



Medicines & Healthcare products
Regulatory Agency



GCP INSPECTORATE

Endpoint Clinical

INSPECTION REPORT

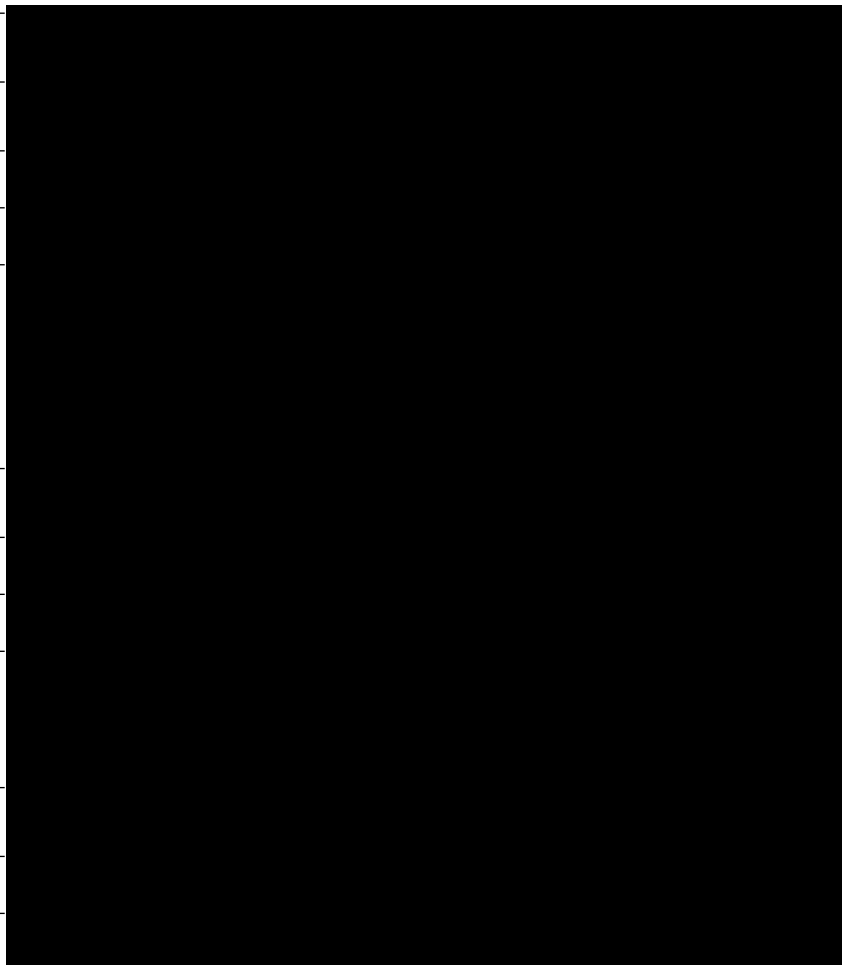
INSPECTION No:
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Head Office:
MHRA
Inspection, Enforcement & Standards Division
10 South Colonnade
Canary Wharf
London
E14 4PU
Telephone: 020 3080 6000

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Sponsor Name & Address
EUDRACT Number
IMP Details
Protocol Reference and Title
Sponsor Name & Address
EUDRACT Number
IMP Details
Protocol Reference and Title
Sponsor Name & Address
EUDRACT Number
IMP Details



Background Information

Endpoint is an IRT vendor for sponsors with offices in 3 locations in the USA, the UK and India. IRT systems have been provided since 1998 and it is currently a wholly owned subsidiary of [REDACTED]. There are currently 375+ staff and Endpoint has provided IRT support for over 850 clinical trials.

The IRT software is [REDACTED] core product and then a trial specific release is configured/built by Endpoint directly from this (or indirectly based on a sponsor specific template).

Further releases of the core product are undertaken by Endpoint R&D, whereas the trial specific builds are undertaken by Operations, the latter having the most resources (over 200 staff compared to 18 in R&D). Over 40 staff are involved in support services (Helpdesk etc.), 14 staff are responsible for the IT services. A quality system is in place comprising SOPs, Work Instructions and template quality records and 13 staff are involved in the Quality Trust and Compliance department responsible for oversight of the QS and QA, including active involvement in the release of software.

This was the first MHRA GCP inspection of Endpoint. Several trials were selected as examples of the IRT provision and an example of the core product release validation was examined. Support services, IT and QS/QA and training were also reviewed by the inspectors.

Endpoint opted to locate the inspection at their office in San Francisco.

Definitions of Findings

Critical:

- a) Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that:
 - i) the rights, safety or well-being of trial subjects either has been or has significant potential to be jeopardised, and/or
 - ii) the clinical trial data are unreliable and/or
 - iii) there are a number of Major non-compliances (defined in (d) and (e)) across areas of responsibility, indicating a systematic quality assurance failure, and/or
- b) Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in (d) and (e))
- c) Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations

Major:

- d) A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, and/or
- e) Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systematic quality assurance failure.

Other:

- f) Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major.

Reference Texts

- UK Medicines Act 1968.
- The Human Medicines Regulations 2012, SI 1916 and the applicable statutory instruments including 2004/1031 (and subsequent amendments)
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (*Official Journal L 121, 1/5/2001 p. 34 - 44*).
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*Official Journal L 262, 14/10/2003 p. 22 - 26*)
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*)
- CHMP/ICH/135/95: "Note for Guidance on Good Clinical Practice".
- Annex 13 to the EU Guide to Good Manufacturing Practice, 'Manufacture of Investigational Medicinal Products', July 2010.
- CHMP/ICH/377/95: (E2A) "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting"
- Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C 82/01)
- Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)

Inspection Findings

Finding Number	CRO Site Findings
1.0 Critical Findings	<p>There were no Critical findings identified during this inspection.</p>
2.0 Major Findings	<p>There were 3 Major findings identified during this inspection relating to Project Management, Data Integrity Control Processes and Computer Systems Validation.</p>
2.1	<p>Project Management</p> <p>No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Regulation 28</p> <p>A person who is a sponsor of a clinical trial in accordance with this regulation may delegate any or all of his functions under these Regulations to any person but any such arrangement shall not affect the responsibility of the sponsor. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Regulation 3</p> <p><u>Relevant Principles of GCP</u></p> <p>Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Schedule 1, Part 2, 2</p> <p>The necessary procedures to secure the quality of every aspect of the trial shall be complied with. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Schedule 1, Part 2, 4</p> <p>All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Schedule 1, Part 2, 9</p> <p>Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance with - (a) <u>the protocol</u> relating to that trial, as may be amended from time to time in accordance with regulations 22 to 25; (b) the terms of - (i) <u>the request for authorisation</u> to conduct that trial, (ii) <u>the application for an ethics committee opinion</u> in relation to that trial, and (iii) any particulars or documents, other than the protocol, accompanying that request or that application, as may be amended from time to time in accordance with regulations 22 to 25; and (c) any conditions imposed by the licensing authority under regulation 18(2) or (6), 19(8), 20(5), 24(4 5) or Schedule 5. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Regulation 29</p> <p>“Conducting a clinical trial” includes - (a) administering, or giving directions for the administration of, an investigational medicinal product to a subject for the purposes of that trial, UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Regulation 2</p>

	<p>Defence of due diligence- (1) A person does not commit an offence under these Regulations if he took all reasonable precautions and exercised all due diligence to avoid the commission of that offence. (2) Where evidence is adduced which is sufficient to raise an issue with respect to that defence, the court or jury shall assume that the defence is satisfied unless the prosecution proves beyond reasonable doubt that it is not. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Regulation 51</p>
2.1.1	<p>There was a lack of formal process for due diligence to ensure that Endpoint does not release updated systems into active use prior to necessary regulatory and ethical approvals being in place. It was stated that for the initial release the sponsor has control of regulatory green light by activating sites, however for amendments all subsequent changes after the initial release would be applied to all trial sites without any due diligence checks that the necessary approvals had been received unless activation on a site level functionality had been requested by the sponsor and configured into the trial specific release.</p> <ul style="list-style-type: none"> For the [REDACTED] trial IRT, the release of the updates to the system was automatically available to all sites that were active in the UK and there was no documentation to show that Endpoint had considered whether the necessary approvals were in place (note: in this case, the sponsor had not got any activated controls to release the amendment on a country/site level). The release of the change to implement Protocol amendment [REDACTED] was on 26JUN19, whilst this was after MHRA approval on [REDACTED] it was BEFORE UK Research Ethics Committee favourable opinion for the protocol amendment which was granted on 01JUL19. This amendment essentially allowed the system to recruit patients that were previously excluded (removed exclusion of prior use of [REDACTED] to align with updated text in Section 5.1 regarding allowed enrolment under limited conditions). Fortunately, there were no patients entered into the trial between 26JUN19 and 30JUN19 with [REDACTED] prior usage and for this reason and that MHRA approval was in place the finding has not been graded as critical. An update to the [REDACTED] trial IRT was made based on protocol amendment [REDACTED] 02AUG18 ([REDACTED] version [REDACTED] 17OCT18) which included updates to the dispensation table for new dispensation visits (addition of cycle 4). This was deployed and went live and was released to production on 18OCT18, whilst this was after MHRA approval on [REDACTED] it was BEFORE UK Research Ethics Committee favourable opinion for the protocol amendment which was granted on 06DEC18. <p>As part of the response to this finding, [REDACTED] should provide a statement for MHRA to review (and details as appropriate) on whether the protocol was implemented and affected any UK patients prior to REC approval.</p>
2.1.2	<p>It was confirmed during interview that an initial build of a system can be released without Endpoint receiving a final signed protocol from the client. In addition, during interview it was stated that a review of the final protocol version would be performed against the specifications, but this review would not be documented.</p> <ul style="list-style-type: none"> The [REDACTED] trial protocol was released based on a draft version of the protocol (11SEP17) on 18OCT18 based on [REDACTED] of specifications dated 07MAR18. Protocol Amendment [REDACTED] (31JAN18) and subsequent protocol amendment [REDACTED]

	<p>(02AUG18) defined a washout period of 7-28 days for cross over subjects who switched from [REDACTED] to [REDACTED] due to disease progression.</p> <ul style="list-style-type: none"> • Protocol amendment [REDACTED] (31JAN18) was the first protocol submitted and approved by the MHRA on 20APR18. • An email dated 20SEP19 showed that protocol amendment [REDACTED] changes were discussed with the sponsor on 01FEB19 who stated that 'There is more information regarding the washout period for patients who started on [REDACTED] and switched to [REDACTED]. This was contained in protocol amendment [REDACTED] (31JAN18). Yet this was not considered as a change to the IRT system by Endpoint even though this discussion took place prior to initial release when Endpoint queried via if there were any changes to 'dispensation, randomisations, stratification visits or visit windows. • The latest version of the system specifications in place at the time of the inspection (version [REDACTED] 26JUN19) stated that 'No system required washout period necessary' <p>Therefore, the IRT system at the time of the inspection could not ensure compliance with the approved protocol and ensure subjects were not crossed over without ensuring a sufficient washout period was observed as required as this had not been included in the system requirements.</p> <p><i>As part of the response to this finding, confirmation is required on whether any cross over subjects had deviated from this protocol requirement.</i></p>
2.1.3	<p>It was explained during interview that [REDACTED] protocol amendment [REDACTED] was received on 12SEP19 and was reviewed by Endpoint and deemed to have no requirement for a change to the IRT system. However, protocol amendment [REDACTED] included removal of the [REDACTED] dose for safety reasons. Therefore, it was unclear why it was decided that no change to the system was required. Also, whilst review of the protocol was not a requirement of Endpoint procedures, it was performed according to the interviewee, but not documented on this occasion. It was noted during the inspection that protocol amendment [REDACTED] had not been submitted to the MHRA for approval at the time of the inspection (it had been provided to the US FDA and Endpoint had a copy of it).</p> <p>Confirmation was received from the sponsor in response to an inspection request that Investigators had not been informed of the safety issue as it was not deemed urgent. However, confirmation was sought from the MHRA CTU Medical Assessor who stated if the change had been implemented it would have been an urgent safety measure.</p> <p><i>It therefore appears that protocol amendment [REDACTED] was not implemented in either in IRT or by informing any UK sites and not yet submitted to MHRA. As part of the response to this finding, the sponsor is required to confirm that protocol amendment [REDACTED] has been or will be submitted to the MHRA and REC as the [REDACTED] dose appears to be unsafe.</i></p> <p><i>Endpoint is also reminded that such changes are subject to regulatory approval prior to implementation unless deemed an USM and is required to notify the sponsor of this finding.</i></p>
2.1.4	<p>Whilst Endpoint's procedures are consistent across the trials, there was no assessment of the regulatory status of the study being placed and therefore any specific regulatory requirements relating to it (e.g. device trial vs medicines trial).</p>

2.2	<p>Data Integrity Control Processes</p> <p>No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Regulation 28</p> <p>The necessary procedures to secure the quality of every aspect of the trial shall be complied with. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Schedule 1, Part 2, 4</p> <p>All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Schedule 1, Part 2, 9</p> <p>The sponsor shall keep a trial master file for a clinical trial. The sponsor shall ensure that the trial master file is readily available at all reasonable times for inspection by the licensing authority or any person appointed by the sponsor to audit the arrangements for the trial. The master file shall at all times contain the essential documents relating to that clinical trial. The essential documents relating to a clinical trial are those which—(a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and (b) show whether the trial is, or has been, conducted in accordance with the applicable requirements of Directive 2001/83/EC, the Directive, the GCP Directive and Commission Directive 2003/94/EC. UK Statutory Instrument 2004/1031 [as amended] “The Medicines for Human Use (Clinical Trials) Regulations”, Regulation 31A</p> <p>Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e., <u>an audit trail should be maintained</u>); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. <u>The investigator should retain records of the changes and corrections.</u> ICH GCP E6 (R2) EMA/CHMP/ICH/135/19951 December 2016, 4.9.3</p> <p>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. ICH GCP E6 (R2) EMA/CHMP/ICH/135/19951 December 2016, 8.1</p> <p>Case Report Form: A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject ICH GCP E6 (R2) EMA/CHMP/ICH/135/19951 December 2016, 1.1</p>
2.2.1	<p>The IRT system was being used for more than IMP management, it was also receiving and making calculations on [REDACTED] data and transferring clinical data to the eCRF. For example, for trial [REDACTED] the data was previous therapy, sums of total tender or swollen joint counts and for trial [REDACTED] it was stool and abdominal pain from [REDACTED] previous drug treatment and eligibility criteria assessment. The implications of the system being used to report clinical data from the investigator site to the sponsor (the IRT meets the definition of a CRF in ICH GCP) in terms of compliance with ICH GCP</p>

	<p>requirements for CRFs had not been considered in terms of the functionality of the system. Indeed, the Endpoint policy on ICH GCP [REDACTED] Version [REDACTED] 22JAN19) specifically (and incorrectly for some trials) states that the [REDACTED] system is not an EDC. Examples of specific requirements of ICH GCP relating to the eCRF include addressing data changes to any investigator entered data should be authorised by the investigator e.g. assessment of ICH GCP requirements 4.9.1 and 4.9.3.</p>
2.2.2	<p>Essential documents may be held by Endpoint on behalf of investigators, but this was not addressed in the ICH GCP policy [REDACTED] 22JAN19 (4.9.5) in relation to the product/processes of Endpoint. Endpoint confirmed that the IRT system could serve as IMP accountability records if the sponsor chooses to do so, but there was no formal procedures that covered the use of the IRT for investigator site essential documents (even to know if this was what the sponsor is intending) and the implications of this from GCP requirements in terms of holding such essential documents.</p>
2.2.3	<p>The Quality System of Endpoint did not adequately address the control of the data by the investigator as required by ICH GCP and that changes to site entered data should be authorised by the investigator as the investigator was unable to change any of their data entered into IRT. In fact the systems were set up that sponsor approval of the changes requested by the investigator was required and SOPs [REDACTED] [REDACTED] in data changes made no mention of the investigator. This was of particular concern for site entered data that was being integrated into the eCRF. Evidence was seen of data change requests from site being required to gain approval in the help desk ticketing system (e.g. [REDACTED]) via Data Change Requests (DCR). The DCRs could also be raised and approved by Sponsor/Client. The [REDACTED] role configurations routed approval of any change requests to the Sponsor/Client and not the investigator for example:</p> <ul style="list-style-type: none"> • For trial [REDACTED], the DCR [REDACTED] was raised and approved by the same user [REDACTED] Study Manager [REDACTED] herefore the sponsor was requesting and approving changes to investigator entered data. The DCR [REDACTED] was "patient on site: need to change question regarding will the subject enrol from 'No' to 'Yes' as subject was a responder". It was confirmed that the response to this question was integrated to [REDACTED] and so the IRT system for this question was also acting as the eCRF. • For trial [REDACTED] the DCR [REDACTED] was raised as a ticket by the CRA on 13FEB19 for site [REDACTED]. The site had entered the tender count erroneously by mistake. The tender count was updated via DCR [REDACTED] subject [REDACTED], OLD value [REDACTED] new value [REDACTED]." The DCR was raised 13FEB19 by [REDACTED] site co-ordinator) and approved by [REDACTED] study manager) on the same date (this was approved by the Sponsor and not the investigator). <p>Finally, back-end changes could in theory be made to the data tables, yet there was no requirement to notify or seek approval from the investigator prior to making these changes if they related to clinical data. (It was noted that during interview, the inspectors were informed that table-level audit trail was switched on).</p>
2.2.4	<p>There were some issues noted relating to the audit trail functionality in [REDACTED]</p> <ul style="list-style-type: none"> • Real-time audit trail was not available to the investigator to ensure control and

	<p>integrity of their trial data (it was explained the audit trail is provided to the client and not the investigator). The [REDACTED] system did not have a visible audit trail within the system and the audit trail was only available via a back-end facility not available to the investigator.</p> <ul style="list-style-type: none"> • The quality for usability of audit trails for review was inadequate (format, structure and ability to identify data due to decoding issues and filtering incompatibility with data structure). The audit trail was complex and required a guided review by an expert user of the system in order for it to be interpretable • For the [REDACTED] audit trial, the reason for change was not captured, a key requirement of GCP and good documentation practices. • There was no requirement within the quality system to ensure the audit trails were provided to the Client/Investigator at the end of the trial as a deliverable. It was confirmed during the inspection that this requirement had been recently updated to be included in a procedure, but this was not effective at the time of the inspection. • The data provided to the client at the end of the trial would not include system access logs defining when user roles were granted and revoked as default. However, it was confirmed that the information could be provided to the client and therefore also the investigator upon request or derived from the final database provided to the client. (also see finding 2.2.7)
2.2.5	Data is provided to the Sponsor/Client at the end of the trial and not directly to the Investigator and therefore the sponsor has exclusive control of this data. The IRT may contain investigator site-controlled drug accountability essential documents that should remain under the control of the investigator at all times.
2.2.6	There was a lack of assessment of data being integrated to EDC systems to determine if clinical/ protocol required data was being entered; in which case the IRT would be an extension of the eCRF.
2.2.7	There was no default functionality in [REDACTED] for the investigator to review users who have/had access to their site data etc.
2.3	<p>Computer Systems Validation</p> <p><i>No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. UK Statutory Instrument 2004/1031 [as amended] "The Medicines for Human Use (Clinical Trials) Regulations", Regulation 28</i></p> <p><i>The necessary procedures to secure the quality of every aspect of the trial shall be complied with. UK Statutory Instrument 2004/1031 [as amended] "The Medicines for Human Use (Clinical Trials) Regulations", Schedule 1, Part 4</i></p> <p><i>When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should: (a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation). ICH GCP E6 (R2) EMA/CHMP/ICH/135/19951 December 2016, 5.5.3</i></p>

2.3.1	<p>There were some issues noted with the risk assessment process as follows.</p> <ul style="list-style-type: none">• The risk assessment undertaken by R&D for development of core software did not address regulatory risks, for example, ensuring that any changes to the system were compliant with GCP.• The risk assessment did not give an identifier for the requirements being assessed (it is understood that this now being piloted as a new process, but not yet a formal process)• Risk Assessment [REDACTED] Version [REDACTED] 26AUG19 contained definitions of severity as Critical, Catastrophic, Minor, low damage etc, yet the definitions of these classifications were not formalised in order to ensure consistent assignment of severity.
2.3.2	<p>There had been no assessment of the functionality of [REDACTED] against the requirements of ICH GCP and that these were captured as part of the system requirements (it is acknowledged that a column to address this for the product in the tabular ICH Policy [REDACTED] 22JAN19 and there is an intention to do this in the future).</p>
2.3.3	<p>For the validation of the [REDACTED] core product release, some deficiencies in the documentation, particularly relating to the Traceability Matrix and the Detailed Test Report indicated that it was potentially insufficient to support the system being in the validated state, which is potentially a critical finding.</p> <p><i>In addition to actions to address the points below, a corrective action is required to audit the documentation for accuracy and completeness to confirm the validated state in response to this finding. It was noted for a number of items processes had since been updated to ensure checks and traceability is available.</i></p> <ul style="list-style-type: none">• There was no documentation retained of the risk assessment meeting performed which involved a number of contributors as per the procedure [REDACTED] Version [REDACTED] 26AUG19 (e.g. QA, Development, Validation and Productions Owner). The risk assessment only contained the name of the product owner. The risk assessment version [REDACTED] 10MAR16 did not contain the identity number to link the functionality to the requirement specification (it is acknowledged that this has now changed with new procedures).• The grooming process to define the project and the requirements to be included in the next release was not fully documented to ensure that the rationale for the decision to select/not select outstanding requirements/issues/enhancements on the backlog and those involved in the process could be reconstructed. Therefore, there was no overall summary of who was involved in the decision for the requirements to be included in release planning for [REDACTED] as only evidence was meeting invites, but this does not demonstrate who actually attended the meeting and no minutes produced.• The unit testing, identified as required in the risk assessment, had not been documented. It is acknowledged that this now in the current processes.• Unit testing was not formally documented for requirement ID: [REDACTED] (audit trail).• The smoke testing was not documented.

- At the time of version [REDACTED] release the traceability matrix was deficient and erroneous. It did not include the test cases for the requirements relating to audit trail content [REDACTED]. The configuration traceability matrix was updated to version [REDACTED] on 13SEP18 significantly after the system was released due to an external audit (incident [REDACTED]). However, this CAPA was deficient as it failed to identify that the [REDACTED] version [REDACTED] was inadequate as there was no reference to the test cases (e.g. [REDACTED] etc.) associated with RQ [REDACTED] (audit trail).
 - Test Case [REDACTED] was created and approved by the same individual.
 - The [REDACTED] review on 16MAR16 for the [REDACTED] release to move to the Testing & Validation environment made no mention of review of the Traceability matrix, Risk Assessment or Test cases as required by [REDACTED] version [REDACTED] 05JUN15 section 5.1.13. The inspectors were informed that a review of these, the requirements and the [REDACTED] project requirements would be undertaken to ensure consistency of all requirements, but there was no evidence that this was undertaken and no SOP was in place to require this as SOP- [REDACTED] version [REDACTED] 05JUN15 states QTC review is required, but it does not specify the details of what the review comprises prior to approval (e.g. consistency check of documents with [REDACTED]).
 - The detailed report of test runs ([REDACTED] 05JUL16) should contain the full run history and results of all test scripts created from [REDACTED]. During the interview, it was identified that for the test scripts related to [REDACTED] (audit trail), i.e., [REDACTED], [REDACTED] these were not contained in the report. The report therefore was incomplete. It was therefore not possible to evaluate quickly that all these scripts had been run and passed and identify and failed runs to ensure issues had been rectified and retested.
 - The [REDACTED] Version [REDACTED] 13JUL16 was inaccurate as it listed specification requirements version [REDACTED] (10MAR16), however the system was developed in accordance with version [REDACTED] 01JUL16 and it did not list all the requirement specifications, for example, [REDACTED] configuration requirements.
 - The [REDACTED] Version [REDACTED] 13JUL16 was finalised after release of the system on 08JUL16
 - [REDACTED] version [REDACTED] 28JUN18 required no high or medium defects to be open when approving the release of the [REDACTED] system to the Testing and Validation or staging environment. However, QA checklist signed 16MAR16 stated that the following tickets were still open:
 - Depot creation issue resolved in [REDACTED] - priority = blocker
 - Message centre issue resolved in [REDACTED] priority = Major
- However, there was no documentation in the tickets or QA checklist to demonstrate that these issues were considered minor and not high or medium defects.
- The [REDACTED] Version [REDACTED] (undated) with an [REDACTED] list of incidents 05JUL16 did not contain details of the defects resolved during the

	<p>release, but instead contained a count of the number of Blocker, Critical, Major, Medium and Minor defects raised and resolved. The report contained 11 critical defects which had all been fixed. However, when recreating this search via a [REDACTED] query (which was used to extract and recreate the critical defect list in the incident summary report) to verify the list matched [REDACTED] only 10 critical defects were identified. It was explained via document request [REDACTED] that this was due to a configuration issue (ticket [REDACTED] being misclassified as the bug was fixed in release [REDACTED] and so should not have appeared in the count of critical defects for release [REDACTED]</p> <ul style="list-style-type: none">• The training materials for the release [REDACTED] were not available in a timely manner as the system was released on 08JUL16, but the training materials were not released on to [REDACTED] (learning management system) until 07OCT16. There was also no documentation retained of when and which individuals were provided with training on the [REDACTED] system [REDACTED]. It was stated in document request [REDACTED] that training was also provided for staff working on the initial trial build for trial [REDACTED] on 28JUL16. However, evidence of this training was not provided as requested.
2.3.4	<p>There were documentation issues concerning the validation of the trial specific configurations as follows.</p> <ul style="list-style-type: none">• The requirements did not consistently capture the protocol version used to create them, for example, for the [REDACTED] trial, the requirement specifications version [REDACTED] 26JUN19 and for the [REDACTED] trial specifications version [REDACTED] 29MAY19, but for the [REDACTED] trial, specifications [REDACTED] 09OCT17 did (Protocol version [REDACTED] 12OCT17).• For the [REDACTED] trial, the requirement specification configuration for the eDRS did not permit approval of DCRs by the investigator only the CRA or CRO Manager.• For the initial build, the code review was undertaken on 22JUN17 prior to the unit testing having been completed, for the example reviewed [REDACTED] which passed on 23JUN17.• For the initial build for the [REDACTED] trial, the test plan 26JUN17 only mentioned 21CFR part 11 as a compliance standard, but not ICH GCP. [REDACTED] version [REDACTED] 26MAR18 for the [REDACTED] trial referred to compliance with 21 CFR Part 11 compliance, but there was no review of UK/EU requirements.• The validation reports Version [REDACTED] (undated) and Version [REDACTED] (26MAR18) for the [REDACTED] trial and [REDACTED] trials respectively did not clearly report that the system was released with known issues or list failures, instead a reference is made to the [REDACTED] Version [REDACTED] (undated) and Version [REDACTED] (undated) respectively. It was noted that the template for the validation report had no section to report known issues. It would be essential that the validation report provides this information.• For the [REDACTED] trial, the system was released to production on 18OCT18, however the final QA review had not been completed until 24JUN19 (it was acknowledged that an SOP deviation was documented).• For the [REDACTED] trial enhancement [REDACTED] risk and impact assessment document version [REDACTED] (undated) (document request [REDACTED]) listed the risks associated with the changes to the enhancement (e.g. addition of cycle 4) and the required testing. However, there was a lack of documented assessment of the data within the trial

	<p>overall to ensure that testing is performed of the entire system and not just the changes (e.g. in order to identify if code impacted elsewhere).</p> <ul style="list-style-type: none"> • For [REDACTED] trial enhancement [REDACTED] for requirement [REDACTED] the UAT test plan was not dated or signed as required by the form. • Validation reports for initial builds were not provided to sponsors/clients and detailed test reports not provided to sponsors/clients for enhancements (no VSR created for enhancements), for example for the [REDACTED] trial. Therefore, sponsor/client would be unable to have sufficient oversight of the validation status of a system prior to release of that system and only UAT approval was required from sponsor/client to release the system. • There was a potential lack of independence of UAT for the [REDACTED] trial enhancement [REDACTED]. A draft UAT test plan was created by Endpoint for the sponsor which contained test scripts with expected results. The test plan was not signed, dated or version controlled. It was confirmed this was a draft written by Endpoint, which the Sponsor confirmed that they didn't want to use. However, by writing the scripts for clients, there is the potential for lack of independence and repeated testing.
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3.0 Other Findings

There were **7 Other findings** identified during this inspection relating to Contracts and Agreements, IT Systems, Record Keeping/Essential Documents, Quality Systems, Training, Investigational Medicinal Products and Quality Assurance.

3.1	Contracts and Agreements
3.1.1	It was stated during interview that client contracts would be reviewed against the requirements of Endpoint's own template MSA, however this review was not formalised as part of a formal procedure within the quality system.
3.1.2	The contract with [REDACTED] made no reference to the standards (other than [REDACTED] SOPs) to which [REDACTED] would comply when performing the statistical services that had been delegated to them by Endpoint.
3.1.3	In contracting with sponsors/clients, Endpoint stated that the contracts specify that both Endpoint and the clients must comply with law (including, but not limited to, applicable regulations) and they do not give areas requested to be highlighted by the inspector any specific consideration in the contract. On a review of [REDACTED] and [REDACTED] contractual documents provided, there was no notable statements concerning investigator control of the data or provision of the data to the investigator at the end of the trial and on a requirement concerning approvals (regulatory approval/ethics approval) prior to use of system. The [REDACTED] and [REDACTED] contractual documents were also not as specific as the [REDACTED] contract on the arrangements for reporting of potential serious breaches/issues to the sponsor.
3.2	IT Systems

3.2.1	<p>Prior to granting access to a user to an eSystem, it would be expected that the user has received appropriate training. Within Endpoint, the following gaps in formal procedures were noted:</p> <ul style="list-style-type: none"> • To check training of sponsor staff prior to granting access to the [REDACTED] system. • To document sponsor training. • To advise the sponsor on ensuring training would be undertaken and documented in the ISF prior to granting access to the [REDACTED] system to investigator site staff.
3.2.2	<p>There was a lack of documentation provided to demonstrate the CAPA undertaken and completed following issues identified during the external penetration testing of the network performed by [REDACTED] on 01FEB19. The report identified a high risk for cross site scripting which appeared systemic in nature. However, there was a lack of documentation to confirm that the issues had been remediated and effectively resolved (e.g. via successful re-testing).</p> <p><i>As part of the response to this finding, confirmation is required of the CAPA undertaken, when it was resolved and what effectiveness checks were performed. Also provide any details of any risk assessment performed of the issue to the integrity of trial data in ongoing trials.</i></p>
3.2.3	<p>There was no formalised procedure for the routine review of [REDACTED] [REDACTED] to ensure that the configurations that were being used were consistent with policy and therefore there was a lack of documentation available to demonstrate [REDACTED] configurations are adhered to by way of a review to ensure configuration is correct and functioning as expected.</p>
3.3	Record Keeping/Essential Documents
3.3.1	<p>Whilst individual SOPs (examples were provided in [REDACTED]) may contain instructions and references to the particular documents and their storage locations, there was no overall formal procedure in place to comprehensively address the management of the Trial Master File and essential documents contained therein given that Endpoint was holding these for the sponsor. As there was some procedural content relating to management of documentation, then this finding as not been graded as Major.</p>
3.3.2	<p>From the SOPs reviewed [REDACTED] [REDACTED] that were provided to demonstrate how the quality system requires Endpoint to document contact with the sponsor, it was clear that Endpoint relied on communicating issues with the sponsor and getting document approval by email. There was no mention in the SOP of adequately documenting any meetings with the sponsor, for example in formal minutes.</p>
3.3.3	<p>The documentation of the discussions, attendees and actions for the Change Control Board (CCB) meeting on the 15MAY19 were deficient as follows:</p> <ul style="list-style-type: none"> • An email was provided summarising the actions, but the list of attendees were not documented to verify that the quorum of the CCB had been met to grant approval (outlook meeting invite responses were provided as evidence; however this was not sufficient as it does not verify who actually attended).

	<ul style="list-style-type: none"> Approval was granted for a disk which had failed on the server but required to be replaced. However, the details of the server (ID) were not documented in order to identify which server had been impacted. Whilst details of the server impacted were provided upon request [REDACTED] no inventory list was provided (as required by the request) in order to review the change and confirm that the disk had been replaced.
3.3.4	<p>It was explained that helpdesk ticket metrics and trend analysis was reviewed at management meetings. In response to a document request [REDACTED] no management meeting minutes were provided for 2019 indicating they were not available.</p> <p><i>As part of the response to this finding, confirmation is required that the documentation sent to the management meeting will be referenced in the minutes including outcome of review and any actions required.</i></p>
3.3.5	Sponsor approval of the UAT plan for [REDACTED] trial Enhancement [REDACTED] was not filed with the trial records and not available at Endpoint during the inspection. Evidence of approval was provided post inspection.
3.4	Quality Systems
3.4.1	There was no formal procedure for assessment of new or updated SOP/Work Instructions/Policies in terms of whether the updated/new procedure applied to each live trial. It was also noted that if a decision was made to continue to follow the previous quality document for a trial, via a prospective deviation, the access to view such documents would not be available as only current documents can be viewed, not retired/previous versions.
3.4.2	The [REDACTED] system had the ability to include 'default codes' and the use of such codes were not part of the quality system instructions or coding standards ([REDACTED]). Therefore, there is a risk that default codes could be used in trial specific configurations which could over-ride error messages and default to data which was not applicable at that moment in time. Use of such codes should be subject to control and review to ensure that default codes are not used inappropriately (e.g. could lead to mis-dosing of subjects).
3.4.3	Internal project kick-off meeting for [REDACTED] enhancement [REDACTED] was not documented. [REDACTED] 01AUG17 and [REDACTED] 01AUG17 require an internal project meeting to take place. It was explained during interview this is only documented if there are any issues/requirements for attention which is insufficient for reconstruction of the process and to confirm the formal procedures had been followed.
3.4.4	There were numerous examples of documents provided to the inspectors that were undated as illustrated in findings contained in this report.
3.5	Training
3.5.1	There was no documented assessment for the training requirements for the new ICH GCP policy [REDACTED] Version [REDACTED] 22JAN19. It appeared to be added to the electronic systems as a training requirement, but nothing was provided to demonstrate that

	Endpoint had considered that “read-only training” was appropriate for this new policy.
3.6	Investigational Medicinal Products
3.6.1	<p>For the [REDACTED] trial, Lot number [REDACTED] was updated from expiry date 31MAY19 to 30JUN20 on 15DEC17 and Lot number [REDACTED] was updated from expiry date 30SEP19 to 30APR20 on 24APR18 as per the following table provided by endpoint from the IRT audit trail.</p> <p>[REDACTED]</p> <p>MHRA approval for the shelf life extension was [REDACTED] and the country release of kits with these was after the approval ([REDACTED] spreadsheet provided). For the 2 updates in the table above, the QP certification for UK for the new expiry date was 07MAR19 and 27JUN19 for lots [REDACTED] and [REDACTED] respectively.</p> <p>An explanation is required on what basis the expiry dates were updated in the IRT system before 2019.</p>
3.7	Quality Assurance
3.7.1	<p>There was no initial assessment of [REDACTED] suitability to provide the contracted services available that was undertaken prior to the use of [REDACTED]</p> <ul style="list-style-type: none"> There was no date on the risk assessment document for [REDACTED] so it could not be determined when this was undertaken. <p>The document provided was an Audit report from March 2014, which was a re-qualification and that confirmed the services could continue.</p>

The following are observations and recommendations to which no response is required.

Observations
<p>IT Systems</p> <ul style="list-style-type: none"> Endpoint uses [REDACTED] for secondary storage of back up data, however the precise location of the data centre storing Endpoint data is not known and therefore no assessment made of the facility. This has been given as an observation and not a finding as it was not the primary back up. The back-up and archival process ([REDACTED] version [REDACTED] 16APR19) stated that checks of physical media would be negotiated with the client during the contract negotiation stage. It was confirmed that no test restores had been performed to date because all data is retained for 30 years and that all data was still in a readable format. Procedures at the time of the inspection did not state what the standard checks would be performed of physical media used to retain back up files at Endpoint (CD/DVD/Blu-Ray discs). The inspectors were informed in a document request [REDACTED] that this had been identified as part of the risk assessment for the discs, however, it is noted that back-up discs could be

recreated using the validated logical repository where an archived copy of the database and documentation is stored.

- Evidence of the disaster recovery plan test for 2019 was provided as part of a document request [REDACTED]. However, the learning points and recommendations from the testing had all been redacted.
- There was no formal procedure to control the deletion of bugs (incidents) raised in [REDACTED]. It was confirmed during the inspection that bugs raised by the [REDACTED] could be deleted by users with the appropriate access.

Quality Systems

- The [REDACTED] software did not have configuration to require sponsor approval for emergency unblinding. However, the inspectors were informed [REDACTED] that this functionality could be built in by customisation if required by the sponsor. The Investigator should have mechanism to perform an emergency code-break and this should not be under the control of or require the approval of the sponsor. Therefore, Endpoint processes and the software could all the trial specific configuration to be non-compliant.
- A Production Deviation was raised on 26SEP19 during the inspection detailing the lack of traceability of the requirements within the [REDACTED] system validation documentation. It was stated during interview on 25SEP19 that a deviation had been raised internally noting the issues but had not been raised until after the interview.

Contracts and Agreements

- It was noted that the consultancy work by [REDACTED] for the validation process for the updated software commenced 30SEP18 which was prior to the formal vendor approval being signed on 18DEC18, however, as the assessment had taken place, this has been given as an observation rather than a finding.

Data Integrity Control Processes

- The auditing software applied to the [REDACTED] software was a [REDACTED] [REDACTED] system called [REDACTED]. There was a lack of documented assessment of the system to determine whether the outputs of the audit trail and format were suitable to facilitate review. It was acknowledged that the audit trail functionality is reviewed as part of the System Development Life Cycle (SDLC) of the [REDACTED] system and so functionality for on-screen audit trail is tested, but this excluded exporting of the audit trail and ability to review the data entries and changes on a trial and subject level.
- The data at the site during the trial conduct via the messages from actions in the system may not contain all the data that was entered by the investigator as the sponsor can define the content. Therefore, continual access to the system would be required at the site to ensure that the investigator could access their data until the confirmation that all the data including any audit trail and data change requests were at the site.

Recommendations

Project Management

- It was recommended that the EudraCT number, the unique EU reference for the trial, is obtained from the trial Sponsor is captured in Endpoint systems for trials and this then confirms whether trial falls under the clinical trial regulations as a clinical trial of an investigational medicinal product (CTIMP) and therefore should be on the dossier list of trials for the GCP inspection process.

Data Integrity Control Processes

- It was recommended that Endpoint ensures the issues concerning potential data integrity of one-way integration of the IRT with the eCRF where the eCRF field is editable (but the data amendment would not be passed to the IRT system) is considered in the quality system and discussed with sponsors during the development of the system requirements/functions.

Computer Systems Validation

- It was recommended the 2-step process for the Quality, Trust and Compliance (QTC) approval to release and the smoke testing in the new environment is documented to reflect the actual process (i.e., the approval to move then the approval of the installation) rather than a single event. For example, for the final release of [REDACTED] of [REDACTED] into production environment, the release took place on 08JUL16, but the QTC was not approved until 13JUL16 . The Validation Report for [REDACTED] was also finalised after release (on 13JUL16).
- For [REDACTED] 15MAR16, it was recommended to increase strength of wording to ensure the all calculations involving assignment of dose (initial and alterations) are required to be fully tested.
- It was recommended to review the audit trails/data entered from the sponsor during their conduct of UAT (particularly where no issues raised by sponsor) to confirm that the sponsor has undertaken UAT and then to notify sponsor of any concerns as part of their acceptance of the system and prior to release. For example, for the [REDACTED] trial, there was no positive affirmation of UAT performed by client and confirm no issues found, instead an over-reliance of sign off of UAT approval form to confirm UAT passed.

IT Systems

- The IT department relies on alerts from systems rather than any proactive risk-based reviews, for example, for the back-ups being taken and system scans for unusual activity. It was recommended that routine reviews are also undertaken to ensure that the system is fully functional, for example, the alerts are actually working, and the activity is being completed.
- It was recommended that Endpoint ensure traceability of actions/recommendations generated from a Disaster Recovery Exercise to CAPA management system to ensure all actions have been completed with due dates. For example, a number of learning points were raised in the exercise performed 20-22 February 2019, however it was not possible to review prior to the end of the inspection if all these had been completed. Therefore, it is recommended these are tracked as they may be reviewed on subsequent inspections.

- The inspectors were informed that the [REDACTED] standards are used, however the quality system made no reference to them. It is recommended that this is included if they are being applied.

Training

- It was recommended that more specific GCP training content related to the Endpoint role in the trial is implemented. For example, the ICH R2 training impact was concerned more about the impact of more sponsor oversight and the impact on Endpoint rather than the additional requirements that affect Endpoint functions directly, for example, the addenda concerning validation and investigator control of data/documents.

Essential Documents

- It was recommended that a TMF plan is arranged with the sponsor/client to determine the control of and access to essential documents, before during and after the trial to enhance the contractual arrangements.

Contracts and Agreements

- It is recommended that Endpoint reviews the Q&A (number 8) for contracting with sponsors.

<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp>

Report Author and Reviewer**Report Author:**

[REDACTED] GCP Inspector, MHRA

Report Reviewer:

[REDACTED] Inspector, MHRA

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

Appendix I Summary of Activities

Clinical Trial	Inspected Organisation			Comment
	Assessed			
	Yes	Partial	No	
		⊕		Used as examples for document requests (e.g. Trial Specifications only)
		⊕		Trial Specific Validation, contracts and audit trail
		⊕		Data transfer and data change aspects
		⊕		Trial Specific Validation and contracts. Data transfer and data change aspects
		⊕		Contract.

Activity	Inspected Organisation			Comment
	Assessed			
	Yes	Partial	No	
Analytical Laboratory			⊕	
Archiving	⊕			
BE/ BA activities			⊕	
Clinical Pathology Laboratory			⊕	
Clinical Trial Reporting			⊕	
Computerised Systems	⊕			
Contracts & Agreements	⊕			
Data Management		⊕		
eCRF / Diaries / IRT		⊕		IRT only
IMP Management		⊕		In relation to IRT only
Medical Affairs			⊕	
Monitoring			⊕	
Pharmacovigilance			⊕	
Project management	⊕			
Quality Assurance	⊕			
Quality Systems	⊕			
R&D Unit (Non-commercial only)			⊕	
Regulatory Affairs		⊕		
Statistical Analysis		⊕		
Technical Facility (i.e. x-ray)			⊕	
Training		⊕		
Trial Master File/Essential Documents		⊕		
Other	⊕			