Medicines & Healthcare products
Regulatory Agency

Leo Pharma UK GCP Inspection Report

Inspection No: Insp GCP 43/32961802-0002

Published 19 March 2025

Contents

Inspection Summary

Inspection & Organisation Information	
Inspection Number	Insp GCP 43/32961802-0002
Purpose of Inspection	Statutory GCP Systems
Type of Inspection	Remote
Organisation Inspected	Leo Pharma
Organisation Address	LEO Pharma UK, Roxborough Way, Foundation Park, Building 5, Maidenhead. SL6 3UD
Organisation Type	Commercial Sponsor
Dates of Inspection	24 - 28 June 2024
Lead Inspector	[redacted] GCP Inspector
Accompanying Inspectors	[redacted] GCP Inspector [redacted], Pharmacovigilance Inspector
Date of Closing Meeting	28 June 2024

Investigator Site - 01	
Name of Investigator	[redacted]
Organisation Inspected	Surrey and Sussex Healthcare NHS Trust, East Surrey Hospital
Organisation Address	Canada Avenue, Redhill. RH1 5RH
Organisation Type	NHS Hospital
Protocol Reference	[redacted]
IRAS ID	[redacted]
Dates of Inspection	19-22 August 2024
Lead Inspector	[redacted] GCP Inspector
Accompanying Inspector	[redacted] GCP Inspector

Date of Closing Meeting	22 August 2024

Investigator Site - 02	
Name of Investigator	[redacted]
Organisation Inspected	Pinderfields Hospital
Organisation Address	Clinical Research Team, Clinical Research & Innovation Building/NRU Building, Aberford Road, Wakefield, West Yorkshire. WF1 4DG
Organisation Type	NHS Hospital
Protocol Reference	[redacted]
IRAS ID / EUDRACT	[redacted]
Dates of Inspection	10-11th October 2024
Lead Inspector	[redacted] GCP Inspector
Accompanying Inspectors	[redacted] GCP Inspector
Date of Closing Meeting	11th October 2024

IMPs Reviewed	
IMP Details	[redacted]

Clinical Trials Reviewed	
Protocol Reference	[redacted]
IRAS ID / EUDRACT Number	[redacted]
Protocol Title	A phase 3 clinical trial to confirm efficacy and evaluate safety of [redacted]
IMP Details	[redacted]

Protocol Reference	[redacted]
IRAS ID / EUDRACT Number	[redacted]
Protocol Title	[redacted]
IMP Details	[redacted]

Protocol Reference	[redacted]
IRAS ID / EUDRACT Number	[redacted]
Protocol Title	A phase 3 trial comparing the efficacy and safety of [redacted]
IMP Details	[redacted]

Inspection Report Version History (For Inspectorate Use Only)	
Inspection Report Date 01	19 March 2025
Response Receipt Date 01	28 May 2025
MHRA Review Date 01	03 September 2025

Inspection Close Date	04 September 2025

Background Information

LEO Pharma A/S is a global pharmaceutical company focusing on medical dermatology and whose headquarters (HQ) lie in Ballerup, Denmark. Following the preclinical development activities managed by Research and Early Development (RED), clinical trials are managed by Development. Only Regulatory Affairs and Safety have operations in the UK affiliate. All other departments involved in the management of clinical trials are part of the global organisation.

The LEO Pharma A/S Development operates out of Denmark Headquarters (HQ) and is made up of project functions and line functions. The four key line functions supporting clinical development are:

- Global Regulatory Affairs (GRA).
- Global Safety (GS).
- Global Clinical Development (GCD).
- Global Clinical Operations (GCO).

The sponsor's last MHRA GCP inspection was 2011, at which there were no critical or major findings.

[redacted]

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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).
- ICH E6 “Note for Guidance on Good Clinical Practice”.
- Annex 13 to the EU Guide to Good Manufacturing Practice, ‘Manufacture of Investigational Medicinal Products’, July 2010.
- ICH 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).
- Heads of Medicines Agencies, Clinical Trial Facilitation & Coordination Group — Q&A Document: Reference Safety Information, November 2017 (RSI).

List of Common Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ASR	Annual Safety Report
ATMP	Advanced Therapy Medicinal Product
CA	Competent Authority
CAPA	Corrective Action Preventive Action
CI	Chief Investigator
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CSV	Computer Systems Validation
CTA	Clinical Trial Authorisation or Clinical Trial Agreement
CTFG	Clinical Trial Facilitation Group
CTIMP	Clinical Trial of an Investigational Medicinal Product
CV	Curriculum Vitae
DE	Dose Escalation
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
eCRF	Electronic CRF
eCOA	Electronic Clinical Outcome Assessment
ePRO	Electronic Patient Reported Outcome
eTMF	Electronic Trial Master File
FIH	First in Human
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ISF	Investigator Site File/Investigator TMF
LLT	Lower level term
LPLV	Last Patient Last Visit
MAA	Marketing Authorisation Application
MHRA	Medicines and Healthcare products Regulatory Agency

MVR	Monitoring Visit Report
PI	Principal Investigator
PIS	Patient Information Sheet
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
QP	Qualified Person
RA	Regulatory Authority
R&D	Research and Development
REC	Research Ethics Committee
RMP	Risk Management Plan
RSI	Reference Safety Information
RWD	Real World Data
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SDR	Source Data Review
SmPC / SPC	Summary of Product Characteristics
SI	Sub-investigator
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TOPS	The Over-volunteering Prevention Scheme
UAT	User Acceptance Testing

Sponsor Inspection Findings

INSTRUCTIONS TO INSPECTED ORGANISATION

Inspection responses and any subsequent clarifications should be completed in the fields provided for each numbered finding. Please ensure there is a different row for each corrective and preventative action with the planned completion dates. Do not append any additional documentation or insert any file links. Please provide any other referenced documents as separate files.

No responses are required to any observations and recommendations.

1. Critical Findings

There were **no Critical findings** identified during this inspection.

2. Major Findings

There were **two Major findings** identified during this inspection relating to Data Integrity Control Processes and Pharmacovigilance.

2.1	**Data Integrity Control Processes** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4)** All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9)** **Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016, 3.9.2, 5.0.1, 5.1.3, 5.2.1, 5.5.6 and 8.1**
2.1.1	For the [redacted] trial the sponsor did not hold a copy of the raw data which was used to generate the final Study Data Tabulation Model (SDTM) datasets (by the CRO delegated service provider) following final database lock. The trial database was locked on [redacted] however the latest version of raw data held by the sponsor was 02 November 2022. The trial [redacted] (version [redacted] 03 May 2021) stated *'After unblinding LEO will receive all data unblinded (eCRF, ePRO, SDTM PK dataset and lab data for all subjects'.*

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

2.1	**Data Integrity Control Processes (continued)**
2.1.2	The sponsor did not ensure the retention of an interrogatable dataset to facilitate data review and inspection. For the [redacted] trial the sponsor was unable to provide access to the trial EDC system as this had been decommissioned in January 2024 just prior to the inspection. The format of the retained eCRF data and audit trials was inadequate as it was presented as a flat PDF.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

2.1	Data Integrity Control Processes (continued)
2.1.3	The sponsor did not have adequate systems in place to ensure archived Data Acquisition Tools could be recommissioned (e.g. eCRF and ePRO) in a timely manner to facilitate inspection. • The sponsor did not routinely specify in contracts with vendors their expectations with regards to decommission/recommission of Data Acquisition Tools, they relied on specifications outlined by the vendors themselves. • The sponsor did not consider the decommissioning process in the trial Risk Categorisation Tool, to assess the risk associated with the timing of any decommission and the terms laid out in vendor working practices in relation to any regulatory activity. For example, where a product may be in in scope for inspection as part of a licensing application.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

This response is accepted

2.1	**Data Integrity Control Processes (continued)**
2.1.4	There was a lack of awareness amongst those interviewed in the DI/DM session of the Sponsors Policy and SOP on Data integrity. The Sponsor had in place a Principle Procedure [redacted] dated 30 September 2023) and an *SOP* [redacted] dated 30 October 2023*)* which sought to provide guidance on the management of data held in computerized systems to ensure data integrity. During interview those present were unable to recall these quality documents and describe how these are implemented and how the principles therein feed into systems and processes in relation to clinical trials.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.1	**Data Integrity Control Processes (continued)**
2.1.5	There was a lack of process to evaluate a Data Acquisition Tool for all the data it contains from use (in addition to the data of interest and its audit trail) to determine if this is required by the sponsor and in what format for use in compliance activities. The sponsor informed that "generally" the data management plan (DMP) would

	define what data from EDC (for example) the sponsor had agreed to be provided from the vendor at the trial end and in what format. However, the DMP for the [redacted] study only defined the package which would be returned to the investigator at the end of the study. It did not define what and how data from the EDC would be retained and/or returned to the sponsor, to allow for future reconstruction of the trial for inspection purposes. For this trial for example the Sponsor did not hold a copy of the final study raw data set, or audit trail dataset, or user access log audit trails.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

2.1	Data Integrity Control Processes (continued)
2.1.6	There was no requirement to review the audit trial following a database unlock/relock to confirm that only the approved changes had been made. It wasn't possible to make this assessment during the inspection for trial [redacted] as the audit trail was not provided in format that could be interrogated.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.1	**Data Integrity Control Processes (continued)**
2.1.7	It was not possible to verify that randomisation lists had been maintained in a restricted environment having been issued to clinical supplies management from the delegated service provider (CRO) following their creation. It was described that the current process is for these to be stored in a restricted area in the eTMF but for the selected trial [redacted] this was not the process, and the sponsor was unable (during the inspection) to provide evidence to confirm these had been stored with restricted access.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.1	Data Integrity Control Processes (continued)
2.1.8	The was no formal procedure to ensure the steps of unblinding (who/when), following analysis of the data and results being made available, was planned and that documentation of when unblinding occurred was completed. For [redacted] for example there was a Treatment Unblinding request form which logged the documentation with should be in place for unblinding to occur, but this did not detail who should/could be unblinded and when and how this would be controlled.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.1	**Data Integrity Control Processes (continued)**
2.1.9	The sponsor had no knowledge of how back-end changes to the clinical trial data would be controlled by delegated service providers and whether such changes would be captured in an audit trail. This information had to be obtained by the sponsor during the inspection from relevant service providers. These stated that the controls to back-end changes were in place because systems users would not be able to make back-end changes to tables, or that SOPs directed systems users to ensure any data changes be made via data query.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.1	**Data Integrity Control Processes (continued)**
2.1.10	There was no specified time limit on when edit check programming should be implemented if released in a staged way (after data entry is commenced by sites). This time limit should be minimised to ensure issues can be detected and resolved in a timely manner.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

2.1	**Data Integrity Control Processes (continued)**
2.1.11	There was no process in place to ensure investigators were provided with audit trails to detail who had had access to their data (in eCRF, ePRO, IRT) during the course of the trial. It is expected that archival datasets include this audit trail in addition to audit trail of changes to data throughout the study

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.1	**Data Integrity Control Processes (continued)**
2.1.12	There was no process in place to ensure sponsor and investigators were provided with data from the IRT system at the end of a trial. • In [redacted] no data were supplied to investigators at the end of the trial and no dataset was held by the sponsor. • Principal Investigator at Site [redacted] for the [redacted] reported that they had not been provided with IRT data at the end of the study.

Inspected Organisation's Response - 01

Evaluation &	[redacted]

Root Cause	[redacted]
Corrective Action(s)	

	[redacted]
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.1	**Data Integrity Control Processes (continued)**
2.1.13	A staff member from [redacted] helpdesk was assigned a primary investigator role (who could unblind) in the IRT system at investigator site [redacted] for [redacted] between 07 August 2019 and 12 December 2019. Whilst the sponsor stated that this individual did not have any activity in the audit trail, the reasons for the need for this type of access remains unclear and appears to be unacceptable. Further information was promised on this issue in the response to inspection request 17, however, this was not provided.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	**Pharmacovigilance** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).** 51: The expectedness of an adverse reaction is determined by the sponsor in the reference safety information. 52. The RSI is contained in the Summary of product characteristics ('SmPC') or the IB. 55: The RSI may change during the conduct of a clinical trial. This is typically a substantial amendment. For the purpose of SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR applies. **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** **Clinical Trial Facilitation Group (CTFG) 'Question and Answers: Reference Safety Information', November 2017.** **ICH guideline E2F on development safety update report 2011**
2.2.1	**Maintenance of the RSI/Expectedness Assessments** There was no process to ensure that substantial amendments to the RSI were not implemented for case expectedness assessment and for DSURs before receiving

	MHRA approval. The SOPs in place over time which defined the effective date of the IB did not address the need for MHRA approval prior to implementation: • Before 08 April 2019 the date of effectiveness was not defined in QMS documents • Between 08 April 2019 and 15 December 2021 (*SOP* [redacted] the effectiveness date of the IB was defined as two months after internal approval of the document. • *SOP* [redacted] *(*version [redacted] 15 December 2021) the effectiveness date of the IB was defined as the date of the first health authority approval following the initial submission. • *SOP* [redacted] (version [redacted] 23 March 2023) stated *'The effective date of an IB indicates when the RSI may be used for the assessment of expectedness of serious adverse events (SAEs). The IB may be used for the assessment of expectedness of SAEs following the first health authority approval following the initial submission.'* It was acknowledged that for the selected IMPs ([redacted] there were no substantial amendments of the RSI, and all the events were considered expected. Therefore, no unreported SUSARs were identified and the grading of this finding. A comparator drug was also reviewed during the inspection ([redacted] in the [redacted] trial) and no substantial amendments were required for this comparator and therefore there was no impact.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]

	[redacted]
Corrective	

Action(s)	[redacted]
Preventative Action(s)	[redacted]

MHRA Review - 01

[redacted]

No further response is required.

2.2	**Pharmacovigilance (continued)**
2.2.2	**Expectedness Assessment** There were a number of examples where pregnancy and overdose cases were incorrectly assigned the regulatory term "expected" during case processing. However, only events that were listed in the RSI should be considered as expected.

Case ID	Case Version	Suspect Drug (Generic)	Event (MedDRA PT)	Event Onset Date
[redacted]				

	[redacted]

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	**Pharmacovigilance (continued)**
2.2.3	[redacted] (version [redacted] dated 17 November 2023) incorrectly defined a number of events as "expected". For example:

	• Drug misuse or abuse. • Foetal exposure in utero. • Maternal exposure before and/or during pregnancy. • Paternal exposure before and/or during pregnancy. • Occupational exposure. • Suspicion of counterfeit product. • Product quality issue. It was acknowledged that this did not lead to underreporting of SUSARs, in the IMPs reviewed during the inspection, since these were not adverse drug reactions requiring reporting. However, only events that were listed in the RSI should be considered as expected.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.2	**Pharmacovigilance (continued)**
2.2.4	An incorrect version of the approved RSI was used to assess expectedness of a case in the [redacted] trial. Case [redacted], event of [redacted] (event onset date [redacted]) for IMP [redacted] was assessed as 'expected'. It was explained in document request [redacted] that [redacted] was listed in RSI/IB for [redacted] version [redacted] (effective [redacted]), however, this version was not submitted to the MHRA for approval. At the time of case processing for this case all serious events were unexpected for [redacted] hence the below should have been considered as unexpected. The event was not related to IMP, so no SUSAR under-reporting occurred.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	**Pharmacovigilance (continued)**
2.2.5	The requirement that an update to the RSI section (for IMPs and comparators) was to be considered a substantial amendment was not adequately defined in the quality management system. *SOP* [redacted] (version [redacted] dated 15 January 2023) stated *'If a safety change to the IB (e.g., RSI part, safety concerns, toxicology findings), which can affect patient safety is required, the SMT must decide whether this change is considered a substantial amendment.'* Therefore, it was not specified that an update in the RSI was always to be considered substantial and in addition, the RSI for comparator (particularly when included in the SmPC) was not stated. It was acknowledged that the IB template (version [redacted] no date available) section 6.3 stated '*note that any changes to the RSI during clinical trial are considered substantial amendments'.* However, this requirement was not included in the relevant procedural documents.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	**Pharmacovigilance (continued)**
2.2.6	There was no requirement to document the RSI version used for comparators in the safety database when the RSI was included in the SmPC. This is required to

	effectively reconstruct the activities followed in relation to determining expectedness and to be able to determine which version was used to assess expectedness of an initial case and can be followed through for any follow-up cases. The requirement to document in the safety database which version of the IB was used for expectedness assessment was introduced with SOP [redacted] (version [redacted] dated 29 May 2022) which stated '*Always state which version of the IB is applicable for assessing expectedness'*. However, this requirement was not mentioned for comparators, particularly when the RSI in included in the SmPC. Examples were noted: • In the SAE listing provided in pre-inspection document request 29 where all cases for [redacted] comparator in one of the trials did not include the RSI version used to make the expectedness assessment. • For cases received after June 2022 for [redacted] in the SAE listings provided in in pre-inspection document request 29.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review – 01	

This response is accepted

2.2	**Pharmacovigilance (continued)**
2.2.7	There was a lack of a procedures to ensure the correct RSI was used from the [redacted] repository (where RSIs were stored) when assessing cases to ensure the RSI in place at date of onset of the event was used (particularly relevant if an SAE was reported late by an investigator). The IB/SmPC to use for expectedness assessment was uploaded onto a [redacted] when it became effective for expectedness assessment (which was not after having received MHRA approval, see finding 2.2.1). However, the [redacted] did not include the start/stop dates for use of an RSI for expectedness assessment (it is acknowledged that for the selected IMPs there were no changes to the RSI and all events were unexpected.)

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01	

This response is accepted

2.2	**Pharmacovigilance (continued)**
2.2.8	There was no documentation to support the decision as to whether updates to the [redacted] IBs edition [redacted] (dated [redacted] and [redacted] (dated [redacted]) constituted substantial amendments. It was explained during the inspection that at that time there were no processes for documenting this decision making. A process was included in [redacted] (version [redacted] dated 20 May 2020) which covered considerations to be made if updates to IBs were required due to a safety reason. However, it did not consider changes impacting the scientific value of the trial or conduct management of the trial for example.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.2	Pharmacovigilance (continued)
2.2.9	The sponsor had no procedural documents which described the process to assess whether MedDRA updates had an impact on RSI.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.2	Pharmacovigilance (continued)
2.2.10	Although the sponsor conducted an impact assessment on the quality system of CTFG Q&A released in November 2017 (dated 15 November 2018) it was not possible to confirm that a retrospective review was performed of all IMPs used in clinical trials, to determine whether underreporting of SUSARs had occurred, as no documentation for the review was available. It is acknowledged that for the selected IMPs there were no changes to the RSI and all cases were considered to be unexpected.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.2	**Pharmacovigilance (continued)**
2.2.11	The process for the regular review (e.g. determined by a risk assessment or at least annually) for any updates to the SmPC (when used as an RSI for the IMP) was inadequate/not followed. The process for regularly checking for updates for non-LEO comparators' SmPCs was described in *SOP* [redacted] (version [redacted] dated 27 May 2024 and versions [redacted] which stated that it was the Clinical Regulatory Affairs Role's (RAR) (Global Regulatory Affairs (GRA) role representing GRA in the trial team) responsibility to check regularly if the submitted market data sheet (e.g. SmPC) for the comparator product had been updated and to provide the Trial Team and Global Regulatory Team (GRT) with the updated version for assessment to decide if a substantial amendment was warranted. However, the process did not describe how often the review was to be conducted, how the checks were performed and documented. Example was noted in the [redacted] trial where the Sponsor could not provide evidence of the regular check of updates to the [redacted] SmPC (comparator).

Inspected Organisation's Response - 01

Evaluation &	[redacted]

Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.2	**Pharmacovigilance (continued)**
2.2.12	There was no process to identify which exact section of the RSI for comparators (when included in the SmPC) was used to determine the expectedness assessments. *Working instruction* [redacted] (version [redacted] dated 20 March 2024) did not define which the exact section of the SmPC (section 4.8) to be used for non-sponsor comparators.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.2	**Pharmacovigilance (continued)**
2.2.13	The following deficiencies were identified with processing of pregnancy reports: • Case [redacted] described an event of [redacted] with a pregnancy outcome of [redacted]. The participant had a [redacted] however, this event was not coded in the safety database and no follow-up was sent to the site to confirm the seriousness of this event and investigator's causality assessment. The rationale provided by the sponsor was [redacted] As per Medical Assessment it had been decided, that since "There is no code for [redacted] or any other good alternative, so I suggest to keep PT [redacted] [redacted] was captured as pregnancy outcome only. However, as per sponsor coding convention (Working instruction [redacted] version [redacted] 03 May 2021), section 9.10.3, 'When *reported* [redacted] *(with no AE/defects in foetus or no information), the LLT selected should be* [redacted] *and* [redacted] *Capture both the clinical consequence and the exposure during pregnancy as events*.' In this case, the LLTs [redacted] or [redacted] could have been used to code this event which were listed in the MedDRA coding version available at the time of receipt of the case.

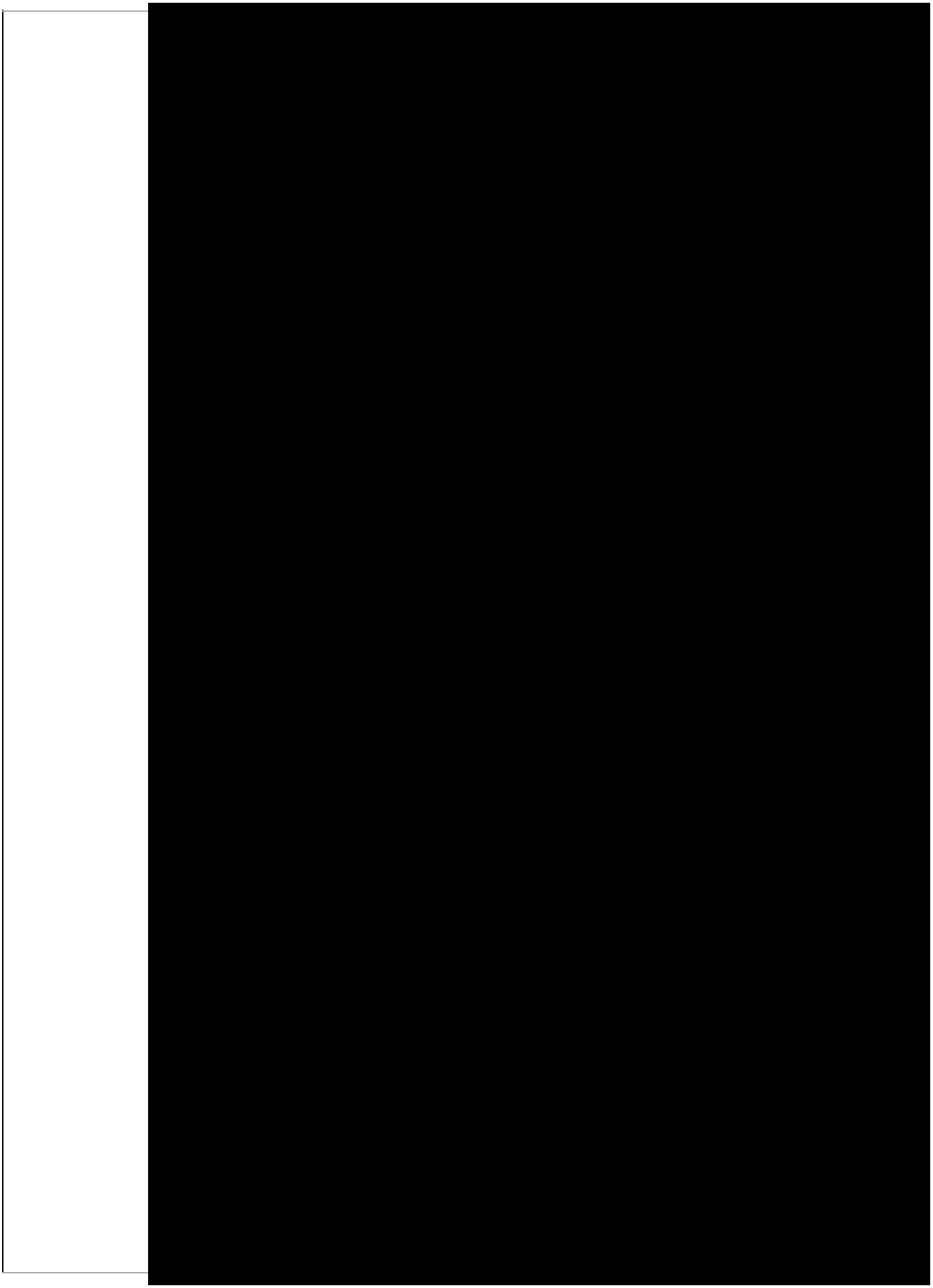
- Three cases of [redacted] had the incorrect pregnancy outcome reported in the safety database where the outcome was reported as “other.” It was confirmed during the inspection that the pregnancy outcomes in the listed cases were entered erroneously during data entry. Examples are noted below:

Case Number	Version	Initial Receipt Date	Trial	Pregnancy Outcome in the safety database	Correct Pregnancy Outcome
[redacted]					

Inspected Organisation’s Response - 01

Evaluation & Root Cause

[redacted]



	[redacted]
Corrective Action(s)	[redacted]

	[redacted]
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	**Pharmacovigilance (continued)**
2.2.14	For DSUR production, there was no procedure to evaluate the data extract from the PV database used for expedited reporting to determine if cases needed to be reassessed against the RSI in place at the start of the reporting period where the RSI has been updated. It was not clearly documented in the QMS that when producing the DSUR, the RSI version in effect at the start of the reporting period was to be applied to all cases contained within the SARs listings.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	**Pharmacovigilance (continued)**
2.2.15	Evidence was identified on inspection of more than one IB being referenced in the DSUR section 7.1 'Reference information' (which defines the RSI used for determining expectedness for the DSUR tabulations). For example, although this is not an exhaustive list: • [redacted] DSUR Reporting period [redacted] Section 7.1 '*The LEO Pharma [redacted] IB, Edition [redacted] (dated [redacted]) and Edition [redacted] (dated [redacted] , were used as reference safety documents for expectedness assessment.* ' • [redacted] DSUR Reporting period ([redacted]): *'The LEO Pharma [redacted] IB, Edition [redacted] (dated [redacted]) and Edition [redacted] (dated [redacted]), were used as reference safety documents for expectedness assessment.* • [redacted] DSUR [redacted] Section 7.1 '*The LEO Pharma IB for [redacted] Edition [redacted] was used as the reference safety document for expectedness assessment. In the beginning of the period the IB, Edition [redacted] was used as reference safety document for determining expectedness for expedited reporting purposes. The IB edition [redacted] is still in effect as reference safety document for potential [redacted] cases*.' • [redacted] DSUR [redacted] Section 7.1 Reference Safety Information*. 'The LEO Pharma IB for [redacted] Edition [redacted] was used as the reference safety document for expectedness assessment. In the beginning of the period the IB, Edition [redacted] was used as*

	reference safety document for determining expectedness for expedited reporting purposes'

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	**Pharmacovigilance (continued)**
2.2.16	There was no process to identify SUSARs in the DSUR listings as per ICH E2F. For example, although this is not an exhaustive list, the below DSURs did not identify SUSARs in the cumulative summary tabulation of SARs:

	• [redacted] DSUR [redacted]. • [redacted] DSUR [redacted]. • [redacted] DSUR [redacted]. • [redacted] DSUR [redacted]. • [redacted] DSUR [redacted]. • [redacted] DSUR [redacted].

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

2.2	Pharmacovigilance (continued)
2.2.17	There was no process to ensure that the RSI for comparators were also included in the DSUR section 7.1. For the [redacted] DSUR (reporting period [redacted]) section 7.1 did not mention which RSI was used for comparators as trial [redacted] was ongoing during the reporting period and was using [redacted] as a comparator.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

2.2	Pharmacovigilance (continued)
2.2.18	The [redacted] DSUR (reporting period [redacted]) Line Listing of Serious Adverse Reactions and Cumulative summary tabulation of Serious Adverse Reactions from Clinical Trials included blinded cases despite having been unblinded. For example, case [redacted] and [redacted]

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

3. Other Findings

There were **four Other findings** identified during this inspection Project/Trial Management**,** Quality Assurance, Training and Medical Oversight.

3.1	**Project/Trial Management**
3.1.1	There was a lack of formalised procedures to fully address amendments during the conduct of the trial: • There was no process to formally document the sponsor's substantiality decision, its rationale, and the decisions on actions to take regarding necessary approvals and updates to documentation and systems including Data Acquisition Tools. Whilst site activation checklists existed for the initial activation, there was no similar process for implementation of amendments, i.e. to check the necessary approvals were in place and relevant updates made.

	• There was no formalised procedure in place in relation to the oversight of trials, both management by the sponsor or when using a delegated service provider to ensure that any Data Acquisition Tools for trials were consistent with the approved protocol, particularly for amendments. Whilst there was some evidence the regulatory and REC approvals had been considered in site activation of eCRFs in the [redacted] trial, there was no formalised procedure to ensure this occurred.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

This response is accepted

3.1	**Project/Trial Management (continued)**
3.1.2	A lack of robust oversight of amendment implementation by the sponsor was noted in the [redacted] trial at Investigator site [redacted]: • The sponsor did not provide clarity on implementation of protocol version [redacted]; an email dated [redacted] was provided to the site to say that documents could be sent to R&D but this was not an authorisation to implement (as requested by document request). The protocol was not signed by the PI until [redacted] The sponsor did not have oversight of this signature and of the R&D approval on [redacted] (the date provided by the sponsor for the implementation of the amendment) to ensure both were in place prior to a clear instruction to implement the amendment at this site. In addition, pharmacy amended documentation on [redacted], implementing amendment too soon (see finding 9.6.2). • The covid addendum dated [redacted] was not signed by the PI unti[redacted] • An email sent to site on [redacted] to implement protocol version [redacted] (although trial conduct had finished) was before R&D approval on [redacted] and the protocol signed by the PI on [redacted] Additionally, review of the change control spreadsheet (pre-inspection document request 19) for trial [redacted], the following observations were made in relation to untimely implementation of amendments and were queried to the sponsor to provide any explanations in document reques[redacted] for which the sponsor appears to have not provided any documentation. • For protocol version [redacted] dated [redacted] the green light was [redacted] (implementation date), however the protocol was not signed by the PI at site [redacted] until [redacted] • For protocol version [redacted] dated [redacted] the implementation date at site [redacted] was [redacted] and site [redacted] was [redacted] however the MHRA did not approve this protocol until [redacted]. • For the protocol addendum ([redacted] it was noted that the protocol signature was after the implementation dates for all sites (aside from [redacted] which had closed). It is also noted that the implementation date was [redacted] for all sites (aside from [redacted]) which was before HRA approval on [redacted]

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

This response is accepted

3.1	**Project/Trial Management (continued)**
3.1.3	There was a lack of a formal procedures to check the consistency of the IRAS application form (for MHRA and REC submissions) with the material particulars also submitted (e.g. the protocol, IC, IB etc.).

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

3.1	**Project/Trial Management (continued)**
3.1.4	Acknowledgements of receipt of archival data packages sent to Investigators at the end of trial [redacted] were in the most part received from a member of staff other than the principal investigator (at UK sites), so it was not possible to demonstrate that investigators maintained control of their data, had reviewed its content and were satisfied of its quality.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

3.2	**Quality Assurance**
3.2.1	There was a decreasing number of internal process/system audits completed since 2020 (based on pre-inspection request 04) and some areas had not been subjected to audit for a number of years:

Year	**Audits completed.**

2020	6
2021	8
2022	4
2023	2
2024	0

- Safety case processing was last audited in 2017, Protocol and Amendments were last audited in 2018, Medical Monitoring was last audited in 2018 and IB/RSI was last audited in 2017.

Whilst it was stated in interview that this was because the quality management system was changing, process/systems audit would still be useful to see whether any changes would address issues that were being identified, i.e. the audit results could inform new processes.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

3.3	**Training**
3.3.1	Principle policy ([redacted] version [redacted] 30 September 2023) was required to be completed by all LEO global clinical development staff however the SOP (SOP [redacted] version [redacted] 30 October 2023) in this area was only required to be read by Managers. The SOP's objective was to *'describe the risk-based procedure for identifying and implementing relevant data integrity controls to ensure the data integrity of regulated electronic data and records.'* It was unclear why it would not be considered as required learning for those staff members managing and handling data throughout the lifecycle of a trial (who were not managers) for example clinical data managers and biostatisticians for the selected studies. It was noted that [redacted] Clinical Data Manager [redacted] had not documented reading and understanding of Principle Procedure [redacted] and Manager [redacted] (Head of statistical programming) had not documented reading and understanding for SOP [redacted]

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

3.4	**Medical Oversight**
3.4.1	For the [redacted] trial, the activation of site [redacted] was on [redacted] At this site, four people were assigned the Primary Investigator (blinded, could unblind) role and of these, three never logged into the system and the fourth only logged in for the first time on 21 January 2020, after activation and IMP shipment on 14 May 2019, therefore the ability for successful log in and emergency unblinding functionality was not confirmed in a timely manner.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

Observations and Recommendations

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

Pharmacovigilance

- The clinical trial SAE listings provided in advance of the inspection included the following incorrect information (pre-inspection document request 29):
    - Case ID [redacted] follow-up case versions [redacted] were assessed as non-medically significant, hence not submitted to the MHRA. However, the submission date (27 August 2018) was entered in error in the SAE listings.
    - Case ID [redacted] case versions [redacted] were not submitted to the MHRA since the case was downgraded in version [redacted] However, the submission date (02 January 2019) was entered in error in the SAE listings.
    - Case [redacted] was downgraded in version [redacted] and hence, the following case versions were not submitted. However, the submission date (19 July 2019) was entered in error in the SAE listings.
- No deviation was raised for a late SUSAR submission to the MHRA (one day late only). Case [redacted] version [redacted] was a SUSAR case received by sponsor on 21 December 2021 and submitted one day late to the MHRA on 06 January 2022. However, a deviation was

not raised despite being required by SOP [redacted] (version [redacted] dated 15 January 2022).

- It was recommended that the email notification template used by PV as the first step in SAE case processing is formalised in the quality system.
- The use of the term "medical assessment" in case processing may not be considered appropriate given that this assessment can be made by a person who is not medically qualified.

Statistics

- It was not possible to confirm during the inspection that the production program [redacted] 26 January 2023 10:23 used to produce Table [redacted] for the [redacted] trial was in the validated state before it was run on 08 March 2023 16:02 to produce the output contained in the CSR ([redacted] as the QC program [redacted] was run on 08 March 16:11 2023 was run afterwards.

  It was not clear that the QC program had been run on this program between 26 January 2023 and 08 March 2023 to confirm the program as "final" in the programming log, as there was no date or time stamp in the log to show when finalisation occurred, which version of the production program it related and which QC program was used. It was recommended that Leo considers the process and its documentation as to whether there is sufficient clarity that a program was fit for purpose prior the final run. It was noted that in the example reviewed, that the production and QC program did not give different output.
- It was recommended that controls around the use of hard coding are covered in the document "good programming practice" that was mentioned to the inspectors and that this is formalised as part of the QMS.

Medical Writing

- Compliance aspects of a trial in relation to preparation of the Clinical Study Report were clearly covered in the CSR kick-off meeting and there were sections in the report to discuss in the template minutes. The compliance with ICH GCP, Declaration of Helsinki and applicable regulations statement in the CSR may need to be qualified as it may not be completely true. The current CSR body template version [redacted] (approved [redacted]) had the statement in section 1.2 and then details of any non-compliance to be covered in section 5.7. It was recommended to add to text to the template in section 1.2 to say to cross reference 5.7 when compliance issues have occurred in the trial and identified in the kick-off meeting.

Data Integrity

- It was recommended that a holistic review of all the inadvertent unblinding incidents is undertaken to examine there are any systemic root causes that could be addressed by CAPA.

Serious Breach Reporting

- It was recommended that the SOP [redacted] (version [redacted] 30 November 2023) was made clearer as to which day should be considered day zero for reporting purposes. Whilst the SOP indicated it was the day of awareness, the cover letter for [redacted] stated day zero was the date that the sponsor decided it was serious breach, and this was 13 days after the awareness date. If a serious breach appears to be likely pending further confirmatory investigation or impact assessment, it was recommended to report the potential serious breach. It was noted that of the three cases reported to MHRA, two were reported beyond seven days of awareness, [redacted] (aware 30 April 2020, notification made 15 May 2020 - 15 days), [redacted] (aware 23 June 2023, notification made 12 July 2023 - 19 days).

Monitoring

- Whilst risk-based quality management (RBQM) was in place, the focus appeared to be on data and monitoring primarily, rather than on protocol and trial design and the impact on all processes, e.g. IMP, safety, CSV etc. The presentation provided in inspection document request [redacted] illustrated this was the aim, but the procedures provided did not reflect this. It was recommended, that as part of implementation of ICH R3, consideration is given to review the quality system to ensure all activities are reviewed for where risk based adaptive approaches, as set out in the guidance, can be fully realised into the formalised procedures.

Investigator Site 01 – Findings

INSTRUCTIONS TO INSPECTED ORGANISATION

If a separate response is provided by inspected organisation and the investigator site, ensure this is clearly differentiated in the responses provided below.

4. Critical Findings

There were **no Critical findings** identified during this inspection.

5. Major Findings

There were **2 Major findings** identified during this inspection relating to CRF Data / Source Data and Medical Oversight by the PI.

5.1	**CRF Data / Source Data** 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. 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. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).** The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).** All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. **UK Statutory Instrument 2004/1031 (as amended) Schedule 1, Part 2 (9)** The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. **Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016; 4.9.0 and 4.9.2**
5.1.1	Processes in place to control the production and use of source data worksheets (developed by the clinical site team) were inadequate. The clinical site used proformas and source worksheets, these were routinely not version controlled and

	there was no process in place to ensure these were reviewed and updated when trial protocol requirements were updated e.g. following substantial amendments.
	• Participant [redacted] was screened on the [redacted] and an eligibility checklist used had a handwritten note on the document stating the checklist is based on version [redacted] of the protocol. This was despite protocol version [redacted] being implemented at the site on the [redacted] It was noted that the inclusion and exclusion criteria did not significantly change between version [redacted] and version [redacted] of the protocol.
	• Printed copies of scoring scales were used as source documents for participants in the study, the labelling of these scores did not reflect that which was defined in the approved study protocol although it was noted the content of the scales was the same:
	  • Participant [redacted] printed sheet was referred to as panel [redacted], but in the approved protocol this was panel [redacted].
	  • Participant [redacted], Definition of subtypes of [redacted] printed sheet was referred to as panel [redacted], but in the approved protocol this was panel [redacted]

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

5.1	CRF Data / Source Data (continued)
5.1.2	There were numerous examples where it was not possible to attribute source records to an individual or recreate the flow of study visits as defined in the protocol. Source worksheets, proformas and worksheet stickers were used to record actions taken at each clinical visit and it was not possible to clearly demonstrate who had conducted each part of a visit. The clinical source record worksheets also did not facilitate the documentation flow of the study visit as defined in the protocol and the source documents did not capture the time that specific processes or procedures were conducted. Therefore, it was not possible to confirm that clinical tasks were performed before or after key events such as consent or randomisation: • Source worksheet stickers included confirmation that bloods had been taken, assessments performed, and eligibility reviewed. However, it was not possible to see who had performed what trial task i.e. a research nurse had completed the vital sign assessments but there was only one space for the PI/Sub-Investigator to signoff the visit on the source worksheet. • The source data worksheets for participant [redacted] contained a demographic and medical history form. This form was not signed and not dated as there was no section on the form for this to be done. The form also contained a list of previous concomitant medications for this participant, but it failed to list all concomitant medications the participant had taken as per the medical notes.

	• The source data worksheets for participant [redacted] contained a demographic and medical history form. This form was not signed or dated. • The medical notes for participants [redacted] contained the printout for the [redacted] ePRO system. These printouts had the average [redacted] score calculated manually (by site staff) which was required to confirm eligibility. The average score calculations were not signed or dated. • For participants [redacted] the [redacted] after IMP source worksheet was not signed or dated. • Printouts from the urine testing at site were routinely filed for all participants but it was not possible to demonstrate who had performed this testing. • The screening source data worksheet for participant [redacted] had a comment outlining the participant's previous treatment of [redacted] This information was required for eligibility; however, the comment was not attributable to a member of the trial team and was not signed or dated and it was not clearly documented as reviewed by a physician. • It was difficult to attribute physicians to their signatures in the clinical notes and the signatures recorded in the site signature log. Different versions were often utilised which did not clearly correspond to the signature log and names were not printed alongside signatures to confirm identity. • The IB receipt forms for edition [redacted] and edition [redacted] contained the typed name of [redacted]; however, the signature between the two forms was significantly different and one of the signatures did not match the site signature log. This was discussed with the clinical site team, and they stated both signatures were that of [redacted] and that [redacted] signature would vary on trial documentation. • The participant notes for participant [redacted] contained a source data worksheet for screening which had a comment outlining the participant's previous treatment of [redacted] This information was required for eligibility; however, the comment was not attributable to a member of the trial team, and it was not clear if it had been reviewed by a physician.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

5.1	CRF Data / Source Data (continued)
5.1.3	It was not possible to identify which areas of the treatment scheme [redacted] had been updated between visits, and which were the original treatment areas. The treatment scheme for participant [redacted] was documented on the treatment scheme as being initially created on the [redacted] and then updated on the [redacted] but as the updates and the original recording were all made in black ink, it was not possible to identify which shaded areas (indicating treatment application) were added to the original treatment scheme and where new [redacted] had been recorded. It was noted that the treatment schemes were used as aids for the participants [redacted] and not for data collection.

Inspected Organisation's Response – 01

Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

5.1	**CRF Data / Source Data (continued)**
5.1.4	There was no visit [redacted] / Week [redacted] source data workbook available for participant [redacted] for the visit conducted on the [redacted]

Inspected Organisation's Response – 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

5.1	**CRF Data / Source Data (continued)**
5.1.5	There was incorrect data recorded and filed in the source notes: • For participant [redacted] the average [redacted] was recorded manually on the ePRO print out to confirm eligibility. This was incorrectly calculated as [redacted] however, the average score of [redacted] was an average of more values than those generated in the [redacted] days prior to baseline as defined in the approved protocol eligibility criteria. These data were recorded in the ePRO correctly as [redacted] and had no impact on the eligibility of the participant. • For participant [redacted] there were a number of source worksheets filed that related to the long-term extension tria[redacted] and not the and not that [redacted] trial. It was noted that these also had similar attributability issues as noted in the [redacted] trial.

Inspected Organisation's Response – 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

5.2	**Medical Oversight by the Principal Investigator** 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. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (11)** No person shall - (a)conduct a clinical trial; or (b)perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Part 4, (28)**
5.2.1	There were a number of examples where it could not be demonstrated that the principal investigator or delegated sub-investigators had reviewed trial data in a timely manner. Therefore, it was not possible to evidence that medical confirmation of eligibility had occurred prior to randomisation: • Participant [redacted] was randomised on the IRT system on the [redacted] The central ECG reading report from the ECG performed at screening, [redacted] was not reported until [redacted] .e. after randomisation had occurred. There was an ECG thermal paper printout filed in the participant medical notes from the [redacted] and this has a comment handwritten on the printout stating, "please provide previous ECG for comparison" and a response stating "1st ECG not available". There was no comment on the ECG stating its clinical significance. There was a signature on the ECG printout, however, this was not attributable to any member of the study team and there was no date of signing. • Participant [redacted] repeat screening blood test results were not signed as reviewed by an investigator until [redacted] which was after randomisation on the [redacted]. • [redacted] and [redacted] who are study coordinators/assistants were delegated to *'Confirms Subject Eligibility (inclusion/exclusion)'* (task 2) despite the delegation log specifying that these roles are only for staff who are medically qualified. • It was not clear from the source records in all cases if the [redacted] score was reviewed by a physician prior to randomisation and before the study coordinators conducted the randomisation in the IRT. • In the medical notes for participant [redacted] the research nurse [redacted] had written a comment stating that the inclusion and exclusion criteria, eDiary, ECG and blood results had been reviewed by Sub-I/PI. This was not countersigned by a Sub-I/PI to evidence that they had performed this review or make the review attributable to a specific investigator.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

5.2	**Medical Oversight by the Principal Investigator**
5.2.2	There was no evidence to suggest that the PI (or any other Sub-investigator) had ever logged in to the IRT system to test the emergency unblinding facility. This was confirmed by reviewing the IRT user access audit trail. The [redacted] Product Handling Manual version [redacted] stated in "*Before dispensing IMP to any subject ensure that at least one investigator at site has an active IRT account in order to be able to unblind via the IRT".*

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

This response is accepted

6. Other Findings

There were **five Other findings** identified during this inspection relating to Archiving, Clinical Sample Management, Facilities and Equipment, IMP Management / Pharmacy and Staff Delegation and Responsibilities.

6.1	**Archiving**
6.1.1	*SOP* [redacted] (version [redacted] 28 March 2024) did not detail how medical records would be flagged to ensure they were retained in accordance with the archiving and retention requirements for CTIMPs. The site randomised five participants on the study but only three of these five participant notes contained a yellow sticker on the front stating '*Clinical trial participant please do not destroy*'; the yellow sticker process was not defined in the SOP. It was understood by inspectors that the trust is planning to move to electronic health records where the facility to label participant records would be available. It is important therefore to ensure that any paper records are marked for retention and any potential migration (via scanning for example) during transition periods retain the flags for CTIMP participants. Additionally, the SOP did not provide detail on the electronic archiving of CTIMP data. The clinical site was able to provide documentation from the electronic archive, a [redacted] filing system, when requested and were able to provide evidence of who had access to the electronic archive; however, there was limited evidence that this filing system had all the control measures required for long term electronic archiving of clinical trial data.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

6.1	**Archiving (continued)**

6.1.2	There was evidence of inadequate QC of the ISF prior to archiving:
	• The regulatory and ethics approvals section of the file were incomplete:
	  • There was no documentation for the submission of the first substantial amendment to the ethics committee.
	  • There was no submission documentation for the first substantial amendment to the MHRA.
	  • Incomplete IRAS forms for a number of submissions i.e. printouts of forms starting at page 9.
	Inspection of all of the ethics and regulatory submissions was difficult due to a significant amount of duplication of the documentation filed in this section of the ISF.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

This response is accepted

6.2	**Clinical Sample Management**
6.2.1	The sample processing worksheets available for this trial were insufficient to demonstrate that the sample processing conducted at the clinical site had been conducted in accordance with the trial laboratory manual (version [redacted], 20 October 2021): • There were a number of examples where the sample processing worksheet was incomplete and therefore it was not possible to verify if processing steps were in compliance with the manual. For example, the requirement to allow the specimen to clot for 30 minutes prior to centrifugation or the requirement to centrifuge the sample for 10 minutes. • Dates and times of shipment were not always recorded on the sample processing worksheet. • It was not always possible to verify who had conducted the sample processing as this field was not always completed/signed on the worksheet.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

This response is accepted

6.2	**Clinical Sample Management (continued)**
6.2.2	The clinical sample preparation prior to shipping was not always compliant with the laboratory manual (version [redacted] 20 October) 2021: • There were five blood samples identified from a review of three of the five participants that were documented as not being left at ambient temperature for the required 30 minutes to allow for clotting prior to centrifugation. • One specimen was noted to have been centrifuged and then stored in a fridge overnight which was not in compliance with the lab manual. The manual [redacted] version [redacted] stated that if it was not possible to ship samples on the day of collection, they should be stored at room temperature as separated serum and sent on the next business day. It was noted that the sample requisition form had a comment added stating the sample was refrigerated overnight and this was included on the laboratory report when reviewed.

Inspected Organisation's Response - 01

Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

6.2	**Clinical Sample Management (continued)**
6.2.3	It was not possible to verify that the [redacted] was appropriately trained on the processing procedures outlined in the lab manual for this study as no training records were available. In addition, [redacted] was not delegated the role of processing biological samples and preparing/executing shipment of samples. From a review of the sample processing logs for the study it was identified that [redacted] was processing and shipping biologic samples. It was not possible to verify how many specimens were processed by this [redacted] due to the lack of attributability of documentation noted in finding 6.2.1. It was described during the inspection that [redacted] would cover the sample processing activities in the absence of [redacted], the former [redacted]

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

6.3	Facilities and Equipment
6.3.1	During a facilities tour a number of pieces of equipment which may be used for clinical research study measurements were not labelled as having been checked and calibrated. Each showed a label stating that re-testing was due in December 2023. Evidence was provided showing that testing was incomplete for the equipment and testing was recorded as completed on the date of the inspection. It was noted that the chair scale selected was not in use during the [redacted] trial, but it was understood that this may have been used for other ongoing studies:

Equipment	Next Test Due	Testing completed
[redacted] BP Machine/Thermometer	December 2023	21 August 2024
[redacted] Scale	December 2023	22 August 2024

	[redacted] Scale (Chair)	December 2023	22 August 2024

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01	

This response is accepted

6.4	**IMP Management / Pharmacy**
6.4.1	Numerous trial specific documents related to IMP management in the clinical site pharmacy were not finalised prior to site initiation. The monitor approved the Green Light Form for release of IMP to the site on the 07 July 2021 and FPFV occurred on the [redacted] • [redacted] version [redacted] dated 05 August 2021, signed off 05 August 2021. • [redacted] version [redacted] 13 October 2021, signed off 13 October 2021. • [redacted] SOP version [redacted] 13 October 2021, signed off 13 October 2021.

Inspected Organisation's Response - 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventativ Action(s)	
MHRA Review - 01	

This response is accepted

6.4	**IMP Management / Pharmacy (continued)**
6.4.2	The destruction and return of IMP were not appropriately documented: • The destruction of [redacted] was not detailed in the site accountability logs. • Kit [redacted] was marked as having been packaged for destruction with end of trial supplies but also marked on the eCRF as being a pack returned unopened by participant [redacted] • IMP was packaged and returned for destruction on 23 December 2021, but the Individual Drug Accountability Form (IDAF) logs were not signed off by the PI or the monitor as required until 27 April 2023.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	

Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

6.5	**Staff Delegation and Responsibilities**
6.5.1	Issues were identified with the delegation of staff at the clinical site: • Pharmacy staff [redacted] and [redacted] were allocated task 21 on the site delegation log '*Processes Biologic Samples and performs urine dipstick test'* rather than task 22 '*IMP weighing (and completion of IDAF)*'. There was no evidence to suggest these staff members performed these clinical duties. • As per finding 5.2.1, the study coordinators/assistants [redacted] and [redacted] were delegated task 2 to '*Confirm Subject Eligibility (inclusion/exclusion)*' despite the delegation log specifying that this role was only for staff who were medically qualified. • The [redacted] was recorded on the delegation log as starting their responsibilities on the study from the 01 July 2022. However, trial duties occurred before this, and it was noted that the year should be 2021 and is likely a typographical error. • As per finding 6.2.3, the [redacted] was not delegated the task of processing biological samples and preparing/executing shipment of samples. From a review of the sample processing logs for the study it was identified that [redacted] was processing and shipping biological samples. • Of the four staff assigned item 12 on the delegation log *'records data in the eCRF (including corrections and resolving data queries)*', two of these appear not to have been assigned roles in the eCRF system [redacted] and the remaining persons were activated in the eCRF prior to delegation, [redacted] delegated 08 May 2019, activated 01 May 2019 and [redacted] delegated 08 May 2019, activated 03 April 2019.

Inspected Organisation's Response – 01

Evaluation & Root	[redacted]

Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

Observations and Recommendations

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

Clinical Sample Management

- The laboratory request forms from the central lab, [redacted], stated that the PI for the study was [redacted] this physician was initially intended to be the PI for the study at the clinical site but was then changed to [redacted] prior to study initiation and the request forms were not updated.
- The laboratory request forms for participant [redacted] stated that the week [redacted] visit [redacted] safety samples were collected at 08:50am, whereas the lab processing worksheet completed by the clinical site stated that the sample was collected at 08:30am.

IMP Management / Pharmacy

- The trust SOP [redacted] (version [redacted] 18 December 2020 and version [redacted] October 2023) did not specify when trial specific procedures should be in place in relation to trial initiation. It was also silent with regards to review and amendment of trial specific procedures in the event of any changes to the study. Recommend review to ensure clarity.

- *During* the inspection, on the 20 August 2024, a number of bottles of IMP for two non-LEO studies were noted to be approaching expiry but resided with dispensable stock. Each bottle contained 70 tablets expiring at the end of August 2024, which should have been quarantined as the product would have been expired before the end of dosing from these bottles. It is acknowledged that these studies were blinded so it is assumed IRT system controls would have preventing dispensing of these packs to a participant.

Serious Breach Reporting

- It was recommended that the trust review its policies with regards to serious breaches of the protocol and/or GCP and escalation of quality issues identified in clinical trials in general. The *SOP* [redacted] (version [redacted] dated 28 March 2024), covered this briefly in that it stated that where a serious breach is identified during an audit or monitoring this would be escalated as appropriate to the sponsor. However, there was no process in place for investigators or the research team to escalate quality issues (including potential serious breaches) internally and onwards to sponsors. The SOP also did not give guidance to advise research team members that they could also report serious breaches directly to the MHRA in cases where there was disagreement (as to whether something constituted a potential serious breach or not) with sponsors.

Investigator Site 02 – Findings

INSTRUCTIONS TO INSPECTED ORGANISATION

If a separate response is provided by inspected organisation and the investigator site ensure this is clearly differentiated in the responses provided below.

7. Critical Findings

There were **no Critical findings** identified during this inspection.

8. Major Findings

There were **no Major findings** identified during this inspection.

9. Other Findings

There were **seven Other findings** identified during this inspection relating to Clinical Sample Management, CRF Data / Source Data, Data Integrity, IMP Management / Pharmacy, Medical Oversight by the Principal Investigator, Record Keeping / Essential Documents and Training.

9.1	**Clinical Sample Management**
9.1.1	There was a lack of records from the pathology laboratory in relation to documenting the steps of receipt, processing and time into and out of the freezer to confirm compliance with the laboratory manual and the site trial specific local procedure [redacted] Trial (versions [redacted] (no date of effectiveness on documents). Note: This document was valid for 30 days from 01 October 2024 indicating it was added post archive as part of the inspection preparation.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

9.2	CRF Data / Source Data
9.2.1	Source data agreement signed 08 May 2019 stated that all paper records (source documents) would be scanned and uploaded to [redacted](the electronic health record (EHR)). This was not the case, examples were seen of documents not being uploaded, including eligibility checklists and the source datasheet for each visit. The EHR was limited to progress/notes and the consent form.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review – 01

This response is accepted

9.2	**CRF Data / Source Data (continued)**
9.2.2	For participant [redacted], prior treatment with [redacted] could not be verified in the clinical trial notes, the GP records or the medical history. This was reported in the IRT system and used as a stratification factor at randomisation. For other participants a previous [redacted] treatment and [redacted] history (SCREENING VISIT) form captures previous [redacted] use; this was not present for this participant.

Inspected Organisation's Response – 01

Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	[redacted]

MHRA Review - 01

This response is accepted

9.3	**Data Integrity**
9.3.1	There were changes made to primary and secondary endpoint data that did not include a documented reason for change and without the participant being present to be able to make the data change. Participant [redacted] attended the site on the [redacted] for their week [redacted] visit, and at this visit the [redacted] (primary endpoint scale) and [redacted] (secondary endpoint scale) were completed as standard. The paper documents for the [redacted] were both amended by the [redacted] on the [redacted] it is not clear how the investigator was able to do this, as there was no evidence that the participant returned to the site, and the scores require observing the participant's [redacted] Additionally, at the week [redacted] visit, the [redacted] made an amendment to the [redacted] source data which was not dated.

Inspected Organisation's Response – 01

Evaluation &	[redacted]

Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01	

This response is accepted

9.4	**IMP Management / Pharmacy (continued)**
9.4.1	Pharmacy SOPs did not address requirements of pharmacy where the sponsor IRT was used to document site level accountability, as the case in this trial.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

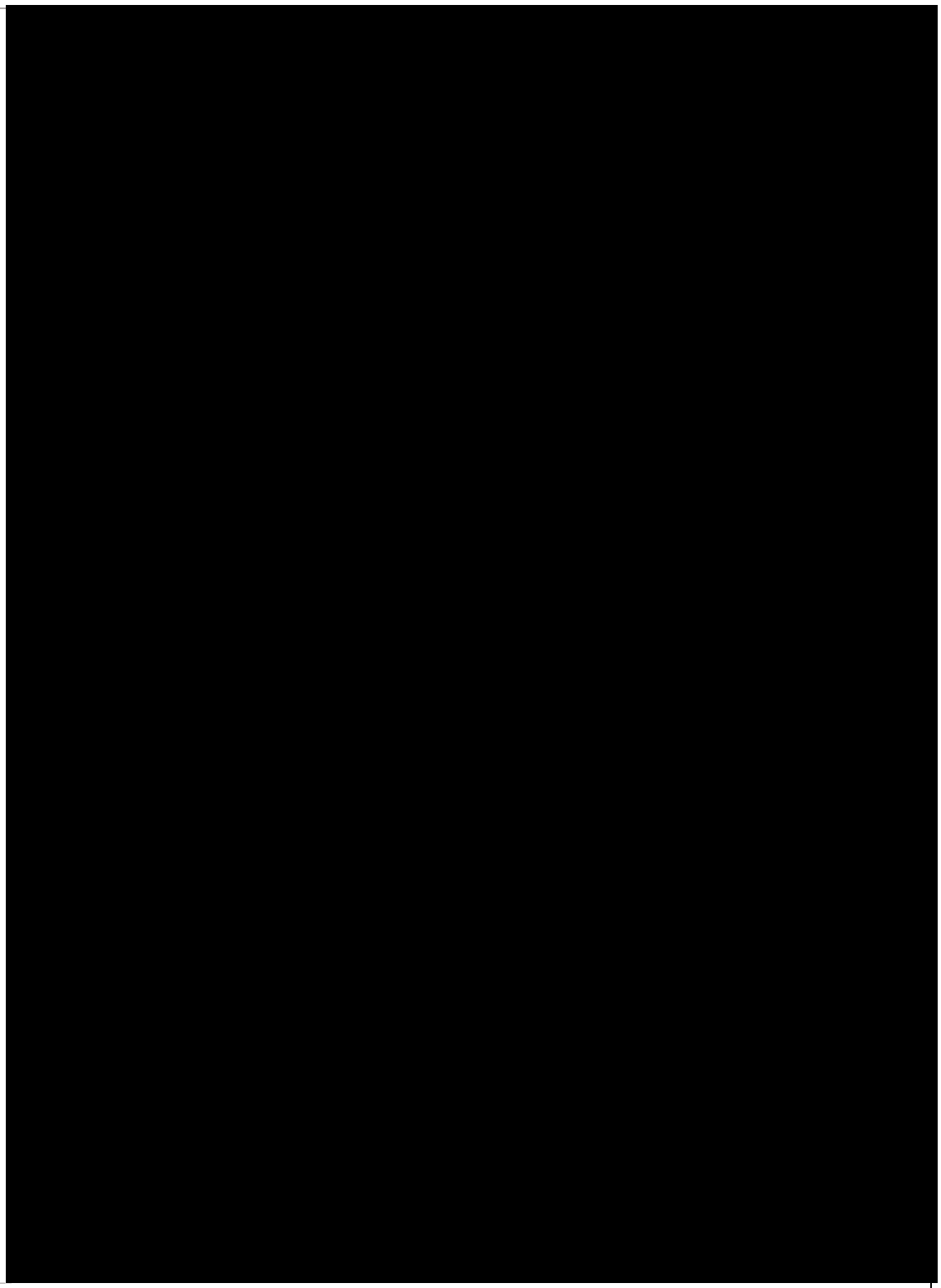
This response is accepted

9.4	IMP Management / Pharmacy (continued)
9.4.2	The chain of custody and accountability of the product was not always documented and reviewed by the pharmacy team. On receipt of the product, the person unpacking the shipment would tick off the kits that were received, but this was not signed or dated. They would then move this to a fridge, it was defined in the dispensing protocol this would be the clinical trials fridge, but a file note found in the pharmacy file also described the IMP being stored in a cold room, the actual location of each kit was not documented. The returned boxes post dosing were not logged back in on an accountability log and were stored until destruction and therefore there was no oversight of what had been returned to the site pharmacy. The site was provided with a reconciliation log from the IRT system by the sponsor and they discussed being provided this at the end of the study; however, there was no documented review of this in the pharmacy folder. There was no documented overall review of accountability performed by the pharmacy team at the end of the trial (including in the [redacted] pharmacy stock control system).

Inspected Organisation's Response – 01

Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	
MHRA Review – 01 This response is accepted	

9.4	**IMP Management / Pharmacy (continued)**
9.4.3	Time taken out of fridge was on the administration checklist record, but this was done in pharmacy initially and was not recorded on the prescription until 19 September 2019 (annotated to do so on dispensing instructions version [redacted]). As a result, it was not possible to verify that dosing was at least 30 minutes after removal for participants prior to this change, for example, participant [redacted] at [redacted] week visit where there was no record of time out of fridge on prescription.

Inspected Organisation's Response – 01

Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

9.5	**Medical Oversight by the Principal Investigator**
9.5.1	The initial confirmation of eligibility form signed at screening for two of the three participants was fully completed and signed by the PI despite the site not having all the information required to confirm eligibility at screening. Additionally, eligibility was confirmed at baseline without a documented review of the mean [redacted] score from the ePRO system: • For participant [redacted] laboratory results were reported on the [redacted] and reviewed by the PI on the [redacted], the eligibility checklist which contained exclusions for laboratory report parameters was signed by the PI on the [redacted] prior to the return of the laboratory results. • For participant [redacted] the ePRO printout for the [redacted] score was printed on the [redacted] despite the eligibility checklist at screening being fully completed on the [redacted] the ePRO printout had not been signed by a member of the trial team indicating review. It was acknowledged that a second eligibility checklist was signed by the PI on the [redacted] on the day of randomisation when all the data required to make the final eligibility decision was available. • For participant [redacted] screening was performed on the [redacted] and the eligibility checklist was completed on the same day to confirm all inclusion criteria were met and none of the exclusion criteria were met. However, the laboratory results were not provided to the site until the [redacted] • For participant [redacted] the ePRO data for the [redacted] scores was printed by a research nurse, and was filed, but this was on the day of baseline and had not been signed and dated to show review. It was acknowledged that the eligibility assessment was repeated and signed by the PI at baseline once all of the data was available.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	
MHRA Review - 01 This response is accepted	

9.5	**Medical Oversight by the Principal Investigator (continued)**
9.5.2	Only the PI had a role assigned in the IRT with the ability to unblind treatment allocation in the case of emergency. The Sub-Investigator was delegated this duty in the absence of the PI, but did not have this functionality allocated to them in the IRT.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

9.5	**Medical Oversight by the Principal Investigator (continued)**
9.5.3	There was no evidence of the review of safety information (provided by the sponsor) by the PI in the ISF for example safety line listings and completed CIOMS forms.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

9.6	**Record Keeping / Essential Documents**
9.6.1	A number of issues were noted with essential documents held in the ISF as follows: • Date of review and date checked were not completed on the R&D Project Checklist. • Principal Investigator GCP training and CV were not filed. • Freezer temperature logs for storage of samples and fridge temperature logs for IMP were not stored in the ISF/Pharmacy Files. (According to Trust SOP - [redacted]22 August 2024, these records would only be retained for 8 years, whereas the trial records would likely be required to be retained for a longer period and therefore copies may need to be retained in the ISF). • Documentation was added to ISF post archiving (see finding 9.1.1).

Inspected Organisation's Response – 01

Evaluation & Root Cause	[redacted]

Corrective Action(s)	[redacted]
Preventative Action(s)	

MHRA Review - 01

This response is accepted

9.6	**Record Keeping / Essential Documents (continued)**
9.6.2	A number of issues were noted with essential documents held in the pharmacy file: • There was no documentation in the pharmacy file to show all the required documentation to allow the trial to commence had been reviewed, the documentation was just filed. • [redacted] documented that relevant documents were removed and superseded for protocol version [redacted] on [redacted] however, this was before an email from the sponsor to implement the amendment on [redacted] (which was the date of R&D approval). It was stated during inspection that SOPs have been updated since to tighten this process. • None of the three dispensing protocols (version [redacted] version [redacted] and version [redacted]) made a reference to which trial protocol they were based upon. • Protocol version [redacted] was not in the pharmacy file. • IB version [redacted] was not filed in the pharmacy file, although a receipt form for this was signed by the Pharmacy Technician. • There were no receipt forms signed for IB versions [redacted] • Trial product handling manuals versions [redacted] in the pharmacy file were not marked as superseded. • There was an accountability record print out from IRT, but this was not dated or signed and no indication that this was the final accountability.

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]

	[redacted]
Corrective Action(s)	
Preventative Action(s)	

MHRA Review - 01

This response is accepted

9.7	**Training**
9.7.1	Staff performing validation of the prescription and dispensing of the IMP/Placebo and [redacted] were not adequately trained for this role as defined by the site's *SOP* [redacted] • From a limited sample of prescriptions reviewed, five prescriptions were seen to have been validated, and often dispensed by, members of staff who had not read the site dispensing protocol. • Training for two persons undertaking dispensing was not available (one who signed the dispensing protocol and one who did not).

Inspected Organisation's Response – 01	
Evaluation & Root Cause	[redacted]
Corrective Action(s)	
Preventative Action(s)	

	[redacted]

MHRA Review - 01

This response is accepted

Observations and Recommendations

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

CRF Data / Source Data

- Source document worksheets although version controlled, did not reference the protocol upon which they are based, and it was recommended that this is added.

IMP Management / Pharmacy

- It was observed that there was an inconsistent approach to the filing of safety information and IBs in the pharmacy file – only partial versions of these were often noted.
- Pharmacy produced dispensing protocols made no reference to which trial protocol version upon which they are based, and it was recommended that this is added.

Report Author:

[redacted]

GCP Inspector, Compliance Team 1, Standards and Compliance, MHRA

Report Reviewer:

[redacted]

[redacted] GCP Inspector, Compliance Team 1, Standards and Compliance, 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

Clinical Trial	Assessed			Comment
	Yes	Partial	No	
[redacted]	✓			If partial, then you must comment on areas of trial/TMF reviewed.
[redacted]		✓		
[redacted]	✓			

Activity	Assessed			Comment
	Yes	Partial	No	
Analytical Laboratory			✓	
Archiving	✓			
BE/ BA Activities			✓	
Clinical Pathology Laboratory			✓	
Clinical Trial Reporting	✓			
Computerised Systems			✓	
Contracts & Agreements	✓			
Data Management	✓			
eCRF / Diaries / IVRS			✓	
IMP Management			✓	
Medical Affairs			✓	
Monitoring	✓			

Pharmacovigilance	✓			
Project Management	✓			
Quality Assurance			✓	
Quality Systems	✓			
R&D Unit (Non-commercial only)			✓	
Regulatory Affairs	✓			
Statistical Analysis	✓			
Technical Facility (i.e. x-ray)			✓	
Training			✓	
Trial Master File/Essential Documents	✓			

Investigator Site 01

Activity	Assessed			Comment
	Yes	Partial	No	
Principal Investigator	✓			
Research Nurse	✓			
Sub-Investigator			✓	
Laboratory	✓			
IMP Management / Pharmacy	✓			
Consents	✓			
CRFs, eCRFs, Participant Diary, IVRS	✓			
Source Data	✓			
Site Master File	✓			
Technical Facility (i.e. x-ray)			✓	

Investigator Site 02

Activity	Assessed			Comment
	Yes	Partial	No	
Principal Investigator		✓		The PI was not available during the inspection due to a long-term absence; however, documentation related to the PI was reviewed.
Research Nurse	✓			
Sub-Investigator	✓			
Laboratory	✓			
IMP Management / Pharmacy	✓			
Consents	✓			
CRFs, eCRFs, Participant Diary, IVRS	✓			
Source Data	✓			
Site Master File	✓			
Technical Facility (i.e. x-ray)			✓	

Appendix II

Inspection Closing Statement

GCP INSPECTION STATEMENT

Inspection & Organisation Information	
Inspection Number	Insp GCP 43/32961802-0002
Purpose of Inspection	Statutory GCP Systems
Type of Inspection	Remote
Organisation Inspected	Leo Pharma
Organisation Address	LEO Pharma UK, Roxborough Way, Foundation Park, Building 5, Maidenhead. SL6 3UD
Organisation Type	Commercial Sponsor
Dates of Inspection	24 - 28 June 2024
Lead Inspector	[redacted] GCP Inspector
Accompanying Inspector(s)	[redacted] GCP Inspector [redacted] Pharmacovigilance Inspector
Date of Inspection Statement	04 September 2025

The organisation has provided corrective and preventative actions in response to the inspection report. These have been reviewed by the GCP Inspectorate and are considered acceptable. This inspection can be considered closed.

In summary:

There were no “critical” findings identified during this inspection.

There were two “major” findings identified during this inspection relating to:

- Data Integrity Control Processes
- Pharmacovigilance.

The factual matter contained in the GCP Inspection Report relates only to those things that the Inspection team saw and heard during the inspection process. The GCP Inspection

Report and Inspection Statement are not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined on this occasion.

Statement Issued by

[redacted]

GCP Inspector, Compliance Team 1, Standards and Compliance, MHRA