Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

CELL THERAPIES LIMITED (TRADING AS CELIXIR) INSPECTION REPORT

INSPECTION No: 46397/18142462-0001

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MHRA
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Inspection Summary

Inspection & Organisation Information	
Inspection Number	INSP GCP 46397/18142462-0001
Type and Purpose of Inspection	Triggered trial specific GCP Inspection
Organisation Inspected	Cell Therapies Limited (Trading as Celixir)
Organisation Address	Cell Therapies Limited (Trading as Celixir) Celixir House, Innovation Way, Stratford Business & Technology Park, Banbury Road, Stratford-Upon-Avon, CV37 7GZ, United Kingdom Investigator site inspected: [redacted] Royal Brompton and Harefield NHS Foundation Trust, Royal Brompton Hospital, Sydney St, Chelsea, London, SW3 6NP
Organisation Type	Commercial Sponsor
Dates of Inspection	Investigator Site visit for Principal Investigator (PI) interview and to seize documents: 22 July 2020 Sponsor Site visit for sponsor and to seize trial related documents: 28-29 September 2020 Office Based Inspection (OBI) of seized documents: 30 and 31 July 2020, 4 and 5 August 2020, 21 and 25 September and 19 to 21 October 2020
Lead Inspector	Investigator Site visit: [redacted] Inspector Sponsor Site visit: [redacted] Inspector OBI: [redacted] Inspector
Accompanying Inspector(s)	Investigator Site visit: [redacted] Enforcement Officer Sponsor Site visit: [redacted] Inspector and [redacted] Enforcement Officer OBI: [redacted] Inspector
Date of Closing Meeting	22 October 2020
Inspection Report Date	4 November 2020

Clinical Trials Reviewed	
Protocol Reference and Title	[redacted] A Phase IIB, Randomised, Double-Blinded, Placebo-Controlled Study of the Efficacy and Safety of [redacted] in [redacted]
Sponsor Name & Address	Cell Therapies Limited (Trading as Celixir) Celixir House, Innovation Way, Stratford Business & Technology Park, Banbury Road, Stratford-Upon-Avon, CV37 7GZ, United Kingdom
EUDRACT Number	[redacted]
REC Reference Number	[redacted]
Investigational Medicinal Product (IMP) Details	Product Name: [redacted]

Investigator Site(s) Inspected	
Name of Investigator	[redacted]
Organisation Inspected	Royal Brompton and Harefield NHS Foundation Trust,
Organisation Address	Royal Brompton Hospital, Sydney St, Chelsea, London, SW3 6NP
Organisation Type	NHS Hospital
Dates of Inspection	Site visit to seize documents and short interview with Principal Investigator (PI) and pharmacy: 22 July 2020
Lead Inspector	Site visit: [redacted] Inspector
Accompanying Inspector(s)	Site visit: [redacted] enforcement Officer
Date of closing meeting	NA, none conducted
Protocol Reference	[redacted] A Phase IIB, Randomised, Double-Blinded, Placebo-Controlled Study of the Efficacy and Safety of [redacted] in [redacted]
EUDRACT Number	[redacted]

Background Information

The MHRA GCP Inspectorate triggered an urgent short notice GCP inspection of trial [redacted] in order to verify and confirm there had been no participant harm following the dosing of a patient in the trial contrary to a commitment on the 6 March 2020 by the sponsor to the MHRA Clinical Trial Unit (CTU) not to dose patients.

A clinical trial application (CTA) for trial [redacted] was originally submitted to the MHRA as a Phase II trial of [redacted] which included previous clinical trial information on the investigational medical product (IMP) [redacted] as part of the protocol and Investigator brochure (IB). The previous clinical information was based on results from a [redacted] clinical trial conducted in 2012 [redacted] However, subsequent to the original UK CTA it was established that the [redacted]

used in the [redacted] trial conducted in 2012 were not the same as those to be used in this UK trial. The IMP in the [redacted] trial also described as [redacted] had a different [redacted] and production [redacted] to the IMP [redacted] proposed to be used in this UK trial. As this was determined by the MHRA to be a different IMP the trial was therefore considered a first in human trial. As a result, a notice of non-acceptance was issued on 2 March 2020 when the sponsor amended the protocol and IB to a first in human (FIH) trial in substantial amendment [redacted] In response to the notice of non-acceptance dated 6 March 2020 the sponsor gave a commitment not to dose any patients in the trial.

As this information was identified during the COVID-19 pandemic, these inspections were conducted in compliance with the government guidance and MHRA policy on regulatory inspections in place at the time. The decision was made to do limited short inspections on-site for key interviews only and seize relevant trial documents, followed by office-based inspection of the seized documentation.

It was confirmed that the trial participant was dosed with placebo and although they subsequently contracted [redacted], which was reported as an SAE, at the time of the inspection there appeared to be no impact on their safety and well-being.

The inspection has identified 9 critical findings and 5 major findings (including 2 major findings at the investigator site). The critical findings include breaches of legislation that may amount to offences. As a result of these breaches a formal MHRA enforcement investigation has commenced. Therefore, the MHRA do not seek a formal response to the inspection report at this time. Any response which you may wish to give to the inspection report will be encompassed within the enforcement investigation.

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)
- Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
- ENTR/F/2/SF/dn D(2009) 35810 Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (Advanced Therapies)

Inspection Findings

Finding Number	Sponsor Findings
1.0 Critical Findings There were **nine Critical findings** identified during this inspection relating to GCP Compliance, Subject Safety; Investigational Medicinal Product (IMP) - Quality; False and Misleading Information; Insurance; Quality Systems; Essential Documents/Record Keeping (Trial Master File); IMP – Management; Training.	
1.1	**GCP Compliance** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **28(1)** 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. **(2)** Subject to paragraph (5), the sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **In particular: Schedule 1, Part 2,** **(1)** The rights, safety, and well-being of the trial subjects are the most important considerations and shall prevail over interests of science and society. **(2)** Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks. **(3)** Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects. **(4)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **(5)** The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial. **(6)** Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki. **(8)** The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial. **(9)** 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. **(10)** Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks. **(12)** A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored. ***Failing to comply with reg 28(1) and (2) is an offence by regulation 49(d)***
1.1.1	It was evident from the number of critical and major findings across a variety of areas set out below that the sponsor organisation failed to conduct the trial in accordance with the conditions and principles of good clinical practice and therefore risked seriously

	jeopardising the rights safety and well-being of trial patients.
1.2	**Subject Safety** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **29** Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance with (a) the protocol relating to that trial, as may be amended from time to time in accordance with regulations 22 to 25; (b) the terms of— (i) the request for authorisation to conduct that trial, ***Failing to comply with regulation 29(b)(1) is an offence by regulation 49(e)***
1.2.1	The Sponsor allowed a subject to be dosed with an IMP without a valid CTA and against the instructions of the MHRA. The sponsor received a notice of acceptance from the MHRA on 27 September 2017 for the clinical trial application which included Protocol version [redacted] investigator brochure version [redacted] and investigational medicinal product dossier (IMPD) version [redacted] The protocol was updated via substantial amendments to [redacted] which were approved by the MHRA on 11 December 2017, 20 December 2018 and 28 May 2019 respectively. These submissions were for a Phase II trial and referenced previous clinical experience of the [redacted] in a previous trial conducted in [redacted] in 2012 [redacted] referred as the [redacted] 2012 trial. The sponsor made a further substantial amendment number [redacted] under regulation 24(3) which was accepted as a valid notice by the MHRA on 21 February 2020. This substantial amendment updated the protocol to version [redacted] and the investigator brochure to [redacted] This update changed the trial to a first in human trial (FIH) and removed any reference to the [redacted] 2012 trial being the same product. The MHRA issued a notice of non-acceptance in line with 24 (5a) on 2 March 2020 and included the following reasons (taken from the non-acceptance letter): • The trial is now first-in-human with [redacted] rather than [redacted] but no explanation for the difference in investigational medicinal product (IMP) was provided, nor does the documentation indicate that a re-classification of the product has occurred. • the designation as a first-in-human trial calls into question the data previously submitted to support this trial that was previously designated as phase II (since a prior trial in [redacted] also used the [redacted] product). • There is a revised hierarchy of primary and secondary endpoints indicating that the interpretation of results will be substantially changed. In summary, all documents in the initial clinical trial application (CTA) and substantial amendment [redacted] submitted previously all indicated that there was previous experience of this IMP in a trial conducted [redacted] in 2012. Therefore, dosing of the IMP would not be in compliance with the approved protocol version [redacted] and investigator brochure [redacted] In addition, the MHRA CTU [redacted] Assessor followed up the notice of non-acceptance with an email dated 04 March 2020 08.58 to [redacted] at Celixir, confirming the rejection of the substantial amendment and requesting a response by 11 March 2020. The email advised: • The trial had changed to a FIH, but previous CTA documents including the IB and protocol clearly stated that [redacted] had been used in a previous trial in [redacted] and that full disclosure of the exact product used in the previous trial in

[redacted] with a clear and detailed comparison to the current product to be used in the above trial in the UK was required. Ideally a full comparison of the manufacturing processes is required, including all [redacted] used to identify the [redacted] and that provide the [redacted] and [redacted]

- Celixir has ceased manufacture of the product in [redacted] Please provide details of how the manufacturing process intends to be conducted in the future, including plans for how Celixir intends to provide batch analysis data and comparability data demonstrating that the change in site has not impacted on quality/safety attributes of the product.
- MHRA is aware that the first patient has been enrolled. Please provide an update on patient enrolment as well as how Celixir intends to safely treat the patient in view of all the above concerns.
  (The MHRA use of enrolled was in relation to consent.)

The sponsor responded to the MHRA's email and notice for non-acceptance to substantial amendment [redacted] on 6 March 2020 as per regulation 25(2). In this response the sponsor committed to not dosing any subjects until there was an agreed resolution with the MHRA.

Quote: Company Response Question 5:

'Three subjects have consented and are undergoing screening. They were due to be enrolled at the time of surgery, the date of which is to be confirmed, but given the concerns expressed above, ***these subjects will not be enrolled until we have an agreed resolution****. To date, no subjects have been treated'.*

In accordance with regulation 25(3) the MHRA had 14 days from receipt of the notice under regulation 25(2) to give written notice to the sponsor setting out further grounds for not accepting the modified or adapted amendment. This notice was sent to the sponsor on the 16 March 2020 (10 days after receipt of the sponsors modification of the rejected proposal). Therefore, the sponsor did not wait the required 14 days (20 March 2020) as required by regulation 25(5) and allowed a subject to be dosed on 16 March 2020 without a valid CTA.

It is the sponsors responsibility to ensure all staff conducting the trial are informed about the status of the trial and there was no evidence of any written or verbal communication of this information to either the CRO [redacted] or the Principal investigator (PI) either in the investigator site file (ISF), during the brief interview between the PI and the inspector or in the documentation provided by Celixir to the inspectors. All Celixir senior management were aware of this notification to the MHRA and all the senior management were involved in discussions about the treatment of the patient. For example:

- The [redacted] provided comments to [redacted] on the response document in an email dated 6 March 2020 at 13.58 in which [redacted] made suggested edits in tracked changes. This document contained the commitment not to dose subjects.
- The site had consented two participants who would be scheduled for surgery and Celixir had an internal meeting regarding this on 11 March 2020 planned for 12.30 (as per email from [redacted] on 11 March 2020 at 12.13).
- Celixir [redacted] and the [redacted] were informed by email on 12 March 2020 from a research nurse at the investigator site that the surgery date for subject [redacted] was [redacted]

As a result, the sponsor committed an offence by breaching regulation 29(b)(i), as the original protocol and investigator brochure was not complied with and there was no valid approved clinical trial authorisation for the IMP, Despite this, the sponsor allowed

	the dosing of participant [redacted] to go ahead [redacted] just prior to notification of the MHRA's instruction to halt the trial on the same day [redacted] The dosing of the participant also breached the sponsor's commitment to the MHRA in their response dated 6 March 2020, where they advised that subjects would not be enrolled (*which in this context means dosed*) until an agreement had been reached. **Therefore, Celixir knowingly put a patient at significant risk by dosing them in a FIH trial without approval by the MHRA, and contrary to specific commitments to the MHRA not to dose.**
1.3	**IMP (Quality)** **Human Medicines Act 1968, Part III, Additional provisions, Section 64** (1) No person shall, to the prejudice of the purchaser, sell any medicinal product which is not of the nature or quality demanded by the purchaser…. (5)Where a medicinal product is sold or supplied in pursuance of a prescription given by an appropriate practitioner, the preceding provisions of this section shall have effect as if— (a)in those provisions any reference to sale included a reference to supply and (except as provided by the following paragraph) any reference to the purchaser included a reference to the person (if any) for whom the product was prescribed by the practitioner, and (b)in subsection (1) of this section, for the words "demanded by the purchaser" there were substituted the words "specified in the prescription". **UK Statutory Instrument 2004/1031 (as amended), regulations** **13**(1) Subject to paragraphs (3) and (4), no person shall, in the course of a business carried on by him, sell or supply any investigational medicinal product to— (a) an investigator, (b) a health care professional who is a member of an investigator's team, (c) a person who provides or is to provide health care under the direction or control of a person referred to in sub-paragraphs (a) and (b), or (d) a subject, for the purpose of administering that product in a clinical trial, unless the conditions specified in paragraph (2) are satisfied. (2) The conditions referred to in paragraph (1) are (a) the licensing authority has authorised the clinical trial for the purposes of which the product is sold or supplied. (bii) the production batch of investigational medicinal products of which the product is a part has been checked and certified by a qualified person pursuant to Article 13(3) and (4) of the Directive. **Annex 13 to the EU Guide to Good Manufacturing Practice, 'Manufacture of Investigational Medicinal Products' points:** **38** Release of investigational medicinal products (see paragraph 43) should not occur until after the Qualified Person has certified that the requirements of Article 13.3 of Directive 2001/20/EC have been met (see paragraph 39). The Qualified Person should take into account the elements listed in paragraph 40 as appropriate. **39(a)**The duties of the Qualified Person in relation to investigational medicinal products are affected by the different circumstances that can arise and are referred to below. Table 2 summarises the elements that need to be considered for the most common circumstances (i)Product manufactured within EU but not subject to an EU marketing authorisation: the duties are laid down in article 13.3(a) of Directive 2001/20/EC.

	43. Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step procedure: certification by the Qualified Person; and release by the sponsor for use in a clinical trial following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor. The Sponsor should ensure that the details set out in the clinical trial application and considered by the Qualified Person are consistent with what is finally accepted by the Competent Authorities. Suitable arrangements to meet this requirement should be established. In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the QP and the Sponsor. ***Failing to comply with Human Medicines Act 1968, Part III, Additional provisions, Section 64 is an offence.*** ***Failing to comply with reg 13(1) is an offence by regulation 49 (b).***
1.3.1	The IMP administered to participant [redacted] was not of a sufficient quality to be supplied for administration to that participant in the clinical trial. During the interview GCP inspectors were advised the IMP was labelled at the time of manufacture. The IMP was manufactured and labelled in [redacted] on 22 April 2019 and the 14 June 2019 (batches [redacted] and [redacted]) and then was shipped to the [redacted] on 10 July 2019. The IMP was labelled and subsequently QP certified on 23 August 2019 and 4 December 2019 with a 12 month shelf-life, although Celixir were aware MHRA approval at the time of labelling of [redacted] was for 3 month shelf-life and at the time of labelling placebo and shipping both IMP products it was for a 9 month shelf-life. This was transparent from the following deficiencies:
1.3.1.1	The IMP and matching placebo had not been QP certified in compliance with the approved clinical trial authorisation (CTA). As a result, the IMP administered to participant [redacted] on 16 March 2020 had expired. This was evidenced from: • The approved CTA on 28 May 2019 included IMPD version [redacted] (dated 19 October 2018) had a stability period of 9 months for both the Placebo [redacted] and [redacted] • The certificate of analysis for the Placebo [redacted] batch [redacted] had a manufacture date of 14 June 2019, therefore the expiry of this product would be 14 March 2020 in accordance with IMPD version [redacted] • The certificate of analysis for [redacted] batch [redacted] had a manufacture date of 22 April 2019. Therefore the expiry of this product at the time of labelling would have been 22 July 2019 based on IMPD [redacted] which was the version approved at the time of labelling; or the expiry of the product would have been 22 January 2020 in accordance with IMPD version [redacted] which would have been the version approved at the time of shipping and QP certification. However, the IMP had been labelled with an expiry date of 22 April 2019, the batch certificates [redacted] and [redacted] for QP certification signed by the QP on 23 August 2019 and 4 December 2019 respectively (which included the kit dosed to the patient [redacted] kit [redacted] both had an expiry date of 22 April 2020, giving a year stability for the product. In addition, the IMP receipt documentation provided by [redacted] and the patient administration log for patient [redacted] showed that Kit [redacted] had an expiry date of 22 April 2020. IMPD version [redacted] dated 31 January 2020) which extended the stability period to 12 months had not been finalised at the time the IMP was manufactured and labelled and

	QP certification was performed and had never been approved by the MHRA. IMPD version [redacted] was not submitted to the MHRA until 20 February 2020, as part of substantial amendment [redacted] which was rejected. This was also contrary to the quality agreement between Celixir and [redacted] dated June 2018, in section [redacted] where it was stated that manufacturing and packaging of supplies would be in accordance with the IMPD as approved by the competent authority. [It was acknowledged that the investigator site would not have been aware of the approved stability period and therefore the correct expiry date of the IMP, as the only document detailing this was the IMPD which they did not have a copy of. No other documents detailed the stability period of the product were found at the investigator site.]
1.3.1.2	The IMP was not QP certified in compliance with the current legislation. The batch certificates [redacted] and [redacted] for QP certification signed by the QP on 4 December 2019 and 23 August 2019 respectively stated, 'I hereby certify that this batch complies with article 62(1) of regulation (EU) 536/2014 and article 4 of delegated regulation 1569/2017'. However, these regulations have not yet been implemented, therefore the Clinical Trial Directive is the legislative reference that is currently in use for QP certification. This was also contrary to the quality agreement between Celixir and [redacted] dated June 2018, in section [redacted] where it was stated that supplies would be certified that the requirements of the CTA, GMP annex 13 and Directives 2001/20/EC had been met.
1.3.1.3	It was unclear if the [redacted] obtained from [redacted] in the [redacted] was of a sufficient grade or quality for the manufacture of IMP for human use. For example: • Regulatory internal team meeting minutes held in the Celixir [redacted] folder [redacted] made reference to the [redacted] being sourced from [redacted] in the [redacted] as being research grade and not for human use. For example: ○ Regulatory internal team meeting minutes 17 November 2016 quoted '*The [redacted] are from [redacted] The CoA from [redacted] describes the [redacted] as 'not for human use'.* [redacted] is looking into the rules, specifically [redacted] and [redacted] Will be sufficient for conformance batches but needs resolving.' ○ Regulatory internal team meeting minutes 18 December 2016 [redacted] quoted [redacted] *believes we can use research grade as we are [redacted] under GMP conditions, even though they state 'not for human use' on CoA.* [redacted] *to discuss options with manufacturer.'* ○ In an email from [redacted] to the MHRA dated 17 December 2019 14.29, it was stated that *'Discussion were had regarding licensing, the company was advised that licensing applies to [redacted] but not for further processing in Celixir's [redacted] manufacturing plant. The [redacted] s labelled 'not for direct human use'*. However, there was no evidence in any of the documentation provided of this discussion between Celixir and the HTA. It was unclear if this question was related just to the need for a licence to import the [redacted] or a question regarding whether the [redacted] were fit to be [redacted] ○ The [redacted] document with product number [redacted] (held in Celixir [redacted] MHRA;regulatory files; [redacted];clinical trials; 1. [redacted] clinical trial applications [redacted] 1.MHRA UK; 3. Agency documents;TOagency) schedule for collection date of 9 March 2018

	stated 'clinical grade' with a volume of 50 ml. However, the shipping documents dated 9 November 2018 (provided to the inspectors by the MHRA CTU) did not detail the product number of the [redacted] and showed a volume of 100ml. As a result, it could not be determined from the documentation available to the inspectors what was actually shipped from [redacted] Therefore, there was no adequate traceability to show a clear and unambiguous link of the [redacted] used to manufacture the IMP, as required by the advanced therapy medicinal products regulation 1394/2007 article 15 and detailed guidelines on good clinical practice specific to advanced therapy medicinal products (ENTR/F/2/SF/dn D(2009) 35810) section 7.
1.4	**False and Misleading Information** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **50**(1) **Any person who** in the course of— (b) making a request for authorisation to conduct a clinical trial (provides to the licensing authority or an ethics committee any relevant information which is false or misleading in a material particular shall be guilty of an offence. (2) Any person who— (a) is conducting a clinical trial authorised in accordance with these Regulations; (b) is a sponsor of such a clinical trial; and who, for the purposes of these Regulations, **provides to the licensing authority** or an ethics committee any relevant information which is **false or misleading in** a **material particular shall be guilty of an offence**.
1.4.1	Celixir have either provided false information, or not provided updated information in a timely manner to the licensing authority and research ethics committee (REC) to ensure the trial was approved and conducted in line with the correct regulatory documentation. Celixir failed to notify the MHRA in a timely manner of relevant new information concerning the trial that may affect the risk/benefit assessment of the trial and allow the MHRA to give this due consideration on whether the trial should continue as required by UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (12). This is transparent from the following evidence:
1.4.1.1	On 11 October 2019 Celixir submitted substantial amendment number [redacted] to the London – West London & GTAC Research Ethics Committee (REC). This substantial amendment contained a letter from [redacted] Celixir, which clearly stated: Quote *'The sponsor agrees the [redacted] used in the 2012 study had a different [redacted] and production [redacted] to the [redacted] we propose to use in this current study. The sponsor has made the changes to the PIS and related documents as requested by the sub-committee. We acknowledge and confirm that recruitment will not commence until the revised PIS has been approved.'* Celixir proceeded to change Patients Information Sheet (PIS), PIS lay summary, Pregnant participant/partners study information sheet, the GP letter, and IRAS form to remove all references to the previous 2012 [redacted] trial and identify the current trial as a first in human trial (FIH). Therefore, Celixir were fully aware the IMP used in this trial was not the same as that used in the [redacted] trial in 2012. However, from the initial clinical trial authorisation submission in July 2017 and three subsequent substantial amendment to the MHRA (in November 2017, November 2018 and May 2019), and then even following the

	agreement with the REC in October 2019 up to and including submission of substantial amendment [redacted] to the MHRA dated 20 February 2020 and relevant correspondence related to the notice of non-acceptance to the amendment dated 2 March 2020, Celixir continued to justify to the MHRA it was the same product. This is substantiated by the following: • The original investigator brochure (IB) version [redacted] (31 August 2017) submitted to the MHRA and version [redacted] (10 November 2017) submitted to the REC in the initial submissions, section [redacted] indicated that the product had been studied in a single centre phase II PoC trial. This formed the basis for MHRA approval of the trial as a phase II trial. However, in substantial amendment [redacted] the IB version [redacted] (12 December 2019) sectior [redacted] states that a "similar" [redacted] ype to [redacted] was studied. Further, IB version [redacted] states that '[redacted] has not yet been tested in human clinical trials, only [redacted] have been tested." This would therefore alter the original approval, as the regulatory review and approval for a First in Human (FIH) trial is very different to that for a later phase trial where there is supporting clinical data. • Celixir continued to justify to the MHRA it was the same product contrary to their agreement with the REC on 10 October 2019 that it was different. For example, the clinicaltrials.gov entry for the previous trial conducted in [redacted] in 2012 initially referred to the [redacted] as [redacted] which was more consistent with the [redacted] not being novel and not being the same as the current [redacted] product. This was noted by a third party and MHRA noted the clinicaltrials.gov entry had been updated in May 2019 to change the investigational medicinal drug for the [redacted] 2012 trial to [redacted] in addition to updating recruitment numbers. Therefore, this information is misleading as it is incorrect. An email was sent by MHRA CTU to Celixir on 4 March 2020 and in the response to those questions on 6 March 2020 Celixir stated that they did not consider the [redacted] were different, for example, in their responses they stated: Quote: *'at the direction of West London GTAC and REC. This was an outcome that Celixir were not entirely satisfied with but understood the motivation and rationale. Nevertheless, the API [redacted] has not changed since prior to the [redacted] study to now'. And 'For clarity, our interpretation of the term [redacted] referred to the formulation as in our view the API [redacted] were the same. We responded to say that we agreed that both the formulation and some elements of the production had changed but that the [redacted] API) were the same. Given that understanding, we took the GTAC / REC letter referred to the change in formulation and this had been discussed and agreed with MHRA. This seemed to be confirmed by the requirement for relatively minor changes in the submission focused on the patient information. An amendment was made and approved based on the above in line with specific changes prescribed by West London REC / GTAC*'. despite already having agreed in October 2019 with the REC that the [redacted] 2012 trial had a different [redacted] and production to the [redacted] proposed to be used in this trial and to change the REC documentation to a FIH.
1.4.1.2	Celixir knowingly failed to update and submit regulatory documents impacted by the change to a first in human trial in a timely manner. For example: • While the changed PIS, PIS lay summary, Pregnant participant/partners study information sheet, the GP letter, and IRAS form were updated to indicate it was a FIH trial in October 2019 (and these were given REC approval on 23 October

	2019) other regulatory documents impacted by this agreement and change were not updated in line with this change and were not submitted to the MHRA or REC in a timely manner to support this significant change to the trial. For example: ○ The IB was not updated with this information until version [redacted] dated 12 December 2019. ○ The protocol was not updated with this information until version [redacted] dated 3 December 2019 and this was not signed off by the Principal Investigator until 19 February 2019. ○ The substantial amendment [redacted] to the MHRA was not submitted until 20 February 2020, more than 2 months after the protocol and IB had been updated and 5 months after Celixir admitted to the REC that the IMP had a different [redacted] • Celixir were aware that the protocol and IB required to be updated and approved and this was documented in meeting minutes in October 2019. For example: ○ Celixir meeting minutes dated 09 October 2019 10:30 stated '*Celixir will check if the changes from PIS will affect other study documents and the updates will be done accordingly*', ○ Celixir meeting minutes dated 16 October 2019 10:30 stated '*Celixir will discuss with [redacted] on 7 October 2019 and it will be decided if changes to the protocol regarding to the primary end points are required*' ○ Celixir meeting minutes dated 30 October 2019 10.30, clearly documented that quote '*According to the REC, this is a first in human trial and the protocol and other documents must be updated accordingly. Submission of the updated documents is planned by the end of November.*' ○ The protocol was confirmed as updated in the minutes dated 18 December 2019 15:00. ○ The trial was given the go head to commence on 10 December 2019 via the IP release form, despite significant changes to the trial and knowing the need to update all the regulatory documents already having been identified.
1.4.1.3	Having already documented in meeting minutes date/time 30 October 2019 10.30 that the REC had informed Celixir that they needed to update the protocol and other regulatory documents, Celixir then proceeded to send a general helpline query to the MHRA on 30 October 2019 at 12.05, after the internal meeting which recorded they knew they needed to update the protocol and other regulatory documents. This email asked that since there had been a change to the informed consent form (ICF) which had been approved by the REC and HRA if the MHRA could confirm that there were no further issues and that they could start the trial. The MHRAs remit does not include review of the patient facing documentation and there was no context provided in the email to suggest that these changes impacted on the MHRA regulatory documents, therefore the MHRA clinical trial helpline issued a standard response there were no regulatory actions from a CTA perspective since they were not aware that these changes impacted on the protocol or IB. Therefore, Celixir knowingly and deliberately withheld relevant information from the MHRA in the query regarding the changes to the ICF and failed to disclose that these were as a result of the trial being reclassified as a first in human and that this required updates to the protocol and IB, regulatory documents which are documents that are approved by the MHRA.

1.5	**Quality Systems** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **28(1)** 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. **(2)** Subject to paragraph (5), the sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **In particular: Schedule 1, Part 2,** **(4)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. ***Failing to comply with regulation 28(1) and (2) is an offence by regulation 49(d)***
1.5.1	The sponsor (Celixir) had no quality system with procedures to secure the quality of every aspect of the trial in place for the conduct of clinical trials if IMP from the start of the trial in (e.g. 1 July 2017 being the date of the initial CTA submission letter) to cover how they would perform their sponsor responsibilities and trial activities to ensure these were performed in compliance with GCP regulations and guidelines. This was confirmed in interview and apparent from the documentation provided to the inspectors during the inspection. During interview Celixir advised they would be using the CRO [redacted] SOPs. However, [redacted] were not involved in any aspect of the trial until the effective date of the contract (29 March 2019) and [redacted] were not responsible for regulatory or ethics submissions, IMP management and sponsors legal responsibility and oversight of the trial. [It was noted that in the sub-folder 'Standard Operating Procedures' with the 'Project Management [redacted] folder provided to the inspectors, one SOP existed [redacted] 17 November 16) [redacted] This covered how documents would be named and filed in [redacted] in the 'regulatory' library.]
1.5.2	Examples where there was a lack of formal processes (this is not an exhaustive list): • For documentation of substantiality review of proposed protocol amendments (this was seen for just one protocol change in an email by Regulatory affairs), despite several protocol changes and some with no submissions to MHRA. • For the creation, review and submission of all regulatory documents (e.g. CTA/IRAS forms, cover letters, protocol, IB, IMPD, ICFs etc.) to ensure these were created, reviewed and approved in compliance with GCP and also were consistent across the various documents. • For the management of serious breaches, or urgent safety measures • For the use and oversight of vendors or consultants to ensure they undertook their delegated tasks in compliance with GCP (e.g. for audit, assessment of competencies, preparing and approving contracts and agreements, continued oversight) • For the management of DSMBs. • For the management of the trial master file (TMF) or sponsor oversight files.

1.6	**Insurance** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **28(1a)** No person shall conduct a clinical trial otherwise than in accordance with the conditions and principles of good clinical practice. **In particular: Schedule 1, Part 2,** **(1)** The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society. **(12)** A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored. **(14)** Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial. ***Failing to comply with regulation 28(1) is an offence by regulation 49(d)***
1.6.1	Policy [redacted] covering 4 July 2019 to 4 July 2020 was renewed on 28 May 2020 to extend to 4 July 2021, however in the policy was the following condition and given the critical findings and breaches of the legislation, the insurance cover for the trial subjects during the trial could be invalidated. Not only did Celixir knowingly put a subject's safety at risk, but they may have also invalidated the subject's provisions for compensation in the event that they were harmed. [redacted]
1.7	**Record Keeping / Essential Documents - Trial Master File (TMF)** **UK Statutory Instrument 2004/1031 (as amended), regulations** **31(A)** **(1)** The sponsor shall keep a trial master file for a clinical trial. **(2)** 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. **(3)** The master file shall **at all times** contain the essential documents relating to that clinical trial. **(4)** 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. **(5)** The essential documents shall contain information specific to each phase of the trial. **(6)** The sponsor shall ensure that any alteration to a document contained, or which has been contained, in the trial master file shall be traceable.

	ICH GCP E6(R2) section 8, essential documents **EMA volume 10, recommendation on the content of the trial master file and archiving July 2006.** ***Failing to comply with reg 31A(1)-(3) and (5) is an offence by regulation 49(ff)***
1.7.1	An electronic trial master file (eTMF) system [redacted] was maintained by the CRO [redacted] on behalf of the sponsor. There were significant deficiencies with the eTMF that impeded the ability to reconstruction of the trial. The inspectors were only able to reconstruct some of the trial with access to additional documentation held separately in Celixir's [redacted] system. For example:
1.7.2	The sponsor had no formal TMF for the trial until 29 March 2019 when this was delegated to [redacted]
1.7.3	The sponsor had no process or summary to define what the TMF was and what systems the full TMF comprised of from the start of the trial in (e.g. 1 July 2017 being the date of the initial CTA submission letter). Celixir [redacted] 17 July 2019) was not in place at the start of essential documents being generated and the sponsor therefore had no processes or official TMF. This plan did not cover [redacted] as part of the TMF. As a result, many documents related to the clinical trial were held outside of the eTMF and therefore missing from the formal eTMF. These included (this is not an exhaustive list): • Section [redacted] (regulatory) had many missing critical documents to reconstruct the trial. For example: ○ Section [redacted] (submission) was missing the Initial MHRA submission package dated 1 July 2017 and substantial amendment [redacted] package dated 20 February 2020 ○ Section [redacted] (regulatory authority decision) was missing The MHRA notice of non-acceptance dated 2 March 2020 and subsequent MHRA halt decision dated 16 March 2020 in relation to the substantial amendment [redacted] package submitted on 20 February 2020. ○ There was no email correspondence with the MHRA in relation to the trial in any of section [redacted] For example, Celixir email responses dated 6 March 2020 to the [redacted] with their commitment not to dose any patients. • Section [redacted] (IP and trial supplies) had many missing documents to enable full traceability of the IMP. For example: ○ There was no information in section [redacted] (shipping documentation) in relation to the shipping of all the batches of IMP to the [redacted] for trial storage. Batches [redacted] (first batch) and [redacted] (second batch) were received by [redacted] from [redacted] on 20 March 2019 and 10 July 2019 respectively. The first batch was returned to [redacted] on 9 July 2019. However, none of this shipping documentation was in the eTMF. [Only the transfer of kit [redacted] to the Royal Brompton and associated temperature record was filed in the eTMF.] • The eTMF section [redacted] (IMP release process documentation) only contained the certificates of analysis and QP certification and the transfer of kit of the second batch of IMP. There was no evidence in the eTMF that a previous batch of IMP had been manufactured and shipped in relation to the trial. • There was no evidence of any correspondence related to the trial in the eTMF this was all held separately in [redacted] and not signposted in the

	eTMF anywhere. • Section [redacted] (Trial Team) had [redacted] 20 March 2020, but the previous version was not present in the eTMF. • Section [redacted] (trial Committee) [redacted] 08 July 2019 replacing [redacted] 12 April 2019 was present, but the previous versions were not filed in TMF. • Section [redacted] (DMP) the DMP refers to Quality Management Plan and Project Management Plan but these were not in the TMF and did not appear to exist. • Only [redacted] of the IB was present in the eTMF in section [redacted] (Investigator Brochure) • No previous protocols before [redacted] in section [redacted](Protocol). • Updated insurance policy (to July 2021) was not in the TMF section [redacted] (Insurance) (this was provided as specific document request). • Section [redacted] (REC) had numerous documents missing in the TMF that were found in [redacted] (for example: reminder for the annual progress report (APR) on 23 March 2020, initial submission documents and response from REC between 23 November 2017 and 30 January 2018, emails and correspondence concerning the [redacted] 31 July 2019, 02 August 2019, 05 August 2019, REC letter acknowledging amendment submitted 13 April 2019, letter from REC 07 October 2019 that triggered a substantial amendment to be submitted 10 October 2019, incomplete submission package 10 October 2019, email from REC 20 October 2019, 24 October 2019, letter from HRA 06 March 2020 re [redacted] acknowledgement email and letter 23 March 2020 from REC, emails 4 May 2020 from REC to update the EudraCT database regarding temporary halt and an email from HRA 23 July 2020 to request a change to the research summary). • Section [redacted] - there were missing CVs that were present in the ISF [redacted] and some present that were not in the ISF [redacted]
1.7.4	In the [redacted], 17 July 2019), the list of key dates for tasks in the plan pre-dated the plan itself (e.g. Access levels matrix 22 April 2019, Project Set Up completion in eTMF 15 April 2019).
1.7.5	Evidence of training of Celixir staff [redacted] showed training on the use of the eTMF was provided to the sponsor on 1 October 2019, therefore this was not in a timely manner as the eTMF was implemented on subcontracting to [redacted] at the end of March 2019.
1.7.6	Only PDFs could be sent to the eTMF according the [redacted] 17 July 2019). Therefore, it was not clear if the source file in native format (aside from email) would be retained, as the plan only covered the certification of paper. Therefore, the eTMF would not follow the principles of ALCOA+ and ensuring the eTMF was attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available.
1.7.7	There was no evidence of the monthly TMF QC in the eTMF as required by the [redacted] 17 July 2019),.

1.8	**IMP (Management)** **UK Statutory Instrument 2004/1031 (as amended), regulations** **13**(1) Subject to paragraphs (3) and (4), no person shall, in the course of a business carried on by him, sell or supply any investigational medicinal product to— (a) an investigator, (b) a health care professional who is a member of an investigator's team, (c) a person who provides or is to provide health care under the direction or control of a person referred to in sub-paragraphs (a) and (b), or (d) a subject, for the purpose of administering that product in a clinical trial, unless the conditions specified in paragraph (2) are satisfied. (2) The conditions referred to in paragraph (1) are (a) the licensing authority has authorised the clinical trial for the purposes of which the product is sold or supplied. (bii) the production batch of investigational medicinal products of which the product is a part has been checked and certified by a qualified person pursuant to Article 13(3) and (4) of the Directive. **UK Statutory Instrument 2004/1031 (as amended), regulations:** **28(1)** 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. **(2)** Subject to paragraph (5), the sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **In particular: Schedule 1, Part 2,** **(4)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **(9)** 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. ***Failing to comply with reg 13(1) and 28(1) and (2) is an offence by regulation 49 (b) and (d)respectively***
1.8.1	There was no associated QP certification to verify that the product was manufactured for the trial and in accordance with GMP and the clinical trial authorisation. Document request [redacted] and [redacted] the certificates of analysis (CoA) stated that batch [redacted] was manufactured on 16 October 2018 and [redacted] was manufactured on 27 February 2019. According to document request [redacted] and [redacted] the expiry(retest) date was 16 July 2019. Therefore, these products have been labelled with a 9 months expiry against the active product. However, the IMPD [redacted] (19 October 2018) with the 9 months stability data was not approved until 28 May 2019, therefore these products only had an approved stability of 3 months at the time of manufacture and labelling.
1.8.2	Doc request [redacted] stated that 50 vials of batch [redacted] was shipped. However, the shipping record dated 18 March 2019 referred to batch [redacted] Although there was a footnote quote [redacted] there was no explanation as to what this was or what it meant. A summary of the products received at the [redacted] was received by the inspectors from [redacted] on 24 July 2020. This only referenced [redacted]. Therefore, it was unclear what was

	actually shipped.
1.8.3	There were discrepancies with the certificates of analysis for the first batches of IMP produced. For example: • The certificate of analysis issue date for batch [redacted] was dated 26 February 2018, prior to the manufacture of the IMP on 16 October 2018 and date of analysis of 1 November 2018. • The certificate of analysis issue date for batch [redacted] was not signed off in a timely manner, as it was dated 23 January 2020 almost a year after its manufacture and 10 months after its date of analysis.
1.8.4	IMP was shipped and received by the [redacted] on the 20 March 2019 and 10 July 2019. For both shipments there were no instructions to quarantine and not to use in the clinical trial until relevant clinical trial regulatory documentation was in place. For example: • Shipment was prior to the contract with the [redacted] for their delegated task being signed on 30 December 2019. • There was no evidence of any assessment of the suitability of the [redacted] to undertake their delegated tasks (e.g. quarantine processes) • Shipment was prior to the regulatory green light release – (IP release) on 10 December 2019. • The IP release form had no requirement to ensure the contract with the [redacted] was in place prior to authorising release of the IMP.
1.9	**Training** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **3(12)** 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. **28(1)** 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. **In particular:** **Schedule 1, Part 2,** **(2)** Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks. ***Failing to comply with reg 28(1) is an offence by regulation 49(d)***
1.9.1	There was a lack of evidence that sponsor staff had appropriate clinical trial experience to be able to adequately conduct a clinical trial and perform their responsibilities as sponsor to ensure the rights safety and well-being of trial subjects were protected and that all aspects of GCP were complied with. For example: • During the interview at the inspection of Celixir on 28-29 September 2020, [redacted] advised [redacted] was responsible for the IMP and had helped set-up the manufacturing site in [redacted] which is a wholly owned subsidiary of Celixir (Cell Therapies Ltd). During the interview session [redacted] joined Celixir in 2011 and advised [redacted] had no previous experience in clinical trials either during [redacted] employment at Celixir or in [redacted] previous employment and this was supported in the training documentation provided to the MHRA (GCP certificate is dated 7 May 2019 however there was no evidence of GMP and in particular GMP Annex 13 training). • There was no sponsor staff with any IMP clinical trial experience, especially in

	the operational and conduct activities. Only [redacted] and [redacted] had regulatory affairs experience in regulatory submissions.

2.0 Major Findings There were **three Major findings** identified during this inspection relating to Pharmacovigilance; Organisational Oversight of Clinical Trials; Contracts and Agreements.	
2.1	**Pharmacovigilance – Reference Safety Information (RSI)** **UK Statutory Instrument 2004/1031 (as amended), regulation 35(1)** As soon as practicable after the end of the reporting year, a sponsor shall, in relation to each investigational medicinal product tested in clinical trials in the United Kingdom for which he is the sponsor furnish the licensing authority and the relevant ethics committees with - (a) a list of all the suspected serious adverse reactions which have occurred during that year in relation to— (i) those trials, whether at trial sites in the United Kingdom or elsewhere, or (ii) any other trials relating to that product which are conducted outside the United Kingdom and for which he is the sponsor, including those reactions relating to any investigational medicinal product used as a placebo or as a reference in those trials; and (b) a report on the safety of the subjects of those trials. **2010/C 82/01(CT-1) paragraph 58** **2011/C 172/01 (CT-3) paragraphs 53, 55, 112** **ICH guideline E2F on development safety update report section 3.7.1**
2.1.1	The Reference Safety Information (RSI) was not sufficiently defined. For example: While the approved IB version [redacted] and the updated version [redacted] had a section [redacted] (Reference Safety Information), this did not contain a list of all preferred terms that would be considered expected serious adverse reactions. It was not adequately defined what would be used for expectedness assessments. Therefore, there was a potential for under-reporting of SUSARs if the expectedness assessment were not performed correctly. [It was acknowledged that although version [redacted] of the IB in section [redacted] did advise in paragraph [redacted] that [redacted] would be considered unexpected, the RSI expected terms were not clearly identified and this version of the IB had not been approved by the MHRA.]
2.1.2	There were numerous issues with the development safety update report (DSUR). For example: • There had been no submission of a DSUR to the MHRA and REC for the reporting period 27 September 2017-2018 based on the MHRA approval of 27 September 2017. • There was no evidence in the TMF of the submission of DSUR [redacted] (4 November 2019) covered reporting period 27 September 2018-2019 to the REC. • DSUR [redacted] referred incorrectly to section [redacted] of the IB as the RSI, rather than section [redacted] which was identified as the RSI in the IB. • DSUR [redacted] had been provided to the PI, however this was an unblinded document therefore had there been any SUSARs this would have unblinded the trial and investigator site team. • DSUR [redacted] was inconsistent with how it described the IMP for the trial (e.g. some

sections used the terminology 'similar' and other sections considered it to be 'the same' as the IMP in the [redacted] 2012 trial), for example:

- The DSUR abbreviates [redacted] as being both [redacted] and [redacted] Therefore, they were not considered to be different, but the same abbreviation [redacted] was used to refer to both [redacted] and the previous product used in the [redacted] trial.
- The executive summary and introduction both stated [redacted] So, the DSUR referred to [redacted] and [redacted] being the same product.
- The executive summary also stated '*No subjects have been enrolled into the* [redacted] *clinical development programme, however, an Investigator Sponsored Study (ISS) using similar* [redacted] *was completed in 2012 with 11 subjects enrolled*.' This would therefore indicate the prior experience was not using [redacted] (thus NOT using [redacted] but a different product (contrary to bullet point 2).
- Section [redacted] stated '*Overall, 11 subjects, scheduled for* [redacted] *have been included in a completed open label uncontrolled investigator sponsored study (ISS) using a similar* [redacted] *completed in 2012*.' This would appear to mix the [redacted] – the prior experience is stated as being [redacted] (which is the same as [redacted] but also that the product is similar (implying not the same as [redacted] Table [redacted] refers to [redacted] but is regarding the prior trial.
- Section [redacted] stated '*With the limited exposure in the investigator sponsored study, using a similar* [redacted]*, and the current prospective double-blind study yet to recruit subjects, to date no SAEs have been reported, during the* [redacted] *clinical development programme, from its initiation (31st December 2009)*.' This is confusing as it refers to a similar [redacted] (not the same [redacted] but still refers to the [redacted] development program as if the [redacted] are considered the same.
- Section [redacted] refers to [redacted] This implies [redacted] was used in the previous study and considered the same product.
- Table [redacted] refers to [redacted] whereas table [redacted] refers to [redacted]. This appears to confuse the [redacted] again. This section should include trials using the product under consideration. Table [redacted] clearly stated the UK trial as phase 2 and not first in human. Whilst table [redacted] referred to [redacted] and not [redacted] this section implies they are considered by the Sponsor as the same product.

If the [redacted] were considered different it would be expected that the DSUR clearly stated the UK trial was a first in human trial. Instead it referred to the [redacted] development program as starting in 2009, therefore considered that the [redacted] were the same. Therefore, overall, there are confusing sentences, but the majority of information still presents the [redacted] in the UK trial as a product called [redacted] which is the same as IMP used in the previous [redacted] trial. There was no indication that the UK trial was now considered a first in human trial.

2.1.3	The [redacted], 9 October 2019) was inadequate for the trial and contained deficient information. For example: • It was unclear how blinding would be maintained as in section [redacted] it advised the ASR (DSUR) would be signed off by the CI, this was also the blinded PI [redacted] • Section [redacted] advised '*the* [redacted] *and a* [redacted] *with a data cut-off date of 21 December (21 December 2011 was the date when the first approval of the Phase II (PoC) Investigator Initiated Trial took place in* [redacted] *and respective submission date by 19 February will be produced… on a yearly basis*' However, the trial in [redacted] was never approved by the [redacted] regulator and there has no valid international birth date for the ASR. There was no regulatory approval of the [redacted] 2012 trial therefore the approval date of 21 December 2011 was incorrect. • Section [redacted] and Table [redacted] – roles and responsibilities point 4 was incorrect as the point 4 stated: Assignment of preliminary causality and expectedness assessment based on the most up-to date Reference Safety Information. This is incorrect and should be the RSI approved at the time of onset of the event. • The SMP did not clearly define the actual RSI it only referred to the IB not the specific section of the IB. • Appendix [redacted] had incorrect details for the MHRA address
2.2	**Organisation's Oversight of Clinical Trials of IMP** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **3(12)** 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. **28(1a)** No person shall conduct a clinical trial otherwise than in accordance with the conditions and principles of good clinical practice. **In particular:** **Schedule 1, Part 2,** **(4)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **(9)** 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.
2.2.1	Celixir allowed patients to be consented to the updated PIS version [redacted] (dated 9 October 2019) which clearly identified the trial as a FIH trial and therefore did not match the description of the trial in the associated and approved protocol version [redacted] and IB version [redacted] Patient [redacted] was consented on 3 February 2020 and patient [redacted] was consented on 7 February 2020 prior to submission of the updated protocol version [redacted] and IB version [redacted] to the MHRA on 20 February 2020.
2.2.2	It was not clear which version of the protocol, IB or IMPD had been used to prepare the [redacted] [redacted] and [redacted] to ensure they had used the most recent and approved regulatory documents for their preparation, as this was not documented anywhere.
2.2.3	There was no evidence of sponsor approval by the way of a signature page for the protocol for any versions of the protocol, as this was only signed by the Principal/Chief Investigator.
2.2.4	There was no evidence of sponsor approval by the way of a signature page for the IMPD or clear evidence via email. Therefore, it was unclear what sponsor

	representatives had input and approved the content of the final version of the IMPD to be submitted to the regulator.
2.2.5	Internal sponsor meetings were not documented, there was only evidence of a few internal regulatory meetings from 2017, which were held in the Celixir [redacted] folder. Only meeting minutes with [redacted] were document in the eTMF.
2.2.6	The trial had the regulatory green light to start issued 10 December 2019. The DSMB was not functional at this point (the trial start) or currently. This was because the charter [redacted] (08 July 2019) required three named members which was never achieved. Therefore, it was not in a position to respond to any safety concerns and there was no evidence that it had ever met, despite a temporary halt being imposed on the trial, which a DSMB would be expected to discuss. The delay and failure to the set-up of the DSMB was because one of the three stated members [redacted] had not signed any agreements (annexe [redacted] of charter and a separate contract) and the remaining two members [redacted] had not signed Annexe [redacted] of the charter until 02 January 2020 and 05 February 2020 respectively and only one of their contracts was signed prior to the trial start signed 06 January 2020 and 24 July 2019 respectively.
2.2.7	There was an update to the eCRF to [redacted] released on 07 February 2020. This related to the implementation of an updated protocol (dates indicated this was protocol [redacted] according to email correspondence in January 2020 as the protocol was sent to the database developer to implement and a go ahead was given to release by the sponsor and release signed off by the sponsor on 7 February 2020. The change to the eCRF in this case was addition of a specific [redacted] on [redacted] and therefore not a significant change (e.g. not a new assessment/new dose, different eligibility criteria etc.) and therefore not a critical finding.  This was due to [redacted] being added as a safety primary objective in addition to efficacy with the protocol update to [redacted] However, the data would have been collected previously as this was a secondary objective in [redacted] of the protocol, but this change appeared to formalise its collection in a specific way in the eCRF following the changes made in protocol [redacted] This was done before this amendment had been submitted to MHRA on 20 February 2020 and which was never submitted to the REC. These issues demonstrated that neither the sponsor nor the CRO had a process to ensure that electronic systems were only released that were consistent with the approved protocol and therefore the release tied into the protocol approval/RGL to ensure protocol amendments were not implemented prior to regulatory approval.

2.2.8	The final version [redacted] of the statistical analysis plan (SAP) dated 24 April 2020 and signed by the sponsor 24 September 2020, [redacted] 6 May 2020 and [redacted] (statistics vendor) on 4 and 5 May 2020 was written in accordance with protocol version [redacted] (3 December 2019). However, this protocol was rejected by the MHRA on 2 March 2020 prior to the instruction to halt the trial on 16 March 2020.
2.2.9	The sponsor provided inaccurate and misleading information to the investigator site, in order to ensure the continuation of the trial. On 11 October 2019, the sponsor informed the investigator site that the REC had notified the MHRA and HRA of their requests, this was not the case. The REC had not informed the MHRA of the changes it had requested to the PIS and it was unclear how the sponsor had established this information.
2.3	**Contracts and agreements** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **3(12)** 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. **28(1a)** No person shall conduct a clinical trial otherwise than in accordance with the conditions and principles of good clinical practice. **In particular:** **Schedule 1, Part 2,** **(4)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **(9)** 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.
2.3.1	The MSA dated 29 March 2019 between Celixir and [redacted] clause [redacted] stated 'The customer (Celixir) is obliged to provide the CRO with all information and documents required by [redacted] to comply with obligations arising from signed work order as well as all applicable laws.' However, there was no evidence that Celixir informed [redacted] of their commitment to the MHRA not to dose any subjects following the GNA of SA number [redacted]
2.3.2	Contracts did not always contain clauses clearly identifying the standard for how the delegated activities would be undertaken. For example: • The contract with [redacted] signed on 30 December 2019 had no clause to ensure the [redacted] would comply with GCP or GMP regulations and guidelines. • There was no requirement in the consultancy agreement for the [redacted] to comply with any GCP regulations or guidelines.
2.3.3	There were no dates of signatures on some of the contracts and agreements (e.g. sponsor signature of [redacted] contract; the signatures on the Quality agreement with [redacted]

3.0 Other Findings

There were **seven Other finding** identified during this inspection relating to Medical Oversight; Data Management; Computer System Validation (CSV); Monitoring; Competent Authority; Research Ethics Committee; Quality System.

3.1	**Medical Oversight**
3.1.1	The protocol [redacted] (11 March 2019), and initiation meeting presentation dated 1 July 2019 both stated that Quote: *'In the case of medical emergency, the investigators will have direct access to unblinded treatment information and a prompt unblinding procedure will be available at the study site via the pharmacy department '* However, this was not the case. Unblinding could only be performed via the IRT system [redacted] or via the unblinded trial statistician at [redacted] (the CRO managing the trial). This was apparent as when asked by the inspectors during the site inspection, the PI could not gain access to [redacted] (despite trying to reset [redacted] password etc) and so had to unblind by contacting [redacted]
3.2	**Data Management**
3.2.1	[redacted] 7 August 2020 was signed by the sponsor on 25 September 2020 and was stated as being based on protocol [redacted] and SAP [redacted] 24 April 2019 and was therefore late. As it was not in place in a timely manner, it made reference to how activities will be done that had already occurred (e.g. eCRF build, edit checks etc.). There was a reference to a risk-based management plan and monitoring plan, but there were no dates referenced therefore it was not clear if these had been issued. It also made no reference to the safety plan concerning the SAE reconciliation processes and handling of SAE data.
3.3	**Computer System Validation (CSV)**
3.3.1	For the [redacted] system eCRF, the edit check specifications were not written in understandable language (example below) to enable non-programmers to review – occasionally the error message will be written in English, but the details of what the check concerned was not.  There was no evidence of sponsor review and approval because the approval form was just signed by [redacted] staff and sponsor approval is optional, therefore the sponsor appeared to have no knowledge of what data quality checks would take place.
3.3.2	The edit check testing trackers whilst they showed evidence of testing, they did not show the outcome (fail/pass action taken etc.) As per this example from checks on 4 February 2020].

	- [redacted] It appeared [redacted] only filed the final document in the eTMF, therefore not allowing full reconstruction of process.
3.3.3	There was no evidence of the user acceptance testing (UAT), who did it when and what issues were identified via completed test scripts. The testing report [redacted] in the introduction stated that this is a report of UAT testing and it was not approved by the sponsor. It appeared that no UAT issues were found or resolved, but there was no documentation available to confirm this. It was not possible from the documentation in the eTMF to see any UAT by the sponsor for the first version [redacted] release of the eCRF. [redacted]
3.4	**Monitoring**
3.4.1	The monitoring visit report for 8 April 2020 gave an incorrect reason for subject recruitment hold as it stated it was due to the COVID-19 pandemic. The trial was on a temporary halt due to instruction by MHRA.
3.5	**Competent Authority**
3.5.1	There had been no submission of Investigator brochure (IB) version [redacted] (10 November 2019) to the MHRA for review and authorisation. This version had been submitted in the initial REC submission which had been approved on 16 March 2018 and there had been changes to the reference safety information (RSI) section (section [redacted] therefore this was a substantial amendment to the RSI requiring approval by the MHRA.
3.5.2	The IMPD was not consistent with the actual conduct of the trial. The approved IMPD version [redacted] dated 19 October 2018 sections [redacted] for both the Placebo [redacted] and [redacted] stated these would shipped direct to the investigator site from [redacted] there was no mention of the storage facility at [redacted] which received the IMP on 10 July 2019 for dispensing to the investigator site.

3.6	**Research Ethics Committee**
3.6.1	No APRs had been submitted to the REC, initial approval was 18 March 2018, and therefore two APRs had become due since that time and a reminder was sent by the REC to the sponsor on 23 March 2020.
3.7	**Quality System**
3.7.1	There was poor version control and management of documents. For example • There were 2 versions for the IMP management plan [redacted] (27 August 2019) and [redacted] (20 November 2019), However, the changes could not be verified as there was no summary of changes, so it was unclear what changes were made without comparing each section of the documents. • Protocol version [redacted] lost its version number and date footer from page 22 onwards. Therefore, if pages had become separated they would not have been identifiable. • Application to MHRA by Celixir 01 July 2017, the Application Form protocol date (Version [redacted] 10 March 2017) was inconsistent with date in covering letter and protocol supplied (Version [redacted] 30 June 2017) and the IMPD Simplified [redacted] 30 June 2017 was stated in covering letter, but IMPD [redacted] 30 June 2017 was actual submitted. • Application made 20 February 2020 by Celixir had a protocol [redacted] 24 January 2020 stated on the cover letter, but actual protocol submitted was [redacted] 03 December 2019.

Finding Number	Investigator Site Findings
4.0 Critical Findings There were **no Critical findings** identified at the investigator site.	

5.0 Major Findings There were **two Major findings** identified during this inspection relating to Medical/PI oversight and Record Keeping / Essential Documents.	
5.1	**Medical/PI oversight** **UK Statutory Instrument 2004/1031 (as amended), regulations:** **28(1a)** No person shall conduct a clinical trial otherwise than in accordance with the conditions and principles of good clinical practice. **In particular:** **Schedule 1, Part 2,** **(6)** Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki. **(9)** 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. **(11)** The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist. **ICH GCP E6(R2), sections 4.1.5, 4.2.4, 4.2.5**
5.1.1	There were numerous examples of the lack of PI or medical oversight in relation to the eligibility and ongoing trial management of the participant. This was transparent from the following examples: • For Participants [redacted] and [redacted] the eligibility checklist was signed by the research nurse [redacted] on 21 February 2020 and 16 March 2020, there was no countersignature to verify a medic had reviewed this. • The visit 1/2 for participant [redacted] assessments were signed by the research nurse [redacted] on 24 February 2020; there was no countersignature to verify a medic had reviewed this. • There was no copy of the [redacted] for participant [redacted] in the trial source documents seized from the site. • [redacted] for participant [redacted] was not signed off by a medic to confirm review. • [redacted] for participant [redacted] was not signed off by a medic to confirm review and any clinical significance. • The [redacted] for participant [redacted] in relation to their [redacted] SAE had not been signed off as reviewed by a medic. *[This is not an exhaustive list and further examples were seen in the seized documents.]*

5.1.2	The [redacted] and the [redacted] for participant [redacted] both recorded that someone (initials [redacted] who had not been authorised by the PI on the trial [redacted] had prepared, dispensed and destroyed the IMP [redacted]
5.2	**Record Keeping / Essential Documents** **UK Statutory Instrument 2004/1031 (as amended), regulations 31(A)** **(1)** The sponsor shall keep a trial master file for a clinical trial. **(2)** 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. **(3)** The master file shall at all times contain the essential documents relating to that clinical trial. **(4)** 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. **(5)** The essential documents shall contain information specific to each phase of the trial. **(6)** The sponsor shall ensure that any alteration to a document contained, or which has been contained, in the trial master file shall be traceable. **ICH GCP E6(R2) section 8, essential documents** **Eudralex volume 10, recommendation on the content of the trial master file and archiving July 2006.**
5.2.1	There was a lack of consistency in the documentation provided and filed at the investigator site. For example: • The PI's investigator site file (ISF) contained IB version [redacted] but the pharmacy site file (PSF) contained version [redacted] These documents had been approved by the MHRA or REC prior to the site initiation visit on 1 July 2019 therefore it was unclear why these were not consistent. • The ISF and PSF only contained copies of the MHRA and ethics approval letters, therefore it was not clear what these approvals were since the submission packages were not present. Without the submission package it is not always transparent what the amendment is for and therefore cannot be reconstructed. For example ○ There was no evidence in the ISF or emails seized from the site that the sponsor communicated their commitment to the MHRA not to dose any trial participants until an agreement had been reached with the MHRA The only communication was the formal trial halt by the CRA on 19 March 2020. Therefore, the site appeared to be unaware that participant [redacted] should not have been dosed. • There appeared to be no ethics approval in the ISF for protocol version [redacted] which was authorised by the MHRA on 20 December 2018. • The MHRA approval for Substantial amendment [redacted] dated 20 December 2018 and the MHRA acknowledgement for the trial halt dated 7 December 2020 were not filed in the ISF. • There was no evidence that the annual safety report (ASR) due on 18 March 2020 had been submitted to the REC. • There were numerous superseded documents that were not in the ISF/PSF (e.g. previous signed version of the protocol, previously approved PIS and participant

	facing documents). • Although a follow letter dated 15 July 2019 for the initiation visit was present in the ISF, the trial initiation visit report for visit 1 July 2019 was not present. • There were no reference ranges in the ISF. • There was a date error on the subject screening log for those screened on 13 January 2020, as it dated 13 January 2019. • Blank eligibility checklist [redacted] 21May 2019 had no reference to the protocol version. • There appeared to be no evidence of the Medical Monitoring Boards ratification of the trial as required in the MMB minutes dated 5 September 2019 in the ISF, PSF or sites Research & Development (R&D) folder.

6.0 Other Findings

There were **five Other findings** identified during this inspection relating to CRF Data / Source Data; IMP Management; GCP Compliance; Training; Staff Delegation.

6.1	**CRF Data / Source Data**
6.1.1	There were numerous issues with source data to verify the activities performed and who performed them or when. For example: • The [redacted] for participant [redacted] had no details of who administered the IMP or any reference to whether this information was documented elsewhere in the trial files. There was also no place to document any QC/verification for the [redacted] and administration on the form. • The medical records for participant [redacted] trial approach and consent, and for visit 6 were completed retrospectively and therefore were not contemporaneous. The trial approach happened on 16 January 2020, but the medical records were not completed until 30 January 2020 by the research nurse [redacted] the consent occurred on 3 February 2020, but the medical notes were not completed until 6 February 2020 by co-investigator [redacted] and the visit 6 occurred on 10 July 2020, but the notes were not completed until 14 July 2020 by the research nurse [redacted] • The visit 3 medical examination had been conducted on 16 March 2020, but it was unclear who had performed this and that it had been done by a physician, as it was not signed and dated. • The medical records for participant [redacted] trial approach and consent, and for visit 1/2 were completed retrospectively and were therefore not contemporaneous. The trial approach and consent happened on 28 January 2020 and 7 February 2020 respectively, but the medical records were not completed until 11 February 2020 by the research nurse [redacted] Also visit 1/2 was conducted on 11 March 2020, but the medical notes were dated the 14 March 2020 (3 days after the visit) by the research nurse [redacted] • The events table checklist for participants [redacted] and [redacted] had been completed as part of the source documents, however it was unclear who had completed this or when as a check that all the procedures had been conducted for the visit. In addition, for [redacted] t appeared that the visit 3 ticks had been deleted, but there was no explanation, initials or date to confirm who deleted these, why or when.
6.2	**IMP Management**
6.2.1	There was a dummy run to test the IMP supply from [redacted] to Royal Brompton conducted on 15 August 2019. However, there were discrepancies in the paperwork related to this activity that did not allow for full and accurate reconstruction. For example:

	• [redacted] was requested by the Royal Brompton on 15 August 2019. However, [redacted] was documented as supplied on 3 September 2019 in response to this request. • There was no evidence of any dummy kits and their associated kit numbers being shipped to [redacted] or where the investigator site and [redacted] obtained the kit number from. • There was no documentation to confirm what happened to the dummy kit, as there was no evidence it was returned to the [redacted] or destroyed at the Royal Brompton.
6.3	**GCP Compliance**
6.3.1	Non-GCP compliant methods had been used to obscure and change data in original trial documents. For example: • Correction fluid had been used to obscure writing in the delegated functions area of row for [redacted] on page 1 of the 'delegation log' • Words had been obliterated by a scribble to make illegible in the PI signature columns of [redacted] row on page 1 of the 'delegation log' • Correction fluid had been used to obscure the participant's names and date of births on the 'subject enrolment and identification log' in the ISF. • The original date by the sub-investigator on the consent form for participant [redacted] was obliterated and therefore unreadable.
6.4	**Training**
6.4.1	There was no CV or evidence of GCP or trial specific training (e.g. attendance at SIV or dummy run) for the person who prepared, dispensed and disposed of the IMP (initials [redacted] as detailed in finding 5.1.2. Therefore, it was unclear if this person was suitably qualified by education, training and experience to have undertaken the activities they were involved in during the trial.
6.5	**Staff Delegation**
6.5.1	The pharmacy staff delegation log was signed off on 13 December 2019, significantly later than the initiation visit on 1 July 2019, therefore not signed in a timely manner.

Report Author and Reviewer

Report Author:

[redacted] 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

Inspected Organisation / Investigator site				
Clinical Trial	Assessed			Comment
	Yes	Partial	No	
[redacted]	✓			eTMF, Sponsor provided [redacted] folder, document requests, ISF, PSF, R&D folder, plus copies of seized emails and participant source documents

Inspected Organisation				
Activity	Assessed			Comment
	Yes	Partial	No	
Analytical Laboratory			✓	Not within scope of this inspection
Archiving			✓	Not within scope of this inspection
BE/ BA activities			✓	NA
Clinical Pathology Laboratory		✓		Seized trial source documents only
Clinical Trial Reporting			✓	Not done at time of the inspection
Computerised Systems		✓		Only review of documents
Contracts & Agreements	✓			
Data Management		✓		Only review of documents
eCRF / Diaries / IVRS		✓		Only review of documents
IMP Management	✓			
Medical Affairs		✓		Only review of documents
Monitoring		✓		Only review of documents
Pharmacovigilance		✓		Only review of documents
Project management	✓			Only sponsor focused
Quality Assurance			✓	Not within scope of this inspection
Quality Systems	✓			
R&D Unit (Non-commercial only)			✓	NA
Regulatory Affairs	✓			
Statistical Analysis			✓	Not done at time of the inspection
Technical Facility (i.e. x-ray)			✓	Not within scope of this inspection
Training	✓			
Trial Master File/Essential Documents	✓			
Other			✓	Not within scope of this inspection

Investigator Site [redacted] Royal Brompton				
Activity	Assessed			Comment
	Yes	Partial	No	
Principal Investigator	✓			Brief Interview during seizure visit
Research Nurse	✓			Brief Interview during seizure visit
Sub-Investigator			✓	Not within scope of the visit
Laboratory			✓	Not within scope of the visit
IMP Management/Pharmacy	✓			Brief Interview during seizure visit
Consents	✓			Seized ISF, PSF, R&D file
CRFs, e-CRFs, Patient Diary, IVRS		✓		Copies of seized questionnaires only

Source Data	✓			Seized trial source documents only
Site Master File	✓			Seized ISF, PSF, R&D file
Technical Facility (i.e. x-ray)			✓	Not within scope of the visit
Other			✓	Not within scope of the visit