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Committees and Inspections

Final summary record – EDC systems and risk-based monitoring in Clinical Trials

Meeting date: 30 November 2015

Meeting room: 3E

Chair: Ana Rodriguez

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Item	Agenda Item
1.	**Welcome and introduction** **Health and safety:** The Chair informed of the closest emergency exits in the meeting room and other health and safety procedures at the Agency. All participants introduced themselves by stating their affiliation and country.
2.	**Overview of ICH-E6 Addendum with focus on Electronic Data Capture (EDC) systems and Risk Based Monitoring (RBM), Germany-BfArM** Germany-BfArM, gave a presentation on the ICH E6 Addendum with a focus on EDC systems and RBM. The scope of the Addendum is to: - supplement ICH E6 with recommendations to facilitate innovative approaches to clinical trial conduct including risk-based quality management and quality-by-design; - introduce standards for the use of IT tools and EDC systems, electronic records and essential documents. The group was reminded that the draft Addendum is currently under public consultation, until 3 February 2016 in the EU, and the final version is planned to be available in November 2016. Comments provided should focus on the Addendum parts rather than the existing ICH text, although comments made on the existing ICH text might be considered too. The inspectors were asked when they will start using the final Addendum as a reference in their inspections. Although this may depend on the standard and specific finding, it should be understood that although the Addendum provides improved GCP standards, the inspectors are currently giving deviations on the points covered by the Addendum, using the existing more general references. Concerns were raised regarding the EU requirement for an independent eCRF at the investigator site. The terms “independent/contemporaneous” for the CRF have not been included in the draft Addendum; however, it is expected that the final addendum will contain a requirement for investigator control, which is considered to be in line with the current interpretation by the EU inspectors regarding the investigators independent, contemporaneous copy as described in the current reflection paper on electronic source documents and related Q&A.
3.	**Electronic Data Systems in Clinical Trials**
3.1	**Cloud Solutions**
3.1.1	*Cloud Services - A Framework for Adoption in the Regulated Life Sciences Industry* The PhUSE presentation on Cloud Service Adoption in Life Sciences outlined a brief history of the development of a framework for both consumers and providers who operate within GxP. Key cloud-related concepts were outlined with focus areas being:

	• ISO-based role definitions - moving onto illustrating those roles in specific relationship scenarios. • The “IT supply chain” concept - the positions of SaaS, PaaS and IaaS in the context of those roles (and responsibilities). • Reference to the PhUSE framework’s check listing approach for those roles. • Specific reference, as example, to EDC (and related) apps in a cloud technology stack. • Cloud approaches/solutions providing benefits of innovation, speed of solution adoption, fixed-cost reduction, on-demand usage etc. • Predicate rules still apply. The GCP IWG had pre-loaded 10 questions that were walked through in detail. Particular areas of interest from those discussions were in and around: • Contractual relationships along the “IT supply chain” and the inspectors’ desire for clarity as well as diligence in formulation and maintenance - including Service Level Agreement and rights of audit/due-diligence. • How data “ownership” is exercised when a cloud model is used and how this can be best addressed through contracts and agreements. • Security and access controls: how to protect data in the cloud from unauthorised access; how to ensure strong authentication. • Data (and application) retention/re-use/re-accessibility; how to achieve the archiving requirements set out in the legislation taking into account that the application initially used may be decommissioned before the end of the retention period. • Change controls. • Sharing of remerging best practices and standards. • GxP awareness of providers in the cloud technology stack in the context of the defined roles. The GCP IWG was very open to follow-up discussions on the above (and more) topics; timing and arrangements are to be confirmed but any follow-up meeting would involve a subset of the GCP IWG and interested parties.
3.1.2	*Pitfalls sponsors should be aware of when contracting out electronic systems in connection with clinical trials* Denmark gave an overview of the most common deviations reported regarding contracts between sponsors and CROs providing services including electronic systems. The deviations regarding contracts are typically sponsor responsibility and include some of the following: missing or only draft contracts, late contracts, contracts not updated, expired contracts; split of responsibilities in contract is unclear also regarding which party retains which parts of the Trial Master File (TMF); standard to which the CRO will conduct its delegated sponsor’s functions not mentioned; that sponsor should have access to conduct audit at the CRO site and that CRO site could be subject to inspections not stated; not specified that the CRO should inform the sponsor in case of deviations discovered by the CRO

	which could potentially affect sponsor data; the CT applications are frequently incomplete regarding information on contracting out e-data capture and/or randomisation. Italy added a point on including subcontracting to other parties in the contract. The inspectors will be considering publishing a Q&A on this issue.
3.2	**Electronic Data Capture in Clinical Trials using Service Providers**
3.2.1	*eCRF's draft white paper* The eClinical Forum (eCF) has prepared a pre-final White Paper documenting best practices for establishing controls and operational procedures that facilitate compliance with evolving regulatory expectations (e.g. EMA Reflection Paper and proposed ICH GCP Addendum). The eCF has engaged with regulators (including the GCP IWG) and industry stakeholders and is developing documentation to complement the white paper. The White Paper focuses on web/cloud based EDC utilising service providers and the delivery of hosting or application management services in a manner that prevents exclusive sponsor control over site entered data. The concept of an investigator "zone of control" is described to assist the ongoing governance of data by respective sites. Such control is facilitated via continuous investigator access to data; use of independent third parties (the i3P); an appropriate documentation framework and task delegation/control. The eCF proposal is not mutually exclusive of other methods of meeting regulatory expectations. EUCROF queried if the eCF position was that a CRO could not host and undertake delegated sponsor tasks as an i3P. eCF responded that this would be possible with robust safeguards albeit EU regulators have previously highlighted concerns with a CRO undertaking such comprehensive involvement in a trial. An i3P is just one valid approach. The EU inspectors generally requests justification of independence and Denmark indicated that close cooperation on several aspects of a trial (monitoring, data management etc.) would probably be considered as not-independent. Germany-BfArM underlined that the EU GCP inspectors do not have a preference for any specific solution and that hosting and data management services can be provided by the same entity as long as the required independence is given and as long as robust procedures are put in place to ensure that the implemented electronic solution(s) before, during and after the clinical trial does not jeopardise the quality and/or credibility of the electronic CRF as compared to a paper CRF. Independency has to be established contractually. A profit sharing or any other financial interest of the CRO in the sponsor's clinical development project would be considered as incompatible with the required independence. In this regard it was also expressed the need to define and how to implement "independence" from the investigator in practice and what is actually meant by "control" by the investigator. The eCF expressed concerns that providing contemporaneous copies to the sites during the trials could increase the complexity of monitoring and site workload.

	Denmark reiterated that any solution (local copy at the site, third party vendor or other solutions) needs to exclude sponsor control and queried the need for investigators to acknowledge the completeness of their data when it originates from an i3P. Investigators cannot be expected to confirm that all data and metadata are as entered by the site. This should be guaranteed by the system and is part of the reason for the requirement for an independent copy of data. The investigator should acknowledge receipt and should access the data (including audit trail) and be shown how data are presented if the presentation of data is different from what was available during the trial. The eCF indicated that cryptography can provide high levels of confidence in archive media (e.g. DVDs); however, Denmark noted that methods presented so far during inspections require investigator action beyond what can be accepted and has not provided sufficient guarantee for independence as encryption codes and the actual DVDs/CDs had also been provided by the sponsor/under sponsor control. The eCF recommended that procedures should address so called “back-end” database changes and to provide for investigator awareness of such changes. Denmark reiterated that “back-end” changes should generally be avoided and that any processes implemented to process the extreme exceptions should be suitably robust i.e. require written procedures, logs etc. at the contractor.
3.3	**Electronic Certified Copies**
3.3.1	*Sponsor certification of electronic certified copies and acceptance of electronic copies from other parties (service providers and investigators) as certified copies* The eCF presented the industry understanding concerning electronic certified copies of both paper and electronic originals. Electronic certified copies from paper originals involves a process requiring manual intervention – the original must be prepared and scanned, all scanned documents must be easily identifiable and the information in them easy to find after the scanning has been performed and the validation of the scanned documents needs to be planned and documented. Electronic certified copies from electronic originals is more straightforward, but there are issues that need to be addressed with respect to the regulatory requirement to include “…all attributes and information from the original”. “All” needs to be defined, how many of the attributes and how much of the information should be included from the original sources, from the systems responsible for collecting that electronic information (e.g. EDC system) and from the IT solutions employed (e.g. Windows versions). The following questions were discussed: • Do aspects of the physical format need to be included in certified electronic copies? The presentation raised the question about whether aspects of the physical environment the data were collected in need to be included in the certified electronic copy, for example when backups were taken on the original system.

	The inspectors consider this to be an integral part of a certified copy, and raised the example that inspection of informed consent forms often included physical examination of the signature to see if the pen had pushed into the paper. It was pointed out that this would not be visible in a certified paper copy of said informed consent forms, so why should it be included in a certified electronic copy. • Who should define what "All" means in the context of a given study? The eCF proposed that the sponsor be responsible for defining what is included in certified electronic copies for their study (i.e. the definition of "all" in that study). The inspectors appeared to be dubious about this, but did not respond concerning whether they could produce a more detailed definition of "all" that could be applied to all studies. • Unclear whether or not the original can be deleted if replaced by a certified copy? Although inspectors stated that the true test of a certified copy was that the original could be destroyed, the inspectors strongly recommended that the original of the trial subjects' written Informed Consent be kept for the duration of the retention period irrespective of whether or not certified copies existed.
3.4	**Electronic Patient Reported Outcome(ePRO)**
3.4.1	*Regulatory Status of ePRO (eSource) and Site Inspections* ePRO Consortim, gave a presentation on Electronic Patient Reported Outcomes(ePRO). The following points were covered: - Definition of source data: Definitions of Source, Source data, Source documents and then of eSource, eSource data and eSource documents were taken from the CDISC Glossary version 8. In the context of ePRO, the first original and permanent source record is the one that is transmitted to the central server. The eSource Guidance says: "If a process is used by which the subject uses the instrument to transmit data to a technology service provider database, the service provider database is the source." No questions were asked regarding this point. - Confirmation of existence of patients entering data: The authorised site staff is responsible for the process of identification of a patient or subject. Also, in the case where the "Assigned" device has a unique code in addition to the ID code, the physical possession of the device is evidence that the individual using the device is the person who was assigned that device. - Back up procedures when using ePROs: Recommendations were given, in case of a device failure, not to allow paper backups but other back-up solutions, e.g. replacement devices. Case studies showing the much better quality of the data when using electronic

	data collection were shown to explain for the gain in data quality and recommendations not to allow paper backups. - Processes for provisions of the investigator sites with certified copies of the ePRO data During the trial, the investigator has access to all patient records. These records are not really copies, but are the electronic instances that are the original digital data on file for the investigator. Only the investigator has the authority to make any changes. After the trial, archival records of the full eSource, including metadata should be provided. This part generated the majority of the questions by the inspectors: • Is the data given to the investigator source data or a certified copy? As mentioned above, the records are not really copies, but are the electronic instances that are the original digital data on file for the investigator. • Can you change the data the patient entered? Yes, but only in a very limited number of cases, only under the authority of the investigator, and only with thorough explanations of why, what, who and when. • Can you change the certified copy that is provided to the investigator? No, each archive provided to the investigator is unique and the logo printed on the CD/DVD is impossible to reproduce. • Metadata - what is collected? Identifying origin (ID of device, timestamp for start, stop, transmission, ID code for subject, signature, etc.) and any additional metadata on the authenticity and provenance of the record, as well as any audit trail, certification that the archival records are identical to the eSource records, explanation of any technical issues and their resolution. Finally, there were questions about BYOD that go beyond the subject of this presentation.
3.5	**European Clinical Research Infrastructures Network (ECRIN) Data Centre Certification Programme**
3.5.1	*ECRIN Data Centre Certification Programme* The chair of the ECRIN Independent Certification Board, gave an overview of the ECRIN Data Centre Certification Programme, which certifies non-commercial trials units in Europe that demonstrate high quality data management, including effective management of their IT infrastructure. The certification process is audit based, and uses a set of 129 open and published standards, developed by ECRIN, describing good practice. So far 6 trials units in 4 countries have been certified and 6 certifications are ongoing. Currently ECRIN, has adopted a 3-years plan for the next phase of the Data Centre Certification Programme. The secretary of the ECRIN Independent Certification Board, provided a closer look at some examples of the standards. He pointed out four recurring requirements, the need for: • a mature quality management system,

	• risk-based management, e.g. for validation and change control, • units to retain responsibility for quality even when provision is outsourced, • comprehensive documentation and record keeping. The point raised in the presentation, that the issue of the 'independent investigator's copy of the CRF' may present a particular problem for the non-commercial sector, where CROs are rare and the data is normally held directly by the sponsor, was followed up in the discussion. The inspector from Denmark made the point that during recent work in Denmark they had also recognised that the 'independent investigator's copy of the CRF' would be a particular problem for investigator led trials (multi-centre) and solutions are needed since the requirement for independent data are also valid in this context. There are already a number of solutions available to the investigators and a number of investigator sites/hospitals have developed their own systems.
4.	**Risk Based Monitoring**
4.1	***TransCelerate approach to Risk Based Monitoring*** The presentation given by TransCelerate covered the basics of the TransCelerate framework for Risk Based Monitoring. At the heart of all of RBM is the assumption that quality by design principles prevail. An early, multi-disciplinary assessment of risks using the RACT (Risk Assessment and Categorisation Tool), should be first utilised to address any improvements to the protocol or CRF before they are finalised. Identification and then focusing on the critical data, is undertaken prior to applying the risk reporting methods. Finally, in the conduct stage, a regular risk reporting and assessment is undertaken to address anomalies. Some particular areas of lessons learned were given more focus and included: • Dispelling some RBM myths • Addressing the uptake of RBM • A summary of Source Data Verification(SDV) and Source Data Review (SDR), and a review of the key points of the TransCelerate paper of using SDV as a quality assessment tool • A new area of two papers to be published in early 2016 on Data Integrity & GCP Misconduct.
4.2	***CRO experience of Risk Based Monitoring*** This presentation was made up of two parts; the first part was given by ACRO and the second by EUCROF. ACRO shared with the group its RBM experience to date. ACRO's member CROs represent over 400 studies conducted with RBM to date. They have found that the 2013 EMA Reflection paper and FDA guidance on RBM have increased the focus on quality where it matters, stimulated multiple streams of innovation while creating new opportunities for enhanced efficiency in the conduct of clinical

trials.

In their experience of adoption of the RBM approaches, the member CROs reflected on the remaining concerns with the current draft addendum, the level of alignment between inspectors on the core elements of RBM and how these will be assessed. In particular, the possible variability in assessment of deployed RBM technology, risk indicators, site and central monitoring practices, as well as the selected critical data and processes, raises concern. A solution could be to further clarify the limits of tolerability.

EUCROF presented on how large full service providers and small CRO experiences were compared to best practices and the following observations were highlighted:

- A timely cross-functional interaction between the sponsor and all stakeholders at the stage of protocol design and throughout the course of the trial is essential and not always in place.
- Challenges may exist when the number of parties involved is high; timely integration of non-eCRF data from third party vendors is critical and if not properly planned may even constitute an obstacle to implementation of RBM.
- The way centralised monitoring is operationalised varies according to the study protocol and risks but is also dictated by other “organisational” factors.
- Site staff awareness of the RBM context and education are not sufficient. Logistical challenges at site should be identified and addressed before study start.
- Monitors need to comply with the RBM model balancing on site and remote activities. SDR is essential but legitimacy of review by sample for critical data and processes is questioned.

The initial discussion focused on SDV and SDR. The inspectors felt there is still very much emphasis on SDV, and that it is necessary with a risk based approach on a trial specific level to develop individual monitoring strategies. The TransCelerate response was that industry is trying to move away from SDV and putting in SDR, but the systems are slow to change and be introduced (validated). These systems still utilise SDV as the key monitoring tool. The introduction of SDR initially proved to be a challenge, but metrics review and recent surveys of the onsite monitors suggest that the main issues are over. The inspectors reminded the group that European regulations do not authorise e-medical records’ access by remote third parties or copies of the medical records to be distributed outside the hospital and that investigators should maintain adequate, accurate and complete source documents for the trial subjects that include all pertinent observations and not only those explicitly asked for by the protocol.

The second main topic from the inspectors, addressed the monitoring. Research suggests that small sites cannot use the same metrics as large sites (site metrics when <5 patients). TransCelerate responded that this point is largely correct, that many of the statistical techniques are not successful on a site basis

with low patient numbers, but TransCelerate utilizes a number of additional methods to use. Firstly, TransCelerate summarises the risks by other factors, such as onsite monitor, country (in multi-national trials) and by overall for the trial. Secondly, other techniques are being referenced that can detect issues anywhere within a trial. A review of the forthcoming TransCelerate Statistical Monitoring paper in Q1 2016 was suggested.

The inspectors asked what consideration had been given to the potential to un-blinding the data with even more centralized monitoring review. Under RBM the risk of un-blinding needs to be considered and the roles of staff must be defined and established in a way which minimises this risk.

Suggestions included: exclude data that break the blind from the aggregated data, separate the team reviewing aggregated data from those who interact with investigator site staff and verify risks during risk assessment.

TransCelerate have dealt with the issue of potential un-blinding in two parts; un-blinding is part of the RACT assessment and mitigation would be put in place at this stage. Secondly, the Central Monitors are not raising the direct data queries, this is with the RDC systems, Data Managers and onsite monitors mainly, whereas management of the risk reports are in general with the Central Monitors.

Request was made by ACRO and TransCelerate to understand how tolerance limits should be defined and if historical data such as protocol deviations (PDs) can provide a robust ground to define those limits. It was emphasised that effectiveness of RBM is not based on the absolute number of PDs but on the relative number and severity of PDs; existence of recurrent critical PDs will indicate that the RBM applied to this study was ineffective.

The inspectors addressed concern that the tolerance levels should not be applied without thinking, and so must be adjusted for orphan indications. TransCelerate agreed “one size does not fit all” projects / trials. Tolerance levels for SAE reporting for an orphan indication with only 120 patients would be different than for a standard programme with 2,500-3,500 patients. Tolerance levels for critical vs non-critical data would differ, but it may still be possible to consider some standard tolerance limits for non-critical data.

Some inspectors expressed a dislike for setting general tolerance levels as acceptable levels will be trial dependent and for some data a few errors can have great impact and they preferred to make their own judgment in an inspection with all information available. TransCelerate felt that this was the current situation and it is not fully satisfactory as it leads to inconsistencies and can only reflect on the inspections.

The chair asked about the number of RBM studies currently initiated; none of the stakeholders was able to quantify this but there was a global consensus that this number is growing. EUCROF also made reference to an increasing number of studies where some limited elements of centralised monitoring were in place.

	It is accepted that RBM must be specifically tailored to the protocol and a generic discussion cannot bring opportunities for specific answers. The chair proposed to organise a more specific workshop on RBM in the next year.
5.	**Conclusions and next steps** The Chair went over the main conclusions of the meeting. She pointed out that it is clear that technology is evolving much faster than regulations and clinical research. However, it remains important that regulators remain assured that any new technology used in clinical trials complies with the GCP requirements outlined in the legislation and relevant guidelines. Therefore, it is crucial to continue engaging in dialogues such as this one, in order for all parties to increase their knowledge and understanding in this area. Such meetings are also important in order to ensure that best practices developed, fulfil the inspectors' expectations and at the same time provide more guidance on this topic. The following points cover the main issues raised during the meeting: • how ownership is exercised when a cloud model is used and how this can be best addressed through contacts and agreements including Service Level Agreements; • how to protect data in the cloud from unauthorised access (in some situations this may not be possible for practical reasons); • how to define and implement "independence" from the investigator data in practice; • what is actually meant by "control" by the investigator; • electronic certified copies, must be defined further what "all" means ("…all of the same attributes and information as the original") in terms of content and format. • how vendors develop and agree on best practice standards. It was agreed that as a next step, a follow-up meeting of a subgroup of experts and GCP inspectors will take place in 2016 to touch upon a number of the issues raised at the meeting. EMA proposed to implement focused work groups for specific issues which may need more discussion and information sharing. These suggestions were supported by several parties.

List of participants

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