such as fire or flood are not as significant a concern for source data in eSource DDC systems due to the electronic nature of the original source and due to the inbuilt back-up functionality, which is standardly available in these types of applications. Both the investigator and the vendor will maintain the source data long term after the completion of the trial.

Question 6: Long term data custody / data permanence

What is EMA's view that, under ICH GCP, source data collected by an eSource data entry system can be as securely maintained, both short and long term, as paper-based source data?

Company position
The eSource DDC approach fully supports the requirements for essential documents described in ICH GCP E6 R2 section 8.1.

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. Source DDC collected data will be maintained both long term by investigators (ICH GCP E6 R2 sections 4.9.0, 4.9.4 and 4.9.5) and by the vendor (via contractual escrow agreements). Contractual safeguards will ensure continued access of source data by investigator and inspectors, e.g. warranting for accessible data back-ups by the vendor and access to the source code to the investigator for business continuity purposes.

Please see Novartis' response to question 5 for information on access to data. It should also be noted that the eSource DDC system has an audit trail, which is ALCOA+ compliant.

Loss of eSource DDC data is unlikely, but just as is the case of paper, it is possible. All feasible steps will be taken to avoid such loss of source data. Certified copies are system generated renditions of the data entered into the eSource forms, not just tables of data. Therefore, if the vendor were to go out of business during the conduct of study or in the case of an unforeseen incident disrupting the study itself, switching data collection to more traditional EDC would be possible, as source data collected in eSource DDC would still be accessible via the copy at the investigational site up until that point.

Novartis has performed the due diligence necessary to ensure that the eSource DDC system is validated and fit for purpose during the normal, expected operations of a clinical study. In addition, technical controls at the supplier have been examined to ensure that the central server that stores the data (both the source entered by the site, and the CRF data transmitted to the sponsor) has the appropriate technical and business controls to ensure the permanence, durability, and availability of the data. The vendor has been qualified to have disaster recovery plans and tests, as well as business continuity processes, to ensure that the data is safe from catastrophic loss and is consistently available at the site.

In the event of a catastrophic system failure, all data is still available on the tablet at the site even after it is transmitted to the server for 14 days, and the server-side recovery time objective (RTO: the amount of time it would take to completely restore the system after a disaster) is one business day.

As an additional safeguard for such situations, the contract between the system provider and the sponsor contains an escrow section on source data, to allow for storage of collected clinical trial data collected through the investigator in parallel and independent to the clinical trial data hosted on the system provider's platform ("Independent Storage"). Within 90 days after the execution date, the system provider will deposit with a mutually agreed escrow agent all, complete, and certified copies and respective updates of the clinical trial data for each clinical trial performed under the respective agreement. The system provider agrees to ensure separate and independent access [means of access to be defined in alignment with investigator] by the investigator, at any time and at the investigator's sole discretion. The investigator will be identified by the sponsor and disclosed to the system provider in writing prior to the time of clinical trial data collection. The sponsor shall have no right to control or gain access to this Independent Storage.

Question 7: Investigator validation of trial tools

Does the EMA have any comments on the proposal that the investigator does not need to directly validate the system, but GCP requirements will be met by ensuring that this validation takes place?

Company position
The ICH GCP E6 R2 sections 4.2.5 and 4.2.6 state that the investigator is responsible for supervising and qualifying any individual or party who performs trial related duties at the trial site. While these regulations could be interpreted as requiring investigators to personally validate eSource DDC tools, precedence with EDC, which is not typically validated by investigators, suggests that this is not the case. However, if required, Novartis could provide a validation package for the investigator to acknowledge the qualification and validation of the eSource DDC tool. This would 'ensure that an

individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated' (ICH E6 R2 section 4.2.6).

Question 8: Patient data privacy according to ICH-GCP E6 R2

Does the EMA have any comments on the compliance with privacy rules as required per ICH GCP E6 R2, in regard to the use of an electronic source direct data entry system?

Company position

The eSource DDC system is designed and validated to have role-based permissions that determine end-user access to data, which guarantees patients´ Privacy rights. Users with a sponsor role in the system cannot access personally identifiable information (PII) and can only view a unique patient number which is assigned by the site to each trial participant (ICH GCP E6 R2, sections 1.58 and 2.11). The site staff is trained not only on the use of the tablets, but also on the Privacy safeguards they have to apply while collecting personal information of patients (such as the correct use of free text fields, the safe use of tablets by not sharing passwords, etc.).

System-level protections and governance (via Novartis Privacy, Quality Assurance and Information Security audits) work to ensure that privacy is maintained. Before entering into any contracts with any third parties who will collect and/or process personal data on Novartis´ behalf, an eSource DDC vendor would be subject to the Novartis third party audit process, in order to determine, amongst others, the adequacy of the vendor for being a data processor that abides by the applicable Privacy regulations, including all necessary technical and organizational measures to protect any type of personal data.

All relationships of Novartis with any data processors are regulated by the appropriate Data Processing Agreements, which contain the necessary provisions to determine that the collection, processing and storage of personal data is conducted according to the applicable regulations and that every party to the agreements is responsible for their activities and those of their staff.

The data generated at the site is encrypted during transmission to the server environment and remains encrypted at rest (in storage).

To conclude, 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.

Question 9: Use of existing eSource data

Does the EMA have any comments on the regulatory adequacy to submit, in support of a marketing authorisation application, eSource data collected in a clinical trial utilizing a specific eSource direct data entry system?

Company position

A randomized, double-blind, placebo-controlled study was conducted. When this study was initiated, the trial allowed for the use of eSource DDC or Novartis's existing EDC system (Oracle Clinical), dependent upon pre-defined criteria.

After the study initiated, Novartis received feedback from EU Health Authorities, and following this feedback, the use of eSource DDC was discontinued in this trial.

Due to the discontinuation of the eSource DDC system, all sites using eSource DDC switched to Oracle Clinical. At the time of discontinuation, 7% were utilizing eSource DDC. These patients switched to the Oracle Clinical system at time of discontinuation. All data collected from eSource DDC on these patients were provided to the sites as certified copies, and all protocol-required CRF data captured on the eSource forms were transferred to the Oracle Clinical system.

As there is no reason to doubt the integrity of the data and the data is GCP compliant, Novartis proposed to include the data captured via eSource DDC in the primary analysis for the trial.

[i] http://www.transceleratebiopharmainc.com/initiatives/esource/

[ii] FDA Guidance for Industry: Electronic Source Data in Clinical Investigations Sept 2013

[iii] eClinical Forum - Electronic Data Capture in Clinical Trials using Service Providers; Clinical Ink - eSource: Reducing Site Workload for Better, Faster, Safer Clinical Trials; Applied Clinical Trials - Data Shows eSource Reduces Site Workload; Target Health – Value Proposition of eSource When Using Target e*CTR*; Clincapture-Electronic Source Data in Clinical Studies

[iv] International Journal of Medical Informatics 103 (2017) 89-94: A comparative effectiveness study of eSource used for data capture for a clinical research registry

[v] Clinical Trials 2012; 9: 408 –417: An eClinical trial system for cancer that integrates with clinical pathways and electronic medical records

[vi] Journal of the American Medical Informatics Association, Volume 20, Issue 1, 1 January 2013, Pages 144–151: Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research

[vii] CenterWatch Monthly (ISSN 1556-3367). Volume 24, Issue 02, 2017

[ix] Principles of **European** Medical Ethics, CEOM 2011