Medicines & Healthcare products
Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

ROCHE PRODUCTS LTD
INSPECTION REPORT

INSPECTION No:
INSP GCP 31/86087-0016

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Table of Contents

Inspection Summary

Inspection & Organisation Information	
Inspection Number	INSP GCP 31/86087-0016
Type and Purpose of Inspection	Statutory GCP Systems Inspection
Organisation Inspected	Roche Products Ltd
Organisation Address	Hexagon Place, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, United Kingdom. AL7 1TW
Organisation Type	Commercial Sponsor
Dates of Inspection	24 January 2020- Office Based Inspection (OBI) 27 -31 January 2020- On-site Inspection 13 and 21 May 2020- OBI 03 and 10 July 2020- OBI
Lead Inspector	[redacted] Inspector
Accompanying Inspector(s)	[redacted] Inspector [redacted] [redacted] Inspector [redacted] Inspector [redacted] Analytical Scientist (observer)
Date of Closing Meeting	31 January 2020- on site 10 July 2020- remote call following OBI
Inspection Report Date	31 July 2020

Clinical Trials Reviewed	
Protocol Reference and Title	[redacted] An Open-Label, Multicenter, Phase II Study to Evaluate the Therapeutic Activity of [redacted]
Sponsor Name & Address	[redacted]
EUDRACT Number	[redacted]
REC Reference Number	[redacted]
IMP Details	Product Name: [redacted]
Protocol Reference and Title	[redacted] A Phase Iii, Multicenter, Randomized, Double-

	Masked, Active Comparator Controlled Study to Evaluate the Efficacy and Safety of [redacted]
Sponsor Name & Address	[redacted]
EUDRACT Number	[redacted]
REC Ref Number	[redacted]
IMP Details	Product Name: [redacted]
Protocol Reference and Title	[redacted] An Open-Label, Multi-Center, Randomized, Dose-Escalation, Phase Ib Study to Evaluate Safety, Pharmacokinetics and Therapeutic Activity of [redacted]
Sponsor Name & Address	[redacted]
EUDRACT Number	[redacted]
REC Reference Number	[redacted]
IMP Details	Product Name: [redacted]
Protocol Reference and Title	[redacted]: A Phase Ib/II Study Evaluating the Safety, Tolerability and [redacted]
Sponsor Name & Address	[redacted]
EUDRACT Number	[redacted]
REC Reference Number	[redacted]
IMP Details	Product Name: [redacted]

	[redacted]

Background Information

This routine GCP inspection was conducted in two parts with an on-site element and office based inspection (OBI) element. The OBI performed post inspection was conducted to review outstanding document requests and follow up on queries raised during the onsite inspection. Whilst investigator site inspections were planned, these were cancelled due to the COVID-19 pandemic.

Roche were inspected in 2016 where a critical finding for Pharmacovigilance was identified (reference INSP GCP 31/86087-0012). The effectiveness of Corrective and Preventative Actions (CAPAs) from the previous Pharmacovigilance critical finding were reviewed during this inspection, which resulted in a subsequent critical finding for Pharmacovigilance.

Roche representatives met with the [redacted] Inspector, [redacted] ([redacted] Medical Assessor [redacted] MHRA Clinical Trials Unit (CTU)) and [redacted] Medical Assessor, CTU) on 06 March 2020 at MHRA offices. During this meeting the critical finding was discussed along with implementation of the Reference Safety Information (RSI) and regulatory requirements (in order to achieve compliance). The critical finding was submitted to the Inspection Action Group for GCP and GPvP (IAG2) and discussed at the meeting on 03 March 2020 where the actions required in the critical finding letter dated 31 March 2020 were agreed.

As part of the responses to the critical finding, Roche will be implementing the RSI following MHRA approval for all trials as an immediate action followed by a larger project to ensure that the RSI is implemented following all European Union (EU) Member State approvals as required by the Clinical Trials Facilitation Group Questions and Answers document on RSI. Roche have committed to providing updates to the MHRA GCP Inspectorate on the progress of this project. Roche will be required to submit quarterly reports on progress of CAPA implementation for the critical finding to the MHRA GCP Inspectorate. The due date for the first quarterly report will be confirmed by email.

Definitions of Findings

Critical:

a) Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that:

   i) the rights, safety or well-being of trial subjects either has been or has significant potential to be jeopardised, and/or
   ii) the clinical trial data are unreliable and/or
   iii) there are a number of Major non-compliances (defined in (d) and (e)) across areas of responsibility, indicating a systematic quality assurance failure, and/or

b) Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in (d) and (e))

c) Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations

Major:

d) A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, and/or

e) Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systematic quality assurance failure.

Other:

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

Reference Texts

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

Inspection Findings

Finding Number	Sponsor Site Findings
1.0 Critical Findings There was **one Critical finding** identified during this inspection relating to **Pharmacovigilance.** No responses are required to the finding as part of the report responses as these have been managed separately as part of the IAG2 process for critical findings.	
1.1	**Pharmacovigilance** *(1) A sponsor shall ensure that all relevant information about a suspected unexpected serious adverse reaction which occurs during the course of a clinical trial in the United Kingdom and is fatal or life-threatening is—* *(a) recorded; and* *(b) reported as soon as possible to—* *(i) the licensing authority,* *(ii) the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted, and* *(iii) the relevant ethics committee,* *and in any event not later than 7 days after the sponsor was first aware of the reaction.* *(2) A sponsor shall ensure that within 8 days of a report in accordance with paragraph (1)(b), any additional relevant information is sent to the persons or bodies listed in that paragraph.* *(3) A sponsor shall ensure that a suspected unexpected serious adverse reaction which occurs during the course of a clinical trial in the United Kingdom, other than those referred to in paragraph (1), is reported as soon as possible to—* *(a) the licensing authority;* *(b) the competent authorities of any EEA State, other than the United Kingdom, in which the* *trial is being conducted; and* *(c) the relevant ethics committee,* *and in any event not later than 15 days after the sponsor is first aware of the reaction.* **UK Statutory Instrument 2004/1031 (as amended), Part 5, Regulation 33.** *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 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).** *Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance* *with—* *(a) the protocol relating to that trial, as may be amended from time to time in accordance* *with regulations 22 to 25;*

(b) the terms of—
(i) the request for authorisation to conduct that trial,
(ii) the application for an ethics committee opinion in relation to that trial, and
(iii) any particulars or documents, other than the protocol, accompanying that request or that application,
as may be amended from time to time in accordance with regulations 22 to 25; and
(c) any conditions imposed by the licensing authority under regulation 18(2) or (6), 19(8),
20(5), 24(4) or Schedule 5.
UK Statutory Instrument 2004/1031 (as amended), Regulation 29.

CT Directive 2001/20/EC: Article 9 (8) and Article 18

Eudralex Volume 10 CT-1 (58 and 122) and CT-3 (55, 129 and 130)

Heads of Medicines Agency, Clinical Trial Facilitation Group (CTFG) 'Question and Answers: Reference Safety Information', November 2017.

Roche were inspected in 2013/14 (inspection reference: 31/86087-0011) and a critical and a major finding were identified for Pharmacovigilance. A subsequent inspection performed in 2016 (INSP GCP 31/86087-0012) also identified a critical finding for Pharmacovigilance which comprised of a number of issues, including the implementation of an updated RSI prior to Regulatory approval. During this 2020 inspection, the CAPA for the previous inspection was reviewed and it was identified that the RSI continued to be implemented without ensuring MHRA approval had been received. Whilst other aspects of the previous critical finding had been addressed (e.g. use of MedDRA Preferred Terms (PTs) only and updating of Investigator Brochures (IB) in line with CTFG guidance), this aspect had not been effectively remediated.

Whilst an impact assessment was performed of the CTFG RSI Q&A in November 2018 (a year after release), Roche stated that it did not agree with the common principles provided by CTFG 'Q11: it is strongly recommended to submit a substantial amendment application that includes an updated RSI to all Member States concerned at the same time' and 'Q12: the RSI in the new IB should be used as the basis for expectedness assessment for suspected SARS following approval of the new IB in all member states where the trial is ongoing'. The agreed approach between Pharmacovigilance and Quality Assurance (QA) was to continue with first EU member state approval plus 35 days at a product level and not ensuring the UK had approved the RSI at a trial level prior to implementation.

Due to the lack of effective CAPA (despite CTFG guidance becoming available to support compliance) and the identification of unreported Suspected Unexpected Serious Adverse Reactions (SUSARs) by the inspector, this finding has been graded as critical.

Roche were required to perform an impact assessment for the findings listed. The plan and methodology for the impact assessment was provided to the Lead Inspector for review. The requirements were as follows:

Pharmacovigilance Impact Assessment:
Scope and purpose of the RSI impact assessment:

- The purpose of the impact assessment is to clearly identify any under-reported or late reported SUSARs due to the findings highlighted below.
- A review of all Serious Adverse Reaction (SARs) expectedness assessments

(initial and follow-up) against the **MHRA approved RSI** at the time of occurrence (onset date) is required. This should be done to determine if there have been any UK-relevant SUSARs that have not been reported correctly.

- The impact assessment should include all clinical trials with a UK site/UK patients which were live since the start of 2017 (as a minimum) and all cases received since 01 January 2017.
- For findings in relation to life threatening and fatal events, the impact assessment should include a summary of how many events were not reported as SUSARs from 01 January 2017 until the RSI had been updated to remove these events as expected and approved by the MHRA. These events should be summarised and listed in the impact assessment. It will be discussed with MHRA CTU whether these will require reporting or not.
- All UK relevant cases for the above which have been received and processed should be included in the review.
- The impact assessment should include all IMPs used on the trial (e.g. Roche/ [redacted] and non-Roche products), including IMP comparator products.
- Cases should be unblinded as appropriate.
- Impact on Development Safety Update Reports (DSURs) should be assessed
- Impact assessment should be based on the CTFG Q&A RSI dated November 2017 which should be consulted when performing the impact assessment to ensure a comprehensive impact assessment is provided.

The impact assessment should be detailed within a clear and transparent report and should contain the following as a minimum;

- The methodology of how the investigation/impact assessment was conducted and what trial data was included.
- Clear outcome confirming the number and percentage of cases that have not undergone expedited reporting i.e. that have been under-reported. Summary of any actions taken to date in relation to any found under/over-reporting.
- Details/listing of each case not reported
- Impact on DSURs
- Details of quality control checks of the information
- Summary at the end of the report of any unreported SUSARs identified.
- List of all supporting source documents available for the report (to be provided upon request if needed)

Please refer to the current CTFG guidance and MHRA RSI blogs;
CTFG RSI Cover Note (March 2018) and Q&A Document (November 2017);

- http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_03_CTFG_RSI_Q_A_Covernote.pdf
- http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf
- https://mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/
- https://mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/

It was acknowledged that Roche had performed an impact assessment of limited scope post inspection for the products selected for review during the inspection (not at the request of the inspector). Roche stated that this identified seven unreported

	SUSARs across seven products reviewed in relation to use of an RSI prior to approval (0.04% of cases). However, this assessment was performed following the issues raised by the inspector and not through Roche's own quality assurance processes.
1.1.1	<u>Incorrect effective date of the RSI</u> The process for RSI implementation was not in accordance with Regulation 29 of UK SI 2004/1031, CT-3 and CT-1 as noted in the findings below. The process implemented by Roche determined the effective date of an RSI at the product level and not the trial level. An algorithm was utilised by Roche to determine the implementation date of the RSI which was the date of the first EU CTA approval (for any trial submission) plus 35 days. After this date, the RSI would be effective for all ongoing trials regardless of whether the RSI had been approved as a substantial amendment for any other trials. The following RSIs were implemented in the selected trials reviewed prior to MHRA approval (note this is not an exhaustive list): [redacted] IB version [redacted] was implemented on 21 August 2018, yet was not approved until 27 September 2018 for the [redacted] trial (this version removed life threatening events as expected in line with CTFG guidance) [redacted] IB version [redacted] made effective (implemented) 30 January 2019: • IB version [redacted] RSI was updated to include cough as an expected event. This was made effective prior to MHRA substantial amendment approval for the [redacted] and [redacted] trials (approved on 29 May 2019 and 18 April 2019 respectively). • [redacted] was added to IB version [redacted] as an expected event. IB version [redacted] was made effective prior to the approval of this version in the [redacted] trial (EudraCT: [redacted]) on 21 May 2019. As a result, an unreported SUSAR for this event occurring in the [redacted] trial was identified by the Inspector. For example, Adverse Event Report (AER) [redacted] (Site [redacted] Subject [redacted]), onset date 13 March 2019 was considered expected, when this should have been unexpected according to the approved RSI at the time of onset. • [redacted] was added to IB version [redacted] as an expected event and was implemented prior to MHRA approval for this version of the IB in the [redacted] (EudraCT [redacted]) trial on 30 May 2019. [redacted] site [redacted], subject [redacted] SAR of [redacted] (onset 10 March 2019) was considered expected when the case was initially received on 18 March 2019. This case was only considered unexpected once the event became fatal (version [redacted] received 17 April 2019). The SUSAR was reported to the MHRA on 28 April 2019 (26 days late). There was therefore a risk of underreporting of SUSARs due to implementation of an RSI prior to approval (and an example of confirmed under-reporting as noted above).
1.1.2	<u>Unreported SUSARs</u> There were examples of fatal and life-threatening (LT) events being considered

	expected despite the RSIs being updated to remove fatal/LT events. As a result, the following unreported SUSARs were identified by the inspector during the inspection (note all the examples below were Serious Adverse Reactions): [redacted] • [redacted]: trial ID[redacted] Site[redacted] Subject[redacted]), LT case of[redacted] onset 15 February 2019 was incorrectly assessed as expected upon receipt of the case (version[redacted] on 19 February 2019. On 16 July 2019 a follow-up was received (version[redacted]) and the PT changed to[redacted] but remained LT. This was again incorrectly assessed as expected. (LT events were removed in IB version[redacted] which was made effective by Roche on 02 January 2019). [redacted] • [redacted]: trial ID[redacted] Site[redacted], Subject[redacted]), LT[redacted] (onset 18 December 2019) was considered expected despite LT events being removed from[redacted] IB version[redacted] (effective date 08 October 2019). • [redacted]: trial ID[redacted] (Site ID[redacted] Subject[redacted] fatal SAR of[redacted] (onset date 16 August 2018). Fatal events were removed from IB version[redacted] which was approved by the MHRA on 10 May 2018 for the[redacted] and[redacted] trials. • [redacted]: a fatal event of[redacted] (onset date 28 July 2018) in trial[redacted] (Site[redacted] Subject[redacted] was considered expected despite fatal events being removed from the[redacted] RSI (IB[redacted] approved by the MHRA on 10 May 2018). It was stated that this was due to the Expected Preferred Terms List (EPTL) being incorrect; Therefore, the impact of this issue on the DSUR listings should also be addressed.
1.1.3	<u>Late Reporting of SUSARs</u> The following events had been reported late as SUSARs due to an incorrect expectedness assessment upon the event becoming Fatal/ LT. [redacted] • [redacted], received on 23 November 2017 (version[redacted]) as a SAR was considered expected. The event became fatal as per follow up (version[redacted] received on 27 November 2017. However, the case was not considered unexpected until version[redacted] of the case was received on 30 November 2017 (considered day 0). The SUSAR was reported to the MHRA on 06 December 2017 (2 days late). [redacted] • [redacted]: LT SAR of[redacted] was received on 10 April 2019 (onset date 07 April 2019). This event was incorrectly assessed as expected as version[redacted] of the IB removed LT events as expected (made effective 18 October 2018). A follow up was received on 15 April 2019 and a new event of[redacted] was added to the case. This was considered unexpected and related and was reported to the MHRA as a SUSAR on 29 April 2019 (12 days late). This demonstrated that the RSI was not being applied correctly to all cases upon initial receipt.

1.1.4	<u>DSUR Impact</u> For the DSUR, the RSI in effect at the start of the reporting period was used, however, this was not necessarily the RSI approved by all member states at the start of the reporting period as recommended by CTFG. As per finding 1.1.1, there was also the risk that the RSI used had not been approved by the MHRA at the start of the reporting period. As part of the response to this finding, the impact on the DSURs should be reviewed. It was agreed by the Lead Inspector and MHRA CTU Medical Assessors, that for the purpose of the impact assessment, the first MHRA approval for the RSI version (e.g. for whichever CTA approved first) would be sufficient to determine if the RSI in effect at the start of the reporting period was accurate.
1.1.5	<u>Late CTFG Q&A implementation for LT events</u> Organisations had until 01 January 2019 to comply with CTFG Q&A guidance. However, a review of Roche products and effective dates demonstrated that there were products where LT events were still considered expected beyond this date. For example, out of 30 IBs with SARs listed in the RSI, 22 /30 IBs became effective after 01 January 2019 (removing LT events), and 8/30 of these became effective after 01 June 2019. Examples included: • [redacted]) IB version[redacted] effective 30 December 2019. • [redacted] IB[redacted] effective 04 November 2019 • [redacted] IB version[redacted] effective 01 October 2019. Therefore, for these products there was the potential for under-reporting of SUSARs and non-compliance with the CTFG Q&A RSI.
1.1.6	<u>No validation of algorithm used to calculate RSI effective date</u> An algorithm was used to calculate the RSI effective date within the IB effectiveness Tracker (IBET). This was referred to by case processors to confirm the effectiveness dates for terms included in the Expected Preferred Terms list (EPTL). This was added to the IB Effectiveness tracker which would calculate when the terms were to be considered effective. However, at the time of the inspection, this algorithm had not been validated. During the inspection the organisation performed a QC of these dates and confirmed that the algorithm had been working correctly for 3 of the selected products ([redacted], [redacted] and [redacted] However, the algorithm had not been validated prior to implementation and use across Roche products.
1.1.7	<u>Lack of follow up of pregnancy reports</u> There was significant lack of follow up of pregnancy reports reviewed during this inspection. [redacted] (effective 31 July 2019) required pregnancy outcomes to be followed up and requests for outcomes should be made three times. However, the following cases were not followed up three times and at the time of the inspection were missing an outcome (not an exhaustive list):

	• [redacted]- received 11 January 2017- pregnancy outcome was ongoing. Follow up performed twice only. • [redacted]- received 12 August 2018- pregnancy outcome was ongoing. Follow up performed once in June 2019 only. The inspector identified 18 cases which had not been followed up and requested a reason from the organisation why they were missing an outcome (request [redacted] . It was confirmed that the lack of follow up was 'due to incorrect utilisation of the automatic output used to identify pregnancy outcomes requiring follow up'. Therefore, due to incorrect use of a spreadsheet report, cases had not been followed up as per procedure. This issue impacted 13 out of the 18 cases identified by the inspector. Furthermore, there was an incorrect classification of a pregnancy in the safety database. Case [redacted] was from a spontaneous/ literature report and not a clinical trial as it was listed. <u>As part of the response to this finding an impact assessment was required to cover all clinical trial pregnancy reports received since 01 January 2016. The impact on pregnancy reporting as Marketing Authorisation Holder (MAH) was also required to be investigated. Where the reports have been received from Investigator Initiated Trials (IITs), the contract should be reviewed for responsibilities for reporting and follow up of these pregnancies. The report was required to follow a similar format to the RSI impact assessment with:</u> • a clear methodology, • outcome including any impact to patient safety / risk: benefit of the IMP • listing of all pregnancy reports which had not been followed up as per the procedure and what actions were taken, reported outcome • summary of all supporting documents should also be available.

2.0 Major Findings There was **One Major finding** identified during this inspection relating to **Serious Breach Reporting.**	
2.1	**Serious Breach Reporting** *(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of—* *(a) the conditions and principles of good clinical practice in connection with that trial; or* *(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.* *(2) For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree—* *(a) the safety or physical or mental integrity of the subjects of the trial; or* *(b) the scientific value of the trial.".* **UK Statutory Instrument 2004/1031 (as amended), Regulation 29A.**

	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).**
2.1.1	There was a failure to identify a significant issue regarding the under-reporting of SUSARs identified by UK Drug Safety as a Serious Breach of GCP. As stated in [redacted] it was identified that there were SUSARS for [redacted] (5) and [redacted] (56) that had not been reported to the MHRA due to UK Drug Safety not being made aware of additional IMPs added to ongoing clinical trials. As a result, there was a lack of resource and oversight of the issue to ensure timely resolution. For example: • There was a delay in ensuring that all unreported SUSARs were reported in a timely manner following identification of the issue on 16 July 2019. The 56 unreported SUSARs for [redacted] were identified 01 August 2019 but not reported to the MHRA until 30 August 2019. • There was a further delay in ensuring that a CAPA action ([redacted]) was completed by the assigned due date. A retrospective review of closed trials was required to be performed and evidence of completion provided to local Quality Assurance (QA) by 30 October 2019, however this was not completed until 12 December 2019. During this investigation, a further 5 unreported SUSARs were reported on 04 Nov 2019 for [redacted] The MHRA Clinical Trials Unit (CTU) were informed of the issue on 16 September 2019, however this deviation did not follow Roche's procedure for Serious Breach identification and reporting and therefore there was no documented assessment by Roche of whether this constituted a Serious Breach of GCP. In the opinion of the inspector, these delays in identification and assessment of safety events did meet the criteria for a Serious Breach and should have been reported accordingly. . See also finding 3.1.3.
2.1.2	A Serious Breach of GCP was identified by the MHRA GCP inspectorate and CTU for the incorrect use of a Dear Investigator Letter (DIL) to change a trial from double-blind to open label without approval via a substantial amendment (reference [redacted] trial [redacted] EudraCT [redacted] raised prior to the inspection). Whilst this had been investigated by the organisation and CAPA had been accepted, this was another example of where an issue had not been identified as a Serious Breach by the organisation's own quality system.
2.1.3	SOP [redacted] (version [redacted] effective 26 June 2019) stated that Serious Breaches needed to be reported within 'seven calendar days after obtaining objective evidence of serious breach'. As a result, there were delays in reporting after the issue was identified. For example:

Serious Breach Reference	Date Issue Identified	Date of Decision That Issue Met Serious Breach Criteria	Date of Reporting
[redacted]	22 March 2016	17 August 2016	23 August 2016
[redacted]	25 May 2018	14 June 2018	15 June 2018
[redacted]	19 October 2018	30 October 2018	31 October 2018
[redacted]	18 February 2019	22 March 2019	26 March 2019

It is expected that within seven days of awareness of the potential Serious Breach, an assessment is made by the organisation to determine if the issue constitutes a Serious Breach of GCP. Where further information is required, an assessment should be made within those seven days of whether there is enough information available to report, whilst the investigation is completed. It appeared that the procedure required the investigation to be completed and evidence of a Serious Breach obtained prior to reporting which is not in line with regulatory requirements.

3.0 Other Findings

There were **two Other findings** identified during this inspection relating to **Urgent Safety Measures** and **Data Management**.

3.1	**Urgent Safety Measures** Note: this finding has not been graded as Major as it was demonstrated during the inspection that Roche had undertaken process improvements within this area following feedback from MHRA CTU on the incorrect use of DILs instead of USMs or Substantial Amendments.
3.1.1	It took more than a year to formalise a change to procedures to ensure the correct use of DILs within the quality system. [redacted] was updated following feedback from the MHRA of incorrect use of DILs (correspondence dated 05 February 2018, 22 February 2018 and 26 February 2018), where it was notified that DILs were being used instead of USMs. An investigation by QA was raised ([redacted] on 13 April 2018. Whilst actions were taken during this period to address the issues, the procedure was not updated and implemented until 21 March 2019 (version [redacted] .
3.1.2	Emails notifying sites of DILs for study [redacted] were not retained in order to reconstruct when they were first informed of the DIL. However, it was acknowledged that evidence of DIL receipt by the PI was available. For example: • Sites [redacted] and [redacted] emails informing the sites of the DIL for [redacted] (dated 24 January 2019) • Site [redacted] emails informing the site of the DIL for [redacted] (dated 20 July

	2018)
3.1.3	There was delayed follow up, lack of CAPA and escalation of a deviation at the [redacted] site ([redacted]) in study [redacted]. Two out of two subjects were not informed of important safety information and reconsented as required following an USM (e.g. DIL [redacted] regarding [redacted] dated 17 June 2019). Both subjects had subsequently died. The USM was provided to site via email on 25 June 2019 and the CRA raised the issue within follow up letters. However, the reason for the delay in sharing this information with these two patients was not provided by the site until January 2020 (after the inspection notification had been sent). For example; • The issue was identified for the first subject [redacted] (randomised 10 July 2019 and died on 13 September 2019) and was documented in follow up letters dated 02 September 2019, 30 October 2019, 02 December 2019 and 07 January 20. • The issue occurred again for subject [redacted] (randomised on 13 August 2019) who was not notified of the risk at enrolment. • Following the email sent to site on 20 January 2020 (4 days prior to inspection), it was identified that subject [redacted] had progressed and would not be re-consented. The patient died on 13 February 2020. Major protocol deviations were raised for both subjects yet there was a lack of timely action and CAPA from site. (Monitoring visit follow up letter sent to the site on 17 February 2020, was still requesting documentation of the issue and CAPA from site). Furthermore, this issue had not been escalated as a potential serious breach to QA for assessment and investigation. <u>As part of the response to this finding, confirmation is required on whether this finding impacts any other sites/ trials.</u>
3.2	**Data Management**
3.2.1	The process for IMP reconciliation between the clinical database and the Interactive Response Technology (IRT) system was not described within the data management quality system.

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

Observations and Recommendations
Project Management • The cover sheet provided in response to document request [redacted] stated 'Protocols are not shared with external laboratories [biomarker exploratory labs] unless specifically requested, with the exception of laboratories performing tests required for eligibility assessments'. It is recommended that the clinical trial protocol and any approved subsequent amendments are supplied to any external laboratory working on the trial as critical information may exist which could impact on the analysis of clinical trial samples. Examples have been seen in the past where the protocol has changed the preservative to be used in blood sampling tubes to something different than that used for the validated method, where concomitant

medication was permitted which could interfere with the assay or the protocol added additional visits which the laboratory was not aware of leading to the delayed analysis of samples.

Report Author and Reviewer

Report Author:

[redacted] Inspector, MHRA

Report Reviewer:

[redacted] Inspector, MHRA

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

Appendix I Summary of Activities

Inspected Organisation				
Clinical Trial	Assessed			Comment
	Yes	Partial	No	
[redacted]		✓		Urgent Safety Measures and Dear Investigator Letters
[redacted]		✓		Monitoring, Regulatory Affairs
[redacted]		✓		Urgent Safety Measures and Dear Investigator Letters
[redacted]			✓	TMF not reviewed during the inspection

Inspected Organisation				
Activity	Assessed			Comment
	Yes	Partial	No	
Analytical Laboratory			✓	
Archiving			✓	
BE/ BA activities			✓	
Clinical Pathology Laboratory			✓	
Clinical Trial Reporting			✓	
Computerised Systems			✓	
Contracts & Agreements		✓		
Data Management		✓		IXRS provision and use
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		✓		Statistical involvement in statistical monitoring approaches
Technical Facility (i.e. x-ray)			✓	
Training			✓	
Trial Master File/Essential Documents	✓			
Other			✓	