



# PHARMACOVIGILANCE INSPECTION REPORT

**Pharmacovigilance System Name:** Bayer AG Pharmaceuticals and  
Consumer Health

**MHRA Inspection Number:** Insp GPvP 10/16303918-0002

## Table of Contents

ABBREVIATIONS .....	3
SECTION A: INSPECTION REPORT SUMMARY .....	5
SECTION B: BACKGROUND AND SCOPE .....	7
B.1 Background information.....	7
B.2 Scope of the inspection .....	8
B.3 Documents submitted prior to the inspection .....	8
B.4 Conduct of the inspection .....	8
SECTION C: INSPECTION FINDINGS.....	10
C.1 Summary of significant changes and action taken since the last inspection.....	10
C.2 Definitions of inspection finding gradings.....	10
C.3 Guidance for responding to inspection findings .....	11
C.4 Inspection findings.....	12
C.4.1 Critical findings .....	12
CR.1 Conduct of post-authorisation safety studies .....	13
C.4.2 Major findings .....	27
MA.1 General obligations of the MAH regarding post-authorisation safety studies 27	
MA.2 Management and reporting of adverse drug reactions from PASS .....	30
MA.3 MAH oversight and governance of PASS .....	48
C.4.3 Minor findings .....	52
MI.1 Conduct of post-authorisation safety studies .....	52
C.4.4 Comments .....	56
SECTION D: CONCLUSIONS AND RECOMMENDATIONS .....	57
D.1 Conclusions.....	57
D.2 Recommendations .....	57
APPENDIX I REFERENCE TEXTS .....	58
APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN.....	59
APPENDIX III EURAS-LCS12 INFORMED CONSENT .....	70

## ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report

PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

**SECTION A: INSPECTION REPORT SUMMARY**

Section  
40 and  
43

<b>Inspection type:</b>	Statutory National Inspection
<b>System(s) inspected:</b>	Bayer AG Pharmaceuticals and Consumer Health PSMF [REDACTED]
<b>Site(s) of inspection:</b>	<p><u>Bayer:</u>          400 South Oak Way,          Green Park, Reading,          Berkshire, RG2 6AD</p> <p>[REDACTED] Field organisation for [REDACTED]          [REDACTED]</p> <p><u>REASSURE study investigator site:</u>          The Leeds Teaching Hospitals NHS Trust,          St James's University Hospital,          Beckett Street,          Leeds, LS9 7TF</p>
<b>Main site contact:</b>	[REDACTED] EU QPPV QPPV Office Building M084, 3/302 13353 Berlin, Germany [REDACTED]
<b>Date(s) of inspection:</b>	<ul style="list-style-type: none"> <li>• 3 – 6 September 2019 (Bayer)</li> <li>• 25 October 2019 [REDACTED]</li> <li>• 11 – 12 November 2019 (St James's University Hospital)</li> </ul>
<b>Lead Inspector:</b>	[REDACTED]
<b>Accompanying Inspector(s):</b>	<p><u>Bayer:</u>          [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<b>Previous inspection date(s):</b>	<ul style="list-style-type: none"> <li>• 19 – 23 March 2018 (Bayer Pharma and Consumer Health)</li> <li>• 6 – 8 October 2009 (Bayer Pharma)</li> <li>• 2 – 5 November 2009 (Bayer Consumer Health)</li> <li>• 10 – 13 March 2008 (Bayer Pharma)</li> </ul>

Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements
Studies selected to provide system examples:	<ul style="list-style-type: none"> <li>• [REDACTED] Agent in non-intervention Safety Study in mCRPC population for [REDACTED]</li> <li>• [REDACTED] European Active Surveillance Study of [REDACTED]</li> </ul>
Name and location of EU QPPV:	[REDACTED]
Global PV database (in use at the time of the inspection):	Argus Safety (version 8.1.2.3)
Key service provider(s):	<ul style="list-style-type: none"> <li>• [REDACTED]             <ul style="list-style-type: none"> <li>○ Berlin Center for Epidemiology &amp; Health Research ('Zentrum für Epidemiologie &amp; Gesundheitsforschung Berlin') (ZEG)</li> <li>○ Mediscys, UK field organisation</li> </ul> </li> <li>• REASSURE study: [REDACTED]</li> </ul>
Inspection finding summary:	1 Critical finding 3 Major findings 1 Minor finding
Date of first issue of report to MAH:	16 December 2019
Deadline for submission of responses by MAH:	Initial: 31 January 2020 Follow-up: 26 February 2020
Date(s) of receipt of responses from MAH:	Initial: 31 January 2020 Follow-up: 26 February 2020
Date of final version of report:	2 March 2020
Report author:	[REDACTED]

Section 40 and 43

## SECTION B: BACKGROUND AND SCOPE

### B.1 Background information

Bayer AG Pharmaceuticals and Consumer Health (hereafter Bayer) was selected for inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines relevant to the planning, conduct and reporting of post-authorisation safety studies (PASS). In particular, reference was made to Regulation 726/2004/EC as amended, Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules.

A list of reference texts is provided at [Appendix I](#).

Bayer is a global pharmaceutical company with divisions responsible for pharmaceuticals, consumer health, crop science and animal health. The pharmaceutical and consumer health product portfolios cover a wide range of therapeutic areas and are covered by a single PSMF (MFL1282). The organisation has seven global PV centres, over 70 local PV sites and four outsourced centres.

At the previous inspection in March 2018, there were a number of documents which were requested by the inspectors prior to and during the inspection which were found to be incomplete and/or inaccurate. This resulted in multiple requests for the same information and therefore a delay in inspection conduct. Many of these delays were in relation to PASS documents which hindered the review of this area during the inspection. Therefore, it was recommended that this topic, along with quality management aspects associated with this topic, were revisited during a future inspection. For this reason, plus the fact that Bayer has a relatively large number of EU-relevant PASS ongoing or completed in the last two years, this inspection focused primarily on this topic. The following two studies were selected for review by the inspectors.

#### Jaydess® (levonorgestrel) study 16470: The European Active Surveillance Study of LCS-12:

The European Active Surveillance Study of LCS-12 (EURAS-LCS12) for Bayer's Jaydess intrauterine contraceptive system (LCS-12) was a prospective controlled epidemiological study to investigate the risk of contraceptive failure, ectopic pregnancy and pelvic inflammatory disease (PID) associated with the use of LCS-12 and established intrauterine devices (IUDs) (Mirena, copper IUDs).

The EURAS-LCS12 study had been imposed as a condition of the Jaydess marketing authorisation by EU national competent authorities and therefore was classified as a category 1 study in the RMP. The current version of the protocol (v2.5) was dated 16-Apr-2018.

The EURAS-LCS12 study was designed to collect data on clinical outcomes of IUD use, as well as drug utilisation of LCS-12, Mirena and copper IUDs. Data was collected via a baseline questionnaire completed by the participating physician and the study participant, and follow-up questionnaires completed by the study participant at 6 weeks, 6, 12, 24 and 36 months after study entry.

The primary clinical outcome of interest for the short- and long-term follow-up was unintended pregnancy. Secondary clinical outcomes of interest were ectopic pregnancy, PID

Section  
43

and uterine perforations. Self-reported events concerning the primary and secondary clinical outcomes of interest underwent a validation process coordinated by the international coordinating centre (ZEG). In the UK, the recruitment of healthcare professionals into the study, enrolment of patients, management of baseline and follow-up questionnaires, and coordination of follow-up activities was managed by the UK field organisation, which was a third-party organisation called [REDACTED]

Xofigo® (Radium-223) study 16913: REASSURE:

The "Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for longteRm Evaluation" (REASSURE) study was an international, prospective, observational, single arm cohort study designed to assess the incidence of second primary malignancies among patients with metastatic Castration Resistant Prostate Cancer (mCRPC) receiving Radium-223 in routine clinical practice. In addition, safety, pain, and overall survival were to be assessed.

The REASSURE study was required as per the EU RMP and therefore was classified as a category 3 study. The current version of the protocol (v5.0) was dated 20-Aug-2018.

The study was conducted by Bayer AG with support of a contract research organisation (CRO) (Kantar Health). There were nine investigational sites in the UK and St James's University Hospital was selected for an inspection site visit.

## B.2 Scope of the inspection

The inspection included a review of the conduct of, and interim reporting from, the REASSURE and EURAS-LCS12 studies and was performed at Bayer AG Pharmaceuticals and Consumer Health's offices in Reading, Berkshire, with additional site visits to MedicyS (UK field organisation for EURAS-LCS12 study) and St James's University Hospital (REASSURE investigator site).

The inspection was performed using interviews and document review (including outputs from the global safety database, the EURAS-LCS12 study databases and from the REASSURE electronic data capture system). The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plans (attached as [Appendix II](#)).

## B.3 Documents submitted prior to the inspection

The company submitted a PSMF (version 25.0, dated 15-Jul-2019) to assist with inspection planning and preparation. Specific additional documents were also requested by the lead inspector and provided by the company prior to the inspection; the detail of these requests is contained within document request sheets A, B, C and D.

## B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. Minor amendments to the Inspection Plan that occurred during the inspection are highlighted using italic text in Appendix II.

Interim closing meetings were held to provide preliminary feedback regarding the inspection findings at the following sites:



- Bayer's office in Reading on 06-Sep-2019
- [REDACTED] on 25-Oct-2019
- St James's University Hospital on 12-Nov-2019

A final closing meeting was conducted via teleconference on 05-Dec-2019 in order to summarise the overall outcome of the inspection.

A list of the personnel who attended the closing meetings is contained in the Closing Meeting Attendance Records, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

## SECTION C: INSPECTION FINDINGS

### C.1 Summary of significant changes and action taken since the last inspection

Since the previous MHRA GPvP inspection in March 2018, the company had made the following significant changes to the pharmacovigilance system:

- The EU QPPV had changed from [REDACTED] in August 2018.
- The Argus safety database had been upgraded in November 2018 to implement ICH E2B(R3).

### C.2 Definitions of inspection finding gradings

**Critical (CR):** a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

**Major (MA):** a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

**Minor (MI):** a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

**Comment:** the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

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.

Findings from any inspection which are graded as critical or major will be shared with the EMA, other EU competent authorities and the European Commission.

Section  
43

### C.3 Guidance for responding to inspection findings

Responses to inspection findings should be clear, concise and include proposed actions to address both the identified deficiency and the root cause of the deficiency. Consideration should also be given to identifying and preventing other potential similar deficiencies within the pharmacovigilance system.

Responses should be entered directly into the table(s) in section C.4. The following text is intended as guidance when considering the information that should be entered into each of the fields within the table(s). 'Not applicable' should be entered into the relevant field if the requested information is not appropriate for the finding in question.

<b>Root Cause Analysis</b> Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.
<b>Further Assessment</b> Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.
<b>Corrective Action(s)</b> Detail the action(s) taken / proposed to correct the identified deficiency.
<b>Preventative Action(s)</b> Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.
<b>Deliverable(s)</b> Detail the specific <u>outputs</u> from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
<b>Due Date(s)</b> Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Further information relating to inspection responses can be found under 'Inspection outcomes' at: <https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp>

## C.4 Inspection findings

### C.4.1 Critical findings

A PASS is defined in Directive 2001/83/EC as amended as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Section  
43

The [REDACTED] included the REASSURE PASS as a category 3 study in Part III (Pharmacovigilance Plan). In Part III it stated *“The REASSURE study is to evaluate the short- and long-term safety profile of Radium-223 dichloride and will assess the safety and tolerability of Radium-223 dichloride and the risk of developing second primary cancers among castration resistant prostate cancer patients receiving Radium-223 dichloride in the routine clinical practice setting. In addition, overall survival and pain-related data will be collected. The study will specifically address the following important potential risks: late bone marrow toxicity, MDS/AML, bone sarcoma, second primary malignancies (other than MDS/AML and bone sarcoma), osteonecrosis of the jaw.”*

The study population consisted of CRPC patients with bone metastasis who were treated with Radium-223. In accordance with the protocol, information on the patients, outcomes, and other variables was to be recorded using Electronic Data Capture (EDC) by the treating physician (medical oncologist, urologist) or designated medical person at different time points.

- At baseline, patients' demographic variables and information about disease characteristics were to be collected from the treating physician (including date of diagnosis, prior treatment, tumour staging information, co-morbidities, prior medication, and concomitant medication), before the first Radium-223 administration.
- For each treatment cycle, treatment information and potential outcomes was to be recorded in the EDC system by the physician or designated medical person. Paper patient questionnaires on pain measurements were also collected at each treatment cycle and entered into the database by the CRO.
- After end of treatment, patient outcome information (second primary malignancy, other safety information, disease progression and overall survival) was to be gathered at regular intervals (approximately 3 and 6 months, 12 months and thereafter yearly for a maximum of 7 years after the last administration of Radium-223) from the patient's electronic health record or during follow-up visits by the recruiting physician or designated person within the treatment team.

Section  
43

St James's University Hospital in Leeds was one of the UK study sites and was selected for an inspection site visit. The REASSURE study opened at this site on 12-Feb-2015 and the first patient was recruited on 08-Apr-2015. In total, [REDACTED] patients had been enrolled at this site. Significant breaches of the CHMP-approved REASSURE study protocol were identified during the visit to the investigational site at St James's University Hospital, which impacted upon the collection of data related to the primary and secondary study end points. As a result of these findings, there was no assurance that the data collected from this site could contribute meaningfully to the overall study objectives. It should be noted that an interim study report was prepared on 11-May-2017 and submitted to the EMA on 14-Jul-2017 (period covered by the report was 20-Aug-2014 to 22-Sep-2016), therefore, the deficiencies noted during this inspection will have impacted to some extent upon the interim analysis

report. A second interim analysis report is due to be submitted at the end of 2019 according to the Xofigo RMP. Consequently, a critical finding for breach of the approved study protocol is reported.

#### CR.1 Conduct of post-authorisation safety studies

##### Requirements:

Regulation (EC) No. 726/2004 as amended, Article 21(1)

Directive 2001/83/EC as amended, Article 104(3)(c)

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance

*Regulation 182(2) "The holder must (as part of its pharmacovigilance system)--  
(c) operate a risk management system for the product in accordance with the risk management plan (if any) for the product (subject to regulation 183);"*

##### Finding CR.1 a)

Information concerning the outcomes of interest (second primary malignancy, other safety information, disease progression and overall survival) had not been collected during the long-term follow-up phase for the patients enrolled in the REASSURE study at the St James's University Hospital site. This was evidenced by the fact that no entries in the electronic Case Report Form (eCRF) had been made for any of the patients at this site at a timepoint greater than 6 months from the last administration of Radium-223. In the protocol, long-term follow-up was defined as the period after 6 months up to 7 years from the last administration of Radium-223.

The study protocol (v5.0) section 9.3 (Variables) stated *"The follow-up will take place at approximately 3M, 6M, 12M, 24M, 36M, 48M, 60M, 72M, and 84M from the last administration of Radium-223 to collect information regarding the outcomes of interest (e.g., second primary malignancy, other information on safety, and OS)."*

Specifically, the defined data variables to be collected from the patients' electronic health records (EHR) during the long-term follow-up phase of the study were as follows:

- Medication (subsequent to Radium-223 administration)
- Anti-cancer therapy (subsequent to Radium-223 administration)
- Adverse events (drug related serious adverse events, all SAEs of second primary malignancies, and AEs of bone fractures and bone associated events)
- Laboratory parameters (for patients with a platelet count or WBC less than the lower limit of normal at 6 months post last dose of Radium- 223 being followed until resolution at a frequency based on local clinical practice)
- Progression (only the first progression post treatment needs to be collected)

Of the [REDACTED] enrolled patients at this site, three were selected by the inspectors and a sample of their EHRs were reviewed. The following examples of potentially protocol-relevant data variables were identified which had not been recorded in the EDC:

Patient [REDACTED] (last treatment date [REDACTED] Aug-2015, patient died on [REDACTED] Feb-2018):

- i. Clinic letters in the EHRs dated in 2017 indicated potential disease progression\* as the patient had received palliative radiotherapy.

Section  
43

- ii. The patient died on [REDACTED] however this was not entered into the EDC until 01-Nov-2019.

Patient [REDACTED] (last treatment date [REDACTED]-Feb-2016, patient died on [REDACTED] Mar-2018):

- iii. A clinic letter dated [REDACTED] May-2016 stated that the patient's prostate specific antigen (PSA) result had increased to over 1800 ng/mL and the physician had stated "*I don't think [REDACTED] has responded to the Radium-223 treatment*". In addition, a letter dated 15-Jun-2016 indicated that the patient had been started on oral dexamethasone 2mg. However, there was no record of disease progression in the EDC and the dexamethasone had not been recorded in the 'Syst. Anti-cancer' page of the CRF.
- iv. There were multiple other letters in the EHRs dating from the time of the last administration of Radium-223 to [REDACTED] Oct-2017 that included information on adverse events (e.g. blisters on roof of mouth), subsequent anti-cancer therapies and disease progression.
- v. The patient died on [REDACTED] Mar-2018, however this was not entered into the EDC until 01-Nov-2019.

Patient [REDACTED] (last treatment date [REDACTED]-Apr-2016, patient died on [REDACTED] Jan-2018):

- vi. There were examples of adverse events reported during the long-term follow-up phase that had not been recorded in the EDC (see finding CR.1 d)).
- vii. The patient died on [REDACTED] Jan-2018, however this was not entered into the EDC until 01-Nov-2019.

-----  
**Background notes:**

1. \* According to the Principal Investigator (PI), assessment of disease progression should be made by clinically trained staff and multiple factors should be considered, such as:
- PSA levels
  - Need for further anti-cancer therapy
  - Use of palliative radiotherapy to relieve symptoms
  - Overall clinical picture

In the CRF page entitled 'Progression post first dose', the following options are available for site staff to select when recording disease progression:

*"How was progression assessed?"*

- *Symptomatic Skeletal Event*  
*(Evidenced by either use of EBRT to relieve skeletal symptoms, new pathological bone fractures (vertebral or non-vertebral), occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.)*
- *Prostate Specific Antigen*
- *Radiological Imaging, please specify*
  - *progression in bone?*
  - *progression in lymph nodes?*
  - *progression in visceral organs?*
- *Unequivocal clinical progression*
- *Other, please specify"*

2. The site level performance reports generated from the EDC on 06-Sep-2019 during the inspection of the MAH (inspection request R1) indicated a high 'lost to follow-up' rate for the St James's University Hospital site [REDACTED] enrolled patients). This may have been an indicator to the MAH that this site was not adhering to the study protocol with

regards to recording outcome information in the long-term follow-up phase.

**Root Cause Analysis**

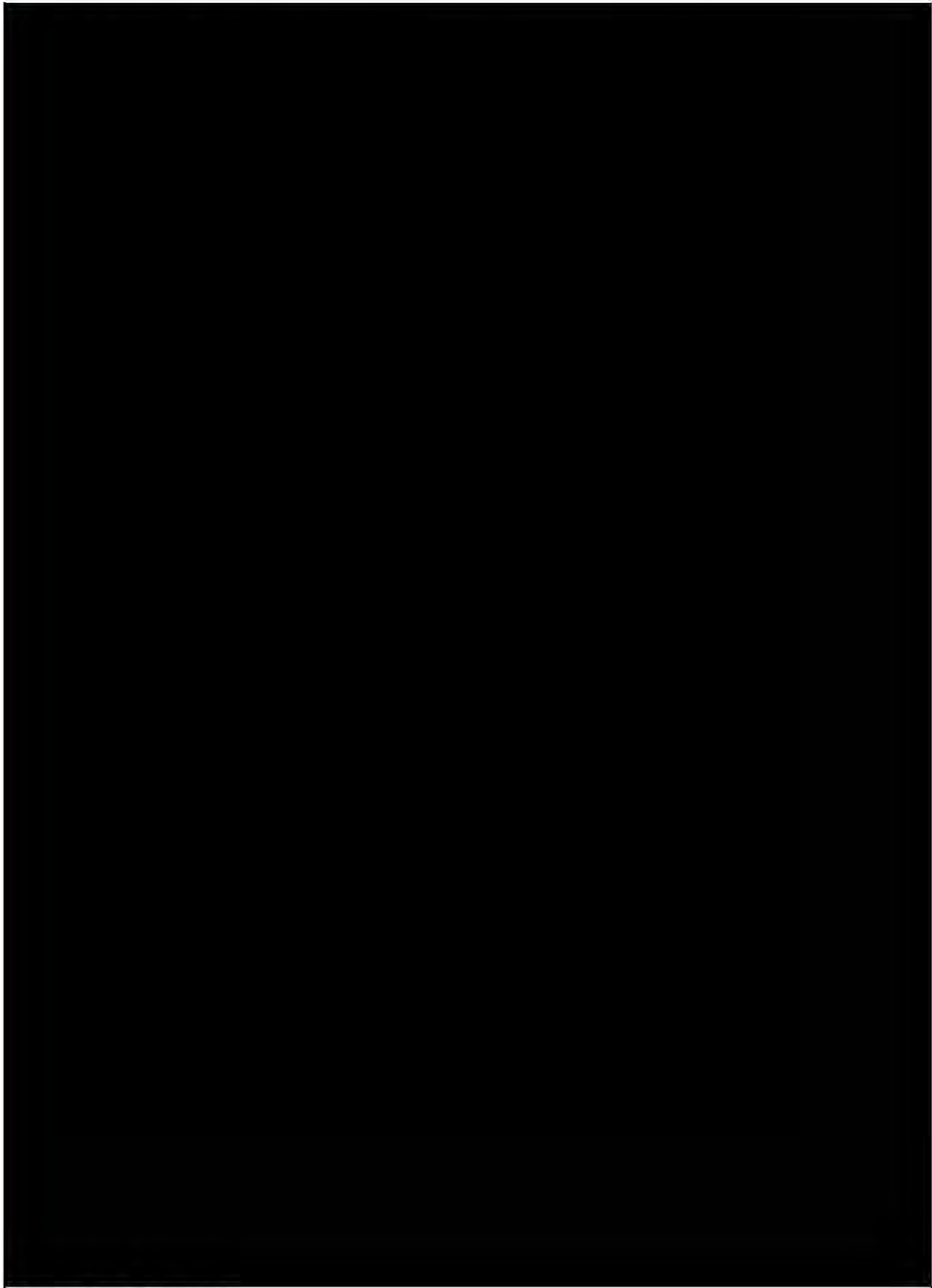


**Further Assessment**

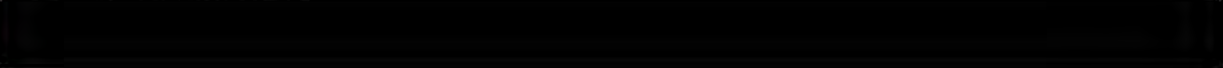


Section  
43

Section  
43

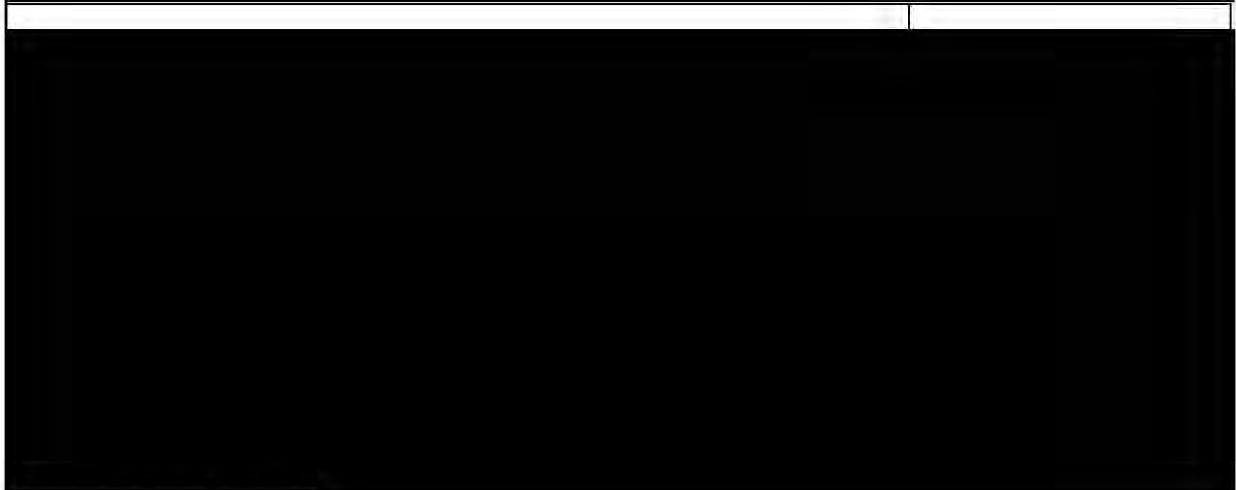
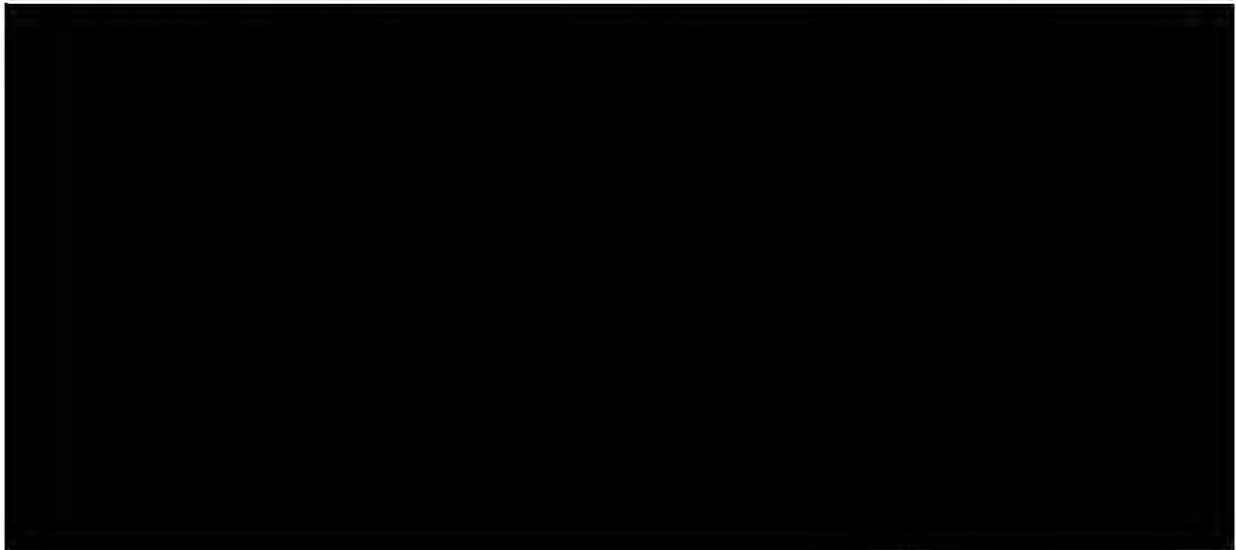


**Corrective Action(s)**

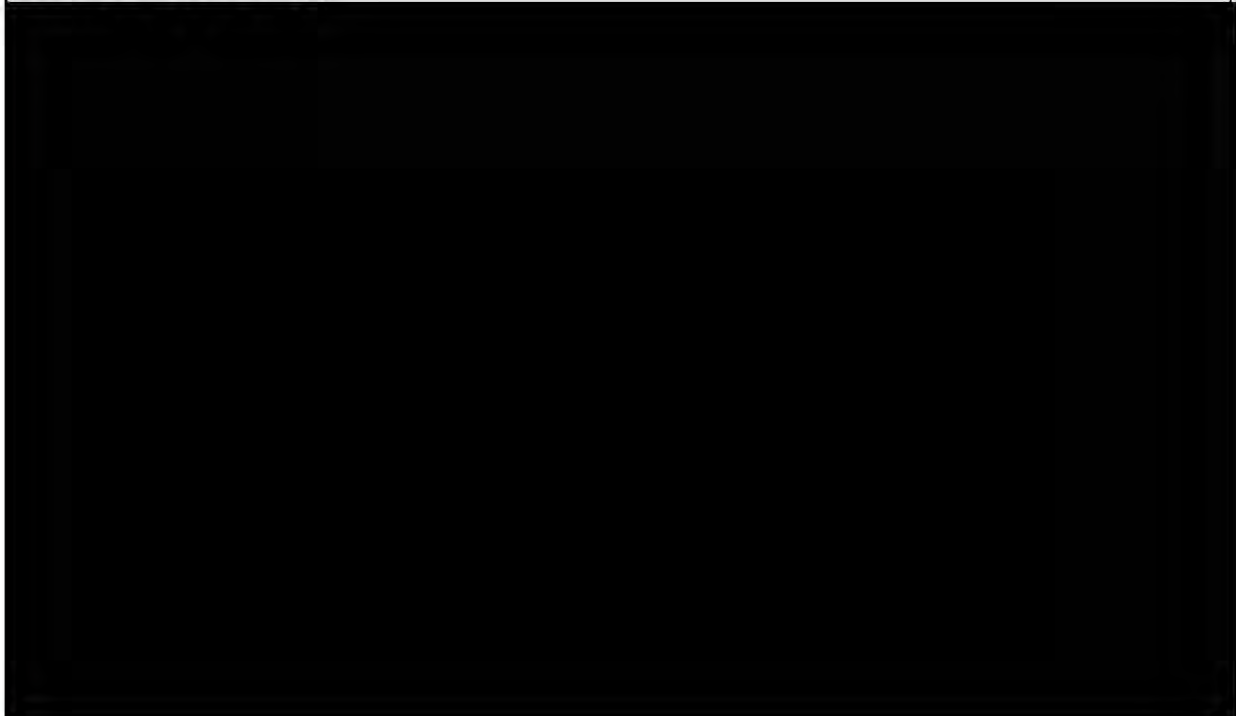




Section  
43



**Preventative Action(s)**



Section  
43

Deliverable(s)	Due Date(s)

**Finding CR.1 b)**

Information concerning the outcomes of interest had not been collected at the '6 Months FU post last dose' visit for ■■■ of the ■■■ enrolled patients at the St James's University Hospital site. This was evidenced by the fact that no entries in the eCRF had been made for these ■■■ patients at a timepoint up to 6 months from the last administration of Radium-223.

The defined data variables to be collected from the patients' EHRs at the '6 Months FU post last dose' visit were as follows:

- **Medication** (subsequent to Radium-223 administration)
- **Anti-cancer therapy** (subsequent to Radium-223 administration)
- **Adverse events** (drug related serious adverse events, all SAEs of second primary malignancies, AEs of bone fractures and bone associated events and all post treatment grade 3/4 haematological toxicities up to 6 months after the last administration of Radium-223)
- **Laboratory parameters** (for patients with a platelet count or WBC less than the lower limit of normal at 6 months post last dose of Radium- 223 being followed until resolution at a frequency based on local clinical practice)
- **Progression** (only the first progression post treatment needs to be collected)
- **Pain measurements** (patient questionnaire)

In addition, it was noted that the protocol referenced a 3-month follow-up in the text in section 9.3 but this was not reflected in Table 2 (Tabulated overview on variables collected during the study) in the same section of the protocol.

Section  
43

<b>Root Cause Analysis</b>	
[Redacted]	
<b>Further Assessment</b>	
[Redacted]	
<b>Corrective Action(s)</b>	
[Redacted]	
<b>Deliverable(s)</b>	<b>Due Date(s)</b>
[Redacted]	[Redacted]
<b>Preventative Action(s)</b>	
[Redacted]	
<b>Deliverable(s)</b>	<b>Due Date(s)</b>
[Redacted]	[Redacted]

<b>Finding CR.1 c)</b>
<p>There were examples of where data entry into the EDC was inaccurate or incomplete:</p> <p><u>Patient</u> [Redacted]</p> <ul style="list-style-type: none"><li>i. There were laboratory results* from a test panel performed on [Redacted] that had not been recorded in the 'Laboratory tests' page of the CRF, despite the fact that other parameters from the same test panel had been entered. Specifically, the missing parameters and results were as follows: [Redacted]</li><li>ii. The laboratory results from the test panels performed on [Redacted] - [Redacted] (after treatment visits 1, 2 and 3 respectively) were not recorded in the EDC.</li><li>iii. There were no source documents available in the site file or in the EHRs to verify the entries made in the 'Treatment' page of the CRF regarding Radium-223 injection date, time of injection and actual injected radioactivity.</li><li>iv. The prostate cancer stage at initial diagnosis was recorded as [Redacted] in the EDC. However, review of the EHRs, along with the advice of the PI, indicated that the prostate cancer was [Redacted] at initial diagnosis. There appeared to be confusion by the data entry staff between 'stage IIB' cancer versus 'T2b' which related to the size of the tumour. It is evident that the decision regarding cancer staging should be made by a clinically trained person, but this was not the case at this site.</li></ul> <p><u>Patient</u> [Redacted]</p>

Section  
43

- v. A clinic letter dated [REDACTED] stated that the patient's current anti-cancer therapy was [REDACTED]. However, this had not been recorded in the 'Syst. Anti-cancer' page of the CRF for the baseline visit, which was on [REDACTED].
- vi. There was reference in the EHRs to the medications that the patient had been taking prior to enrolling in the study. However, these had not been recorded in the 'Medication' page of the CRF. Medications included:



- vii. There were no source documents available in the site file or in the EHRs to verify the entries made in the 'Treatment' page of the CRF regarding Radium-223 injection date, time of injection and actual injected radioactivity.
- viii. There were laboratory results recorded in an annotation in the EHR dated [REDACTED] (after treatment visit 2) that had not been recorded in the EDC.
- ix. There were laboratory results from a test panel performed on [REDACTED] (after treatment visit 3) that had not been recorded in the EDC.
- x. There were laboratory results from a test panel performed on [REDACTED] (after treatment visit 4) that had not been recorded in the EDC.
- xi. There were laboratory results from a test panel performed on [REDACTED] (after treatment visit 5) that had not been recorded in the EDC.
- xii. The patient experienced nausea on [REDACTED] and this was entered into the EDC. However, the concomitant medications taken for the nausea, cyclizine and haloperidol, were not entered.

**Patient [REDACTED]:**

- xiii. The 'Syst. Anti-cancer' page of the CRF for the baseline visit had an entry recording that the patient had started [REDACTED] therapy in [REDACTED]. However, an annotation in the EHRs dated [REDACTED] indicated that the patient was already on [REDACTED] at that time.
- xiv. There were no source documents available in the site file or in the EHRs to verify the entries made in the 'Treatment' page of the CRF regarding Radium-223 injection date, time of injection and actual injected radioactivity.
- xv. There were laboratory results from nine test panels that were performed between [REDACTED] (during the treatment phase plus 30 days post-treatment) that had not been recorded in the EDC.

**Background notes:**

\* The protocol stated "Following local routine medical practice, laboratory parameters will be documented, e.g. sodium, potassium, chloride, calcium, phosphate, magnesium, aspartate transaminase (ASAT,) alanine transaminase (ALAT), lactate dehydrogenase (LDH), gammaglutamyltranspeptidase (GGT), creatinine, urea, bilirubin, albumin, ALP, PSA, protein, hematocrit, hemoglobin, platelet counts, red and white blood cell counts, and differential white blood cell count. Laboratory abnormalities considered to be clinically

*significant and drug-related should be also documented on the AE page.”*

**Root Cause Analysis**

**Further Assessment**

**Corrective Action(s)**

**Deliverable(s)**

**Due Date(s)**

**Preventative Action(s)**

**Deliverable(s)**

**Due Date(s)**

**Finding CR.1 d)**

There were adverse events recorded in the patients' EHRs which had not been recorded in the adverse events page of the CRF and there was no evidence of a seriousness or causality assessment outside of the EDC system to determine whether they met the protocol-defined criteria for inclusion in the study dataset.

**Patient [REDACTED]:**

- i. Following treatment visit 1 on [REDACTED], there was a clinic letter dated [REDACTED] reporting that the patient had experienced [REDACTED]
- ii. Following treatment visit 2 on [REDACTED] there was a clinic letter dated [REDACTED] reporting that the patient had experienced [REDACTED]
- iii. Following treatment visit 3 on [REDACTED] there was a clinic letter dated [REDACTED] reporting that the patient had experienced [REDACTED]

**Patient [REDACTED]:**

- iv. On the same date as treatment visit 3, there was a clinic letter dated [REDACTED] reporting that the patient had experienced [REDACTED]
- v. Following treatment visit 4 on [REDACTED] there was a clinic letter dated [REDACTED] reporting that the patient had experienced [REDACTED]
- vi. 30 days post-treatment, there was a clinic letter dated [REDACTED] that reported the patient had experienced [REDACTED]

**Patient [REDACTED]:**

- vii. Following treatment visit 5 on [REDACTED] there was a clinic letter dated [REDACTED]

Section  
43

Section 43

- ██████████ reporting that the patient had experienced ██████████
- viii. In a letter dated ██████████ (during the long-term follow-up phase), there was reference to an adverse event of ██████████
  - ix. The patient was admitted to hospital on ██████████ with suspected deep vein thrombosis.
  - x. The patient was admitted to hospital on ██████████ with acute confusion.

It is acknowledged that adverse events identified from the EHRs may not meet the protocol-defined criteria for collection, which are

- o *All SAEs and drug-related AEs are collected during treatment and up to 30 days after the last administration of Radium-223.*
- o *Drug related Serious Adverse Events (SAEs) are collected up to 7 years after the last administration of Radium-223.*
- o *All SAEs of second primary malignancies are collected up to 7 years after the last administration of Radium-223.*
- o *AEs of bone fractures and bone associated events are collected up to 7 years after the last administration of Radium-223.*
- o *All post treatment grade 3/4 haematological toxicities are collected up to 6 months after the last administration of Radium-223.*
- o *For patients receiving subsequent chemotherapy, all AEs/SAEs of febrile neutropenia and haemorrhage will be recorded up to 6 months after the last administration of chemotherapy.*

However, there was no evidence that AEs had been identified and assessed to determine whether they met the criteria for inclusion in the study dataset.

Root Cause Analysis

Further Assessment

Corrective Action(s)

Deliverable(s)

Due Date(s)

Section  
43

Preventative Action(s)	
[REDACTED]	
Deliverable(s)	Due Date(s)
[REDACTED]	

**Finding CR.1 e)**

There were examples of delays in reporting SAEs to Bayer. The study protocol stated that all SAEs will be forwarded immediately (within 24 hours of awareness) to the pharmacovigilance country personnel at Bayer.

- i. For patient [REDACTED] there was an AE of [REDACTED] which had a start date of [REDACTED] and was entered into the EDC on [REDACTED]. The AE was upgraded to serious on [REDACTED] following a query raised by Bayer on 11-Jan-2018 which requested that an upgrade should be considered because this event is on the EMA's Important Medical Event (IME) list.

The IME upgrade process was introduced in the Medical Review Plan [REDACTED] as follows:

*"The IME list is a tool to ensure consistency in defining the seriousness of Adverse Events. It is used as a basis for identifying potentially Serious Adverse Events. All non-serious Adverse Events documented during the study will be checked against the IME-list after each coding run. During regular medical review the OS Medical Expert reviews potential matches and decides whether a request to the investigator for potential upgrade of these identified AEs to serious AEs should be initiated. Final decision on seriousness is with the investigator."*

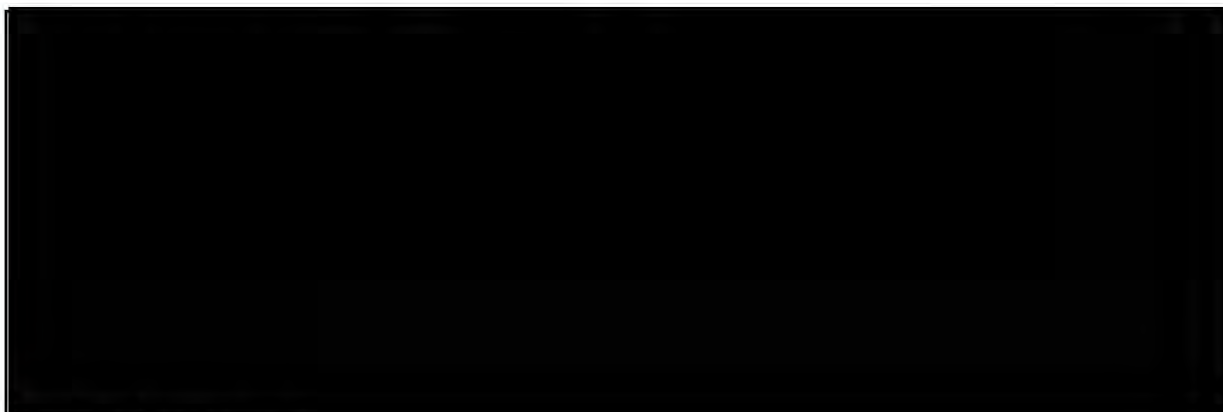
Despite this process being in effect since [REDACTED] there was a delay of 2.5 years to send the upgrade query to the site and a further delay of 14 months to upgrade the event to serious. To compound the issue, the PI did not sign off on the AE page until [REDACTED] resulting in Bayer not receiving the SAE report until this date, which was 4.5 years since the event was initially recorded in the EDC. This delay in PI sign-off is an issue as this was the only opportunity for the PI to review the AE and confirm the seriousness and causality assessment.

- ii. For patient [REDACTED] there was an SAE of [REDACTED] which had a start date of [REDACTED] but which was not entered into the EDC until [REDACTED]. This SAE report was subsequently sent to Bayer on [REDACTED].

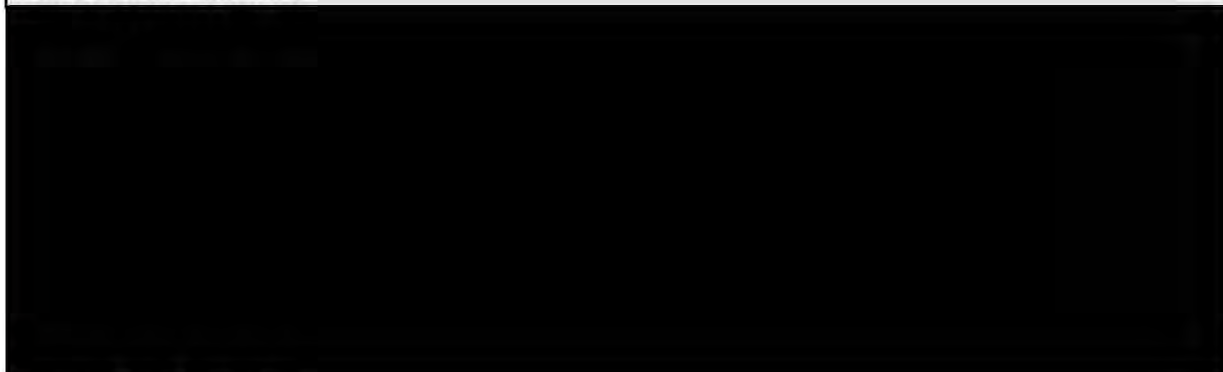
**Root Cause Analysis**

[REDACTED]

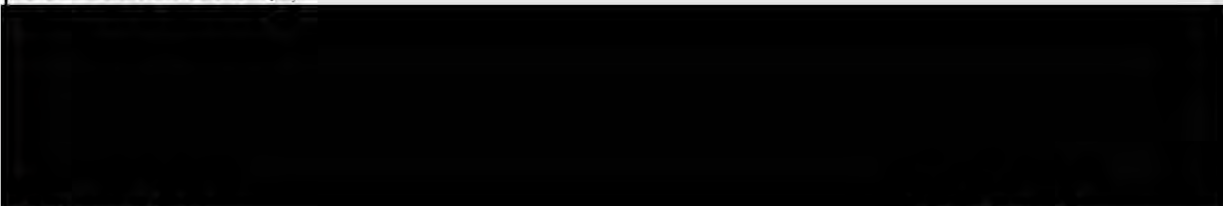
Section  
43



**Further Assessment**



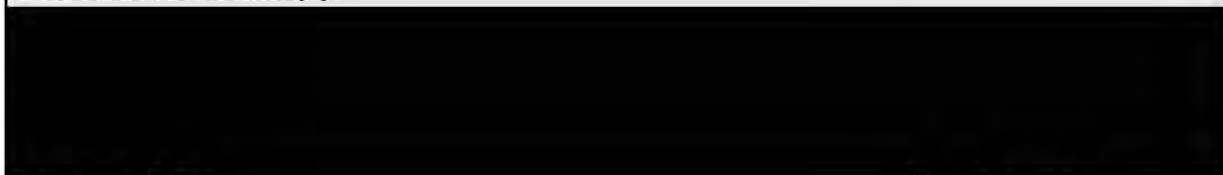
**Corrective Action(s)**



<b>Deliverable(s)</b>	<b>Due Date(s)</b>
-----------------------	--------------------



**Preventative Action(s)**



<b>Deliverable(s)</b>	<b>Due Date(s)</b>
-----------------------	--------------------



**Finding CR.1 f)**

The protocol-defined inclusion and exclusion criteria were as follows:

Inclusion criteria:

- The treatment decision to Radium-223 needs to be made independent from and before



patient enrolment in the study.

- Patients with histologically or cytologically confirmed castration resistant adenocarcinoma of the prostate with bone metastases.
- Signed informed consent.

Exclusion criteria:

- Patients previously treated with Radium-223 for any reason.
- Patients currently treated in clinical trials including other Radium-223 studies.
- Patients are planned for the systemic concomitant use of other radiopharmaceuticals for treatment of prostate cancer or for other use.

There was no record of who performed the eligibility assessment for the patients enrolled in the REASSURE study at this site and when they were performed. It was stated verbally that the study nurses performed the eligibility assessment.

**Root Cause Analysis**

[Redacted]

**Further Assessment**

[Redacted]

**Corrective Action(s)**

[Redacted]

**Deliverable(s)**

**Due Date(s)**

[Redacted]

**Preventative Action(s)**

[Redacted]

[Redacted]

**Finding CR.1 g)**

Signed consent forms were missing for the following three patients: [Redacted] and [Redacted]

**Root Cause Analysis**

[Redacted]

Section 43

Section  
43

[Redacted]	
<b>Further Assessment</b>	
[Redacted]	
<b>Corrective Action(s)</b>	
[Redacted]	
<b>Deliverable(s)</b>	<b>Due Date(s)</b>
[Redacted]	[Redacted]
<b>Preventative Action(s)</b>	
[Redacted]	
<b>Deliverable(s)</b>	<b>Due Date(s)</b>
[Redacted]	[Redacted]

## C.4.2 Major findings

### MA.1 General obligations of the MAH regarding post-authorisation safety studies

#### Requirements:

##### Health Research Authority requirements

<https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/hra-approval/>

##### Commission Implementing Regulation (EU) No. 520/2012

Article 12 "*Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires.*"

Article 36(3) "*The marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.*"

The following findings were identified in relation to the EURAS-LCS12 study:

#### Finding MA.1 a)

Bayer did not seek approval from the UK Health Research Authority (HRA) to conduct the European Active Surveillance Study of LCS-12 in the UK.

The MAH completed the HRA online decision tool (<http://www.hra-decisiontools.org.uk/research/>) and concluded that the study was not considered research. However, preliminary advice from the HRA provided to the MHRA inspectorate has indicated that the findings from this study would be generalisable and, as such, the study is considered to be research.

Consequently, the HRA should be contacted via the following email address to seek advice on the next steps: [HRA.Queries@nhs.net](mailto:HRA.Queries@nhs.net)

The MHRA inspectors also had some concerns about the content of the informed consent forms that were being provided to the study participants and these concerns are outlined in [Appendix III](#). These concerns will be shared with the HRA who will have the ultimate decision regarding the suitability of the informed consent process.

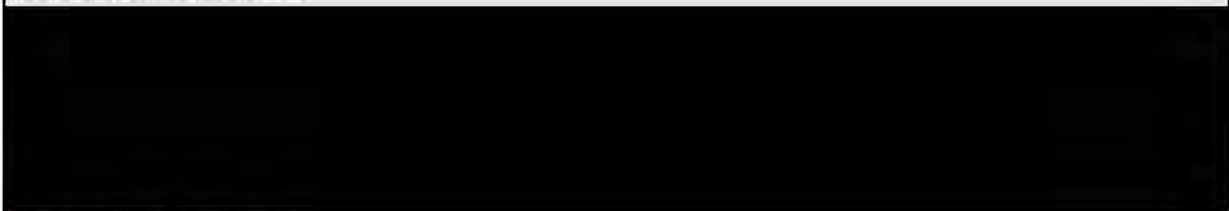
#### Root Cause Analysis

Section  
43

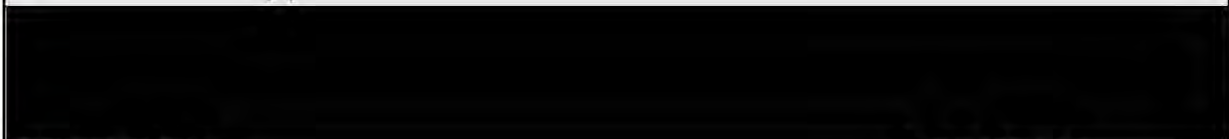
Section  
43



**Further Assessment**



**Corrective Action(s)**



**Deliverable(s)**

**Due Date(s)**

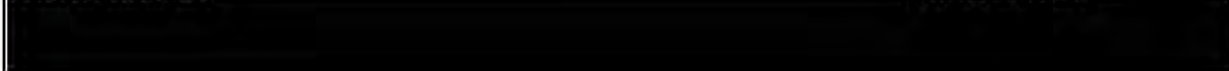


**Preventative Action(s)**



**Deliverable(s)**

**Due Date(s)**



**Finding MA.1 b)**

The contract with ZEG [REDACTED] did not include provision for the transfer of electronic study data and meta-data at the end of the study to the MAH. Section 3.1.5 stated “ZEG shall retain all documents relating to the Study for a period of at least fifteen (15) years after finalization of the Study.”

**Root Cause Analysis**



Section  
43

<b>Further Assessment</b>	
[Redacted]	
<b>Corrective Action(s)</b>	
[Redacted]	
[Redacted]	
<b>Preventative Action(s)</b>	
[Redacted]	
<b>Deliverable(s)</b>	<b>Due Date(s)</b>
[Redacted]	[Redacted]

## MA.2 Management and reporting of adverse drug reactions from PASS

### Requirements:

#### **Regulation (EC) No. 726/2004 as amended**

Article 28(1)

#### **Directive 2001/83/EC as amended**

Article 107(1) *“Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.*

*Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.”*

Article 107(3) *“Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the ‘Eudravigilance database’) information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.”*

#### **The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance**

Regulations 187-188

#### **Commission Implementing Regulation (EU) No. 520/2012**

Article 25(1) *“For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, Member States, marketing authorisation holders and the Agency shall apply the following terminology:*

*(a) the Medical Dictionary for Regulatory Activities (MedDRA) as developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), multidisciplinary topic M1;”*

#### **GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)**

VI.B.6.4. *“In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reactions may require to be submitted within a 15-day time frame [...]. Medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases.”*

VI.B.6.5. *“Correct data entry, including the appropriate use of terminologies [...] should be quality controlled, either systematically or by regular random evaluation. Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. With regard to this, the source data (e.g. letters, emails, records of telephone calls, which include details of an event) or an image of the source data should be easily accessible.”*

In the EURAS-LCS12 study, adverse events could be reported in response to several questions in the follow-up questionnaire (version identifier: [REDACTED] February 21<sup>st</sup>, 2014), for example:

- Q3a. Have you had problems with the IUD/IUS?
- Q6b. Did you get pregnant despite having an IUD/IUS in place?
- Q8. Since our last contact in [month/year], did you have an inflammation/infection of the pelvic organs (uterus, ovaries, tubes)?
- Q9. Since our last contact in [month/year], have you had any serious illnesses or conditions for which you received medical attention (e.g. deep venous thromboembolism, pulmonary embolism) or outpatient surgical procedures (e.g. cervical conization, laser treatment on the cervix, sterilization)?
- Q10a. With the exception of child delivery, have you been admitted to a hospital (for at least one night) since [month/year]?

As per the study protocol, non-serious ADRs were not required to be reported to EU regulatory authorities within expedited reporting timelines, only serious ADRs were required to be reported in an expedited manner.

The following findings were identified in relation to the management and reporting of ADRs from the EURAS-LCS12 study:

**Finding MA.2 a)**

There was evidence that Bayer had failed to report serious adverse drug reactions to EudraVigilance within the 15-day timeframe stipulated in EU legislation.

The Safety Management Plan section 4.2 stated *“The clock for reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria (GVP Module VI.B.7) has been brought to the attention of ZEG Berlin (Day 0).”*

In accordance with the study protocol, self-reported events concerning the primary and secondary clinical outcomes of interest underwent a validation process coordinated by ZEG. Only events that were medically confirmed following this validation process were sent to the MAH as individual cases within two business days; however, this may be many months (or years) since initial receipt. Therefore, the MAH could not meet its 15-day reporting obligation for cases that met the reporting criteria outlined in GVP Module VI (Rev 2). For example:

- i. [REDACTED] – A follow-up questionnaire was received by [REDACTED] on 09-Jul-2018 with sufficient information to meet the minimum reporting criteria for an ICSR. However, this ICSR was not reported to EudraVigilance until 09-Aug-2019, over a year beyond the regulatory deadline from the date it was first received. The patient had reported in response to Q2d and Q3a that [REDACTED]

The wording of Q3a indicated a causal relationship of the event to the IUD and, as uterine perforation is a serious event, this represented a serious valid ICSR. Bayer did not receive the case from ZEG until 05-Aug-2019 as the CRO was incorrectly awaiting medical confirmation of the event from the healthcare professional before forwarding it to the MAH.

- ii. [REDACTED] – The event validation process was initiated as a result of the patient answering ‘no’ to Q2d ‘Was the IUD/IUS in the right position?’. Follow-

Section  
43

up information was received by [REDACTED] on 26-Jul-2016 confirming the occurrence of uterine perforation, at which point this represented a serious valid ICSR. This information was forwarded to ZEG Berlin on the same day, however, the date of validation decision by ZEG was not until 28-Nov-2016, and the case was subsequently reported to Bayer on 01-Dec-2016. The ICSR was reported to EudraVigilance on 01-Dec-2016, which was nearly four months beyond the regulatory deadline from the date when the minimum reporting criteria was first received.

It was apparent that the processes for medical confirmation of an event and causality assessment to determine whether the event was related to the IUD had been somewhat merged together under the event validation process. It is the opinion of the MHRA inspectors that a more conservative approach should be taken, particularly in relation to Q3a of the follow-up questionnaire where, due to the wording of this question, it is reasonable to say that any problems with the IUD reported by the patient in response to this question should be considered 'related'. If the reported event is serious, this should be reported to the EudraVigilance database within 15 days, irrespective of subsequent efforts to obtain medical confirmation of the event. The outcome of the medical confirmation by a healthcare professional should be recorded in E2B(R3) field E.i.8\* and an ICSR follow-up report submitted accordingly.

\* E.i.8 user guidance: "If an event is reported by a non-healthcare professional (e.g. lawyers, consumers), this data element indicates whether the *occurrence* of the event was subsequently confirmed by a healthcare professional."

#### Root Cause Analysis





Section  
43

**Further Assessment**

**Corrective Action(s)**

<b>Deliverable(s)</b>	<b>Due Date(s)</b>

**Preventative Action(s)**

Finding MA.2 b)

There was a non-conservative approach to the reporting of lack of efficacy reports in line with GVP Module VI (Rev 2), in that reports of unintended pregnancy despite IUD use that could not be medically confirmed due to lack of further information, or where the patient did not seek medical confirmation of the pregnancy, were not sent to Bayer by ZEG. This resulted in a failure to submit these reports to EudraVigilance within the 15-day timeframe.

Q6b of the follow-up questionnaire stated, '*Did you get pregnant despite having an IUD/IUS in place?*'. When a response of 'yes' to this question is received, it is reasonable to consider this as a lack of efficacy report. In relation to Mirena, Jaydess and Kyleena (Bayer products), evidence was provided showing that five reports of unintended pregnancy were unconfirmed due to lack of medical confirmation (two of which were from the UK) and two reports of unintended pregnancy were unconfirmed as further clarification was not possible. This was in the context of a total of 47 confirmed unintended pregnancy reports with these products. Examples included:

- i. [REDACTED] – Follow-up questionnaire 3 had "*termination of pregnancy due to failure of coil*" with a date of the termination entered for Q9 ('*Since our last contact... have you had any serious illnesses...*'). The questionnaire was completed by the study participant on [REDACTED] and stamped as received on 10-Jul-2017. The ZEG assessor asked the UK field office [REDACTED] to follow-up with the physician to obtain medical confirmation of the pregnancy. There were 20 follow-up attempts made from [REDACTED] to contact the physician and then the patient, as the patient had moved GPs. No information was received to medically confirm the pregnancy and, as such, the report remained unconfirmed and had incorrectly not been sent to Bayer.
- ii. [REDACTED] – Follow-up questionnaire 4 contained a 'yes' answer for Q6a '*Since our last contact, have you been pregnant?*' and a 'yes' for Q6b '*Did you get pregnant despite having an IUD/IUS in place?*'. There was also a delivery date of the baby provided. The questionnaire was completed by the study participant on [REDACTED] and stamped as received on 08-Oct-2018. The ZEG assessor asked the UK field office [REDACTED] to follow-up with the patient and physician to obtain medical confirmation of the pregnancy and to find out when the IUD/IUS had been expelled or removed. There were 13 follow-up attempts from [REDACTED]. There had been a response from the patient on the [REDACTED] confirming the date the device was removed; however, no information was received to medically confirm the pregnancy and, as such, the pregnancy remained unconfirmed and had incorrectly not been sent to Bayer.
- iii. [REDACTED] – Follow-up questionnaire 2 contained information which stated the IUD/IUS was not in place when an ultrasound was performed, it was in the patient's cervix, and the IUD/IUS had been removed on the same day because of a pregnancy. The study participant had answered Q6a and Q6b as 'yes'. The questionnaire had been completed on [REDACTED] and was stamped as received on [REDACTED]. The ZEG assessor had asked the UK field office [REDACTED] to follow-up with the physician to obtain medical confirmation of the pregnancy. There were 19 follow-up attempts from [REDACTED] however, no information was received to medically confirm the pregnancy and, as such, the pregnancy remained unconfirmed and had incorrectly not been sent to Bayer.

Section  
43

Section  
43

In addition, at the time of the inspection, for Jaydess, Mirena and Kyleena there were [REDACTED] reports of unintended pregnancy where efforts to obtain confirmation of the pregnancy were in process (validation requests sent to the local field organisations >one month ago). These had not been reported to Bayer.

As per GVP module [REDACTED] reports of lack of therapeutic efficacy with contraceptives should be submitted within a 15-day timeframe. It is the opinion of the MHRA inspectors that a more conservative approach should be taken and any reports of pregnancy despite having an IUD/IUS in place should be reported to Bayer in an expedited manner and onwards to EudraVigilance in accordance with GVP Module VI (Rev 2), section [REDACTED]. The outcome of the medical confirmation by a healthcare professional should be recorded in [REDACTED] field E.i.8 and an ICSR follow-up report submitted accordingly.

**Root Cause Analysis**

[REDACTED]

**Further Assessment**

[REDACTED]

**Corrective Action(s)**

[REDACTED]

**Deliverable(s)**

**Due Date(s)**

[REDACTED]

**Preventative Action(s)**

[REDACTED]

Section  
43

Deliverable(s)	Due Date(s)
[REDACTED]	

**Finding MA.2 c)**

There was the potential that reported adverse reactions that met the ICH E2A seriousness criteria would not be reported to EU regulatory authorities in an expedited manner.

The Safety Management Plan [REDACTED] section 4.2 (Case processing at ZEG Berlin) stated *“Per protocol, ZEG Berlin will send all confirmed solicited events (Appendix 4) under a Bayer AG product to Bayer AG electronically within 2 business days of Day 0 on CIOMS-I forms”*. However, Appendix 4 (List of solicited events to be reported using expedited reporting timelines) only included the primary and secondary clinical outcomes of interest and neuropsychiatric disorders for levonorgestrel containing-IUDs.

Therefore, there is the potential that events considered lower priority in the context of the study, but which nonetheless meet regulatory seriousness criteria, would not be reported to Bayer using expedited reporting timelines.

The study protocol section 11 (Management and reporting of adverse events / adverse reactions) stated *“Serious adverse drug reactions will be reported to the relevant marketing authorisation holder within two working days.”*

As an example, Q9 of the follow-up questionnaire solicited information from the patient on serious illnesses and/or conditions that had occurred since the previous contact; however, if these were not primary and secondary clinical outcomes of interest or neuropsychiatric disorders, there was no assurance that those considered potentially related to the IUD would be reported to the MAH in an expedited manner. It was noted that Bayer did not receive any listings of low priority / non-serious events in order to make its own assessment of seriousness for the purposes of meeting its regulatory obligations.

**Root Cause Analysis**

[REDACTED]
------------

**Further Assessment**

[REDACTED]
------------

Section  
43

[Redacted]	
<b>Corrective Action(s)</b>	
[Redacted]	
<b>Preventative Action(s)</b>	
[Redacted]	
[Redacted]	

**Finding MA.2 d)**

AEs that were reported during the follow-up with physicians as part of the event validation process were not captured in the study database and did not undergo a causality assessment to consider whether they refer to suspected adverse reactions. Consequently, potential ADRs were not available for inclusion in ICSRs or periodic reports such as PSURs and interim study reports, as appropriate.

This is particularly relevant for the outcome of interest – pelvic inflammatory disease (PID). Q8 of the follow-up questionnaire stated, '*Since our last contact, did you have an inflammation of the pelvic organs?*'. If this was selected as 'yes', the case automatically flagged for event validation. As of 03-Sep-2019, 4140 reports of PID had been medically not confirmed via event validation. Of these, 2086 reports were confirmed to be other infections/inflammations of the external genital organs or urinary tract and 866 reports were confirmed to be other conditions of the female genital tract. For these reports, PID had been excluded, however the new information represented AEs or ADRs that were not re-coded in the study database, and hence were not forwarded via any route to the MAH or included in the interim study reports. For example:

- i. [REDACTED] – Patient selected 'yes' to both Q3a and Q8 of follow-up questionnaire 3 (no further information provided in the questionnaire). Follow-up information was received from a healthcare professional confirming the patient had uterine fibroids. PID was subsequently not confirmed, however the event was not re-coded to uterine fibroids in the study database.
- ii. [REDACTED] – Patient selected 'yes' to both Q3a and Q8 of follow-up questionnaire 4. Further information was provided under Q9 stating "*inflammation (strong pain)*". Follow-up information received from a healthcare professional confirmed the patient had uterine fibroids. PID was subsequently not confirmed, however the event was not re-coded to uterine fibroids in the study database.

**Root Cause Analysis**

[REDACTED]

**Further Assessment**

[REDACTED]

Section  
43

Section  
43

[Redacted]	
<b>Corrective Action(s)</b>	
[Redacted]	
<b>Deliverable(s)</b>	<b>Due Date(s)</b>
[Redacted]	[Redacted]
<b>Preventative Action(s)</b>	
[Redacted]	

Section  
43

Deliverable(s)	Due Date(s)
[Redacted]	

Finding MA.2 e)
-----------------

Bayer was not in compliance with Article 107(1) of Directive 2001/83/EC as non-serious ADRs were not being collected and collated at a single point in the EU.

The MAH did not receive non-serious ADR reports from the EURAS-LCS12 study in either aggregate listings or as individual cases. The EURAS-LCS12 study protocol stated that expedited reporting of non-serious ADRs was not required within the context of this study. However, in order to comply with Article 107(1) of Directive 2001/83/EC, it would be expected that all non-serious ADRs reported within this study are provided to the MAH in some manner, so that all ADR reports are accessible at a single point in the Union.

Bayer only had sight of the non-serious ADRs reported in response to Q3a of the follow-up questionnaire in the six-monthly interim study reports (Table 24: Adverse events / drug reactions).

Root Cause Analysis
---------------------

[Redacted]
------------

Further Assessment
--------------------

[Redacted]
------------

Corrective Action(s)
----------------------

[Redacted]
------------



Section  
43

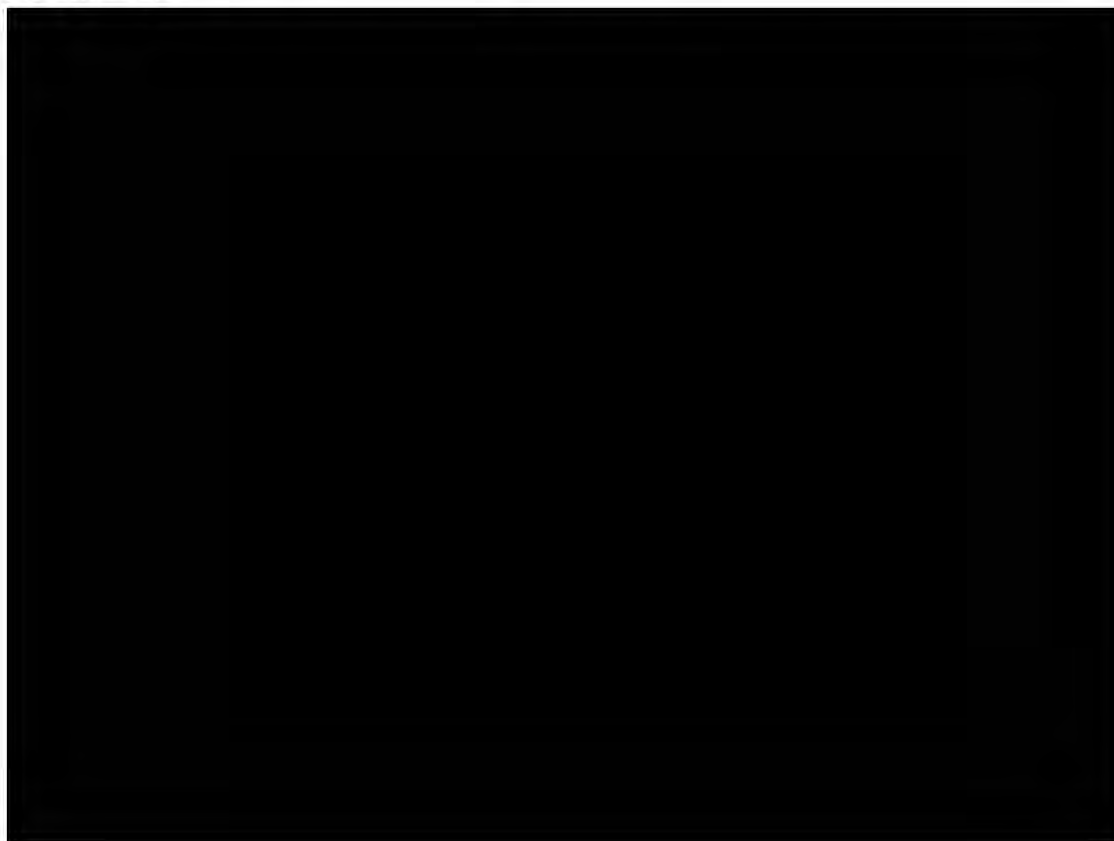
Deliverable(s)	Due Date(s)
Preventative Action(s)	
Deliverable(s)	Due Date(s)

**Finding MA.2 f)**

The safety data presented in the 9th Study Interim Report based on study status at 31-Aug-2018 (report dated 13-Feb-2019) was misleading in the context of the data that had been received in the study.

- i. Table 24 (Adverse events / drug reactions (per end of August 2018)) in section 9.4.9 of the interim report was described as including *“Adverse events / reactions reported by the study participant as problem with the IUD in any follow-up”*. The title of the table (‘Adverse events / drug reactions’) was misleading as the table only included problems reported by the study participant in response to Q3a of the follow-up questionnaire (‘*Have you had problems with the IUD/IUS?*’). The wording of the question implied a causal relationship of any reported events with the IUD and therefore the table should be entitled ‘Adverse drug reactions’.
- ii. Adverse events reported in response to Q9 (‘*Since our last contact in [month/year], have you had any serious illnesses or conditions for which you received medical attention (e.g. deep venous thromboembolism, pulmonary embolism) or outpatient surgical procedures (e.g. cervical conization, laser treatment on the cervix, sterilization)?*’) were not included in the interim report (with the exception of cervical conization in section 9.4.6).
- iii. The report only included medically confirmed reports of the main study outcomes of interest. Bayer should be more transparent about the number of unconfirmed reports in the ZEG event validation database (EVDB). For example, the number of

unintended pregnancies that could not be confirmed due to lack of further clarification, or where the patient did not seek medical confirmation of the pregnancy.

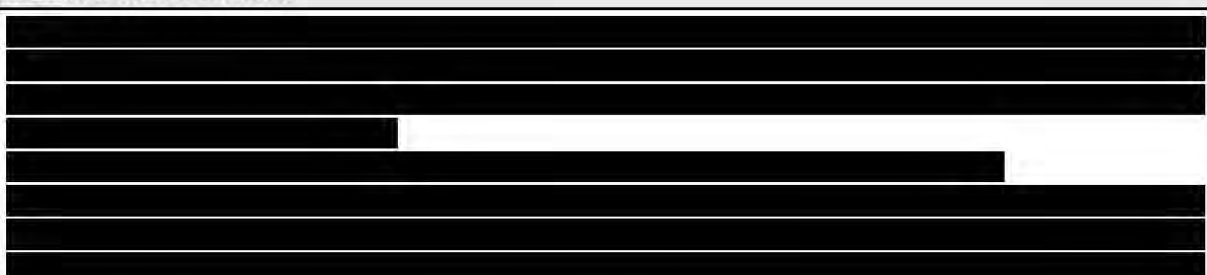


Section  
43

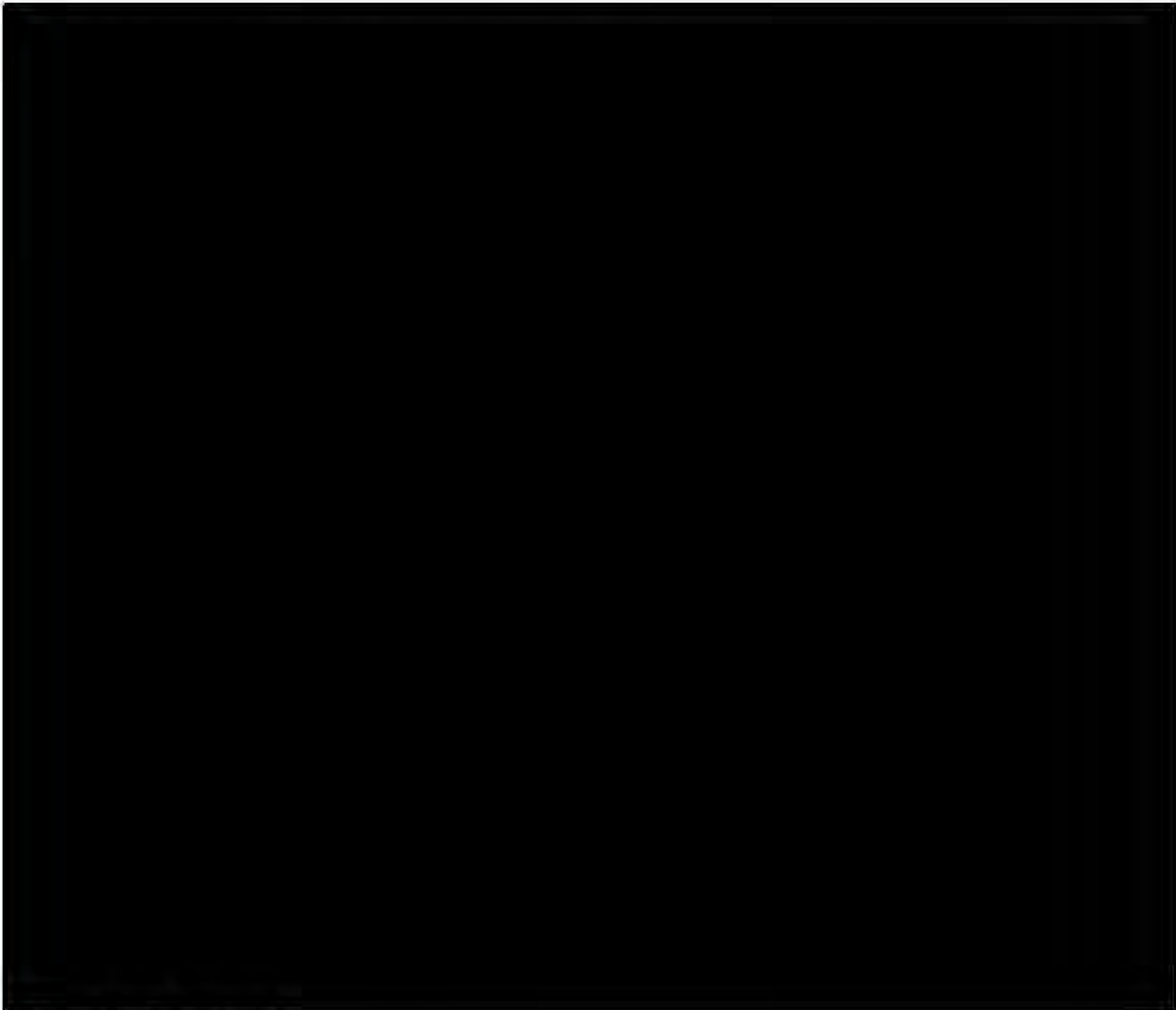
**Root Cause Analysis**



**Further Assessment**



Section  
43



**Corrective Action(s)**

[Redacted]

Deliverable(s)	Due Date(s)
[Redacted]	[Redacted]

**Preventative Action(s)**

[Redacted]

Deliverable(s)	Due Date(s)
[Redacted]	[Redacted]

**Finding MA.2 g)**

Adverse events / reactions reported in the interim study reports were coded in ICD-10 (International Classification of Diseases) and not the Medical Dictionary for Regulatory Activities (MedDRA).

As per the Commission Implementing Regulation (EU) No 520/2012, pharmacovigilance information should be classified, presented and communicated using the MedDRA dictionary. The interim reports were prepared every 6 months and the 9<sup>th</sup> interim report was submitted with variation procedure [REDACTED] to the RMS (SE) and concerned CMSs on 14-Mar-2019.

It is recommended that the MSSO Recommendations for MedDRA Implementation and Versioning for Clinical Trials (MSSO-DI-99090-1.0.0 1 August 2012) are consulted regarding the coding of adverse drug reactions from this study.

**Root Cause Analysis**

**Further Assessment**

**Corrective Action(s)**

**Deliverable(s)**

**Due Date(s)**

Section  
43

Section  
43

Preventative Action(s)	
[REDACTED]	
Deliverable(s)	Due Date(s)
[REDACTED]	

**Finding MA.2 h)**

There was no quality control of the entry of questionnaire data into the ZEG study database and Bayer did not receive copies of the patient questionnaires or the source documents relating to subsequent validation attempts. Individual cases eligible for expedited reporting were sent to Bayer via CIOMS forms which had been generated based on single data entry. Therefore, Bayer could not ensure the accuracy of the data reported in the ICSRs.

The inspectors conducted a source data verification of questionnaire data entry for 14 enrolled patients and some minor data entry errors were noted, although these would not be expected to impact on the study conclusions.

- Patient [REDACTED] – Follow-up questionnaire 2 Q4b: 'Missing' was entered in the ZEG study database but should be 'No'.
- Patient [REDACTED] – Follow-up questionnaire 1 Q4b: 'Missing' was entered in the ZEG study database but should be 'No'.
- Patient [REDACTED] – Baseline Q19: The dates of previous use of an IUD were entered as 03 2013 to 05 2016 in the ZEG study database but should be 03 2013 to 05 2014.

**Root Cause Analysis**

[REDACTED]

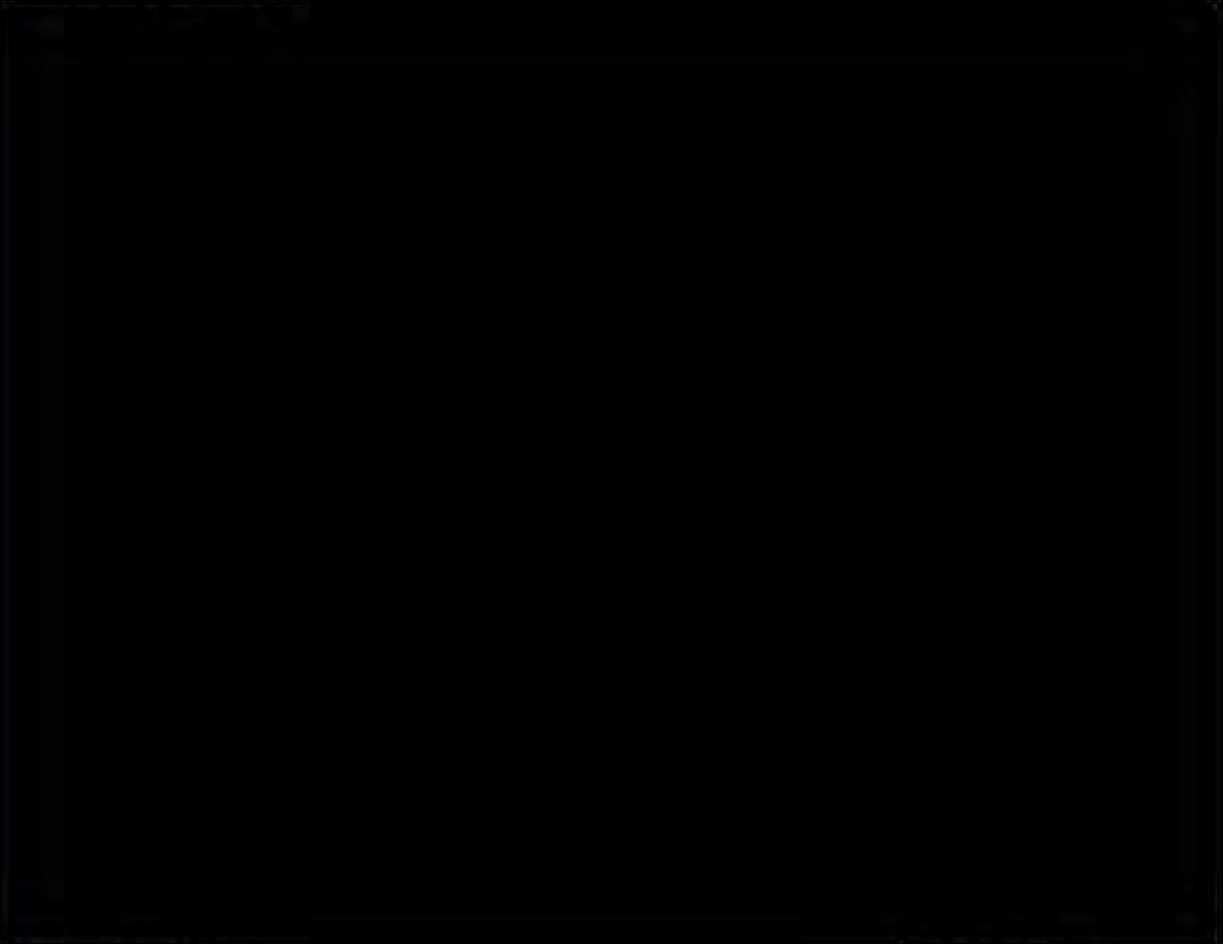
**Further Assessment**

[REDACTED]

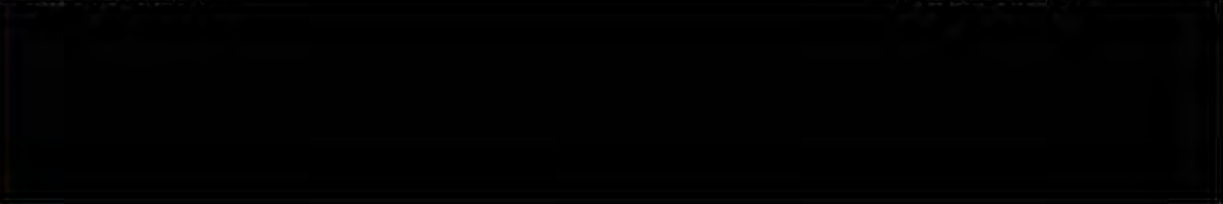
Section  
43



**Corrective Action(s)**



<b>Deliverable(s)</b>	<b>Due Date(s)</b>
-----------------------	--------------------



Section  
43

[Redacted]	
Preventative Action(s)	
[Redacted]	
[Redacted]	[Redacted]
[Redacted]	

### MA.3 MAH oversight and governance of PASS

#### Requirements:

Commission Implementing Regulation (EU) No. 520/2012, Article 13(1)

#### GVP Module I – Pharmacovigilance systems and their quality systems

I.C.1.5. *“The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties [...]The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the marketing authorisation holder.”*

#### GVP Module IV – Pharmacovigilance audits (Rev 1)

IV.B.2.1. *“The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system including: [...]*

- *pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties, such as contract organisations and other vendors).”*

#### Finding MA.3 a)

Several findings were identified with regards to oversight of non-interventional studies. [REDACTED]

[REDACTED] (Create oversight for observational study [REDACTED] section 3.1 included the requirement to agree study oversight measures and for the OS CR (Observational Study Conduct Responsible) and OS DM (Observational Study Data Manager) to create and distribute oversight reports, as agreed.

- Bayer did not have any mechanisms of oversight of the EURAS-LCS12 study, to ensure adherence to the study protocol or the reporting of adverse drug reactions from the study.
- For the REASSURE study, country- and site-level performance reports could be generated from the EDC system; however, there was no defined frequency for how often these should be generated. It was stated verbally by the REASSURE UK Local Project Manager (LPM) that country-level reports were generated ‘either monthly or quarterly’ and site-level reports were not routinely generated.
- [REDACTED] section 3.1 also included the requirement to prepare and maintain a communication plan to ensure that all involved parties were properly updated on study status and potential actions. A communication plan for the REASSURE study had not been prepared and it was stated that this was because the study had been ongoing for a long time. (Note: The communication plan was not requested for the EURAS-LCS12 study and Bayer should confirm in the response to the inspection report whether such a plan is in place).
- Vendors used for non-interventional studies were not included in the risk-assessment for PV audit planning, instead they were audited upon request. The vendor ZEG had not been audited by or on behalf of Bayer.



Section  
43

**Root Cause Analysis**

**Further Assessment**

**Corrective Action(s)**

**Deliverable(s)**

**Due Date(s)**

**Preventative Action(s)**

Section  
43

[Redacted]	
Deliverable(s)	Due Date(s)
[Redacted]	

**Finding MA.3 b)**

There was no evidence of QPPV approval of the following versions of the EURAS-LCS12 and REASSURE study protocols:

- EURAS-LCS12 protocol versions [Redacted] (current).
- REASSURE protocol versions [Redacted] (current).

**Root Cause Analysis**

[Redacted]
------------

**Further Assessment**

[Redacted]
------------

**Corrective Action(s)**

[Redacted]
------------

Section  
43

Deliverable(s)	Due Date(s)
[Redacted]	
Preventative Action(s)	
[Redacted]	
Deliverable(s)	Due Date(s)
[Redacted]	

**C.4.3 Minor findings**

**MI.1 Conduct of post-authorisation safety studies**

The following findings were identified in relation to the EURAS-LCS12 study:

Section  
43

Finding MI.1 a)	
<p>There was no documented process at [REDACTED] for determining patient eligibility for inclusion in the study when informed consent forms and baseline questionnaires were received late (more than one-month post device insertion). [REDACTED] applied specific criteria to determine whether the patient was eligible for inclusion in the study and it is recommended that this is formalised in a written procedure.</p>	
Root Cause Analysis	
[REDACTED]	
Further Assessment	
[REDACTED]	
Corrective Action(s)	
[REDACTED]	
Deliverable(s)	Due Date(s)
[REDACTED]	[REDACTED]
Preventative Action(s)	
[REDACTED]	
Deliverable(s)	Due Date(s)
[REDACTED]	[REDACTED]

Finding MI.1 b)	
<p>The EURAS-LCS12 Statistical Analysis Plan [REDACTED] did not include the current 'Other study endpoint' of 'Neuropsychiatric disorders (anxiety, panic attacks, mood swings/depression, persistent difficulties with sleeping and restlessness)'.</p>	
Root Cause Analysis	
[REDACTED]	

Section  
43

<b>Further Assessment</b>	
█	
<b>Corrective Action(s)</b>	
<b>Preventative Action(s)</b>	
<b>Deliverable(s)</b>	<b>Due Date(s)</b>

<b>Finding MI.1 c)</b>
<p>In response to document request Y1, ZEG described a process whereby all reports of unplanned hospitalisations indicated by the response to Q10a of the follow-up questionnaire were triaged to a Medical Advisor for causality assessment. Those events that were suggestive of a potential causal relationship with the IUD were then flagged for the ZEG event validation process.</p> <p>ZEG could not provide any documented procedures that described this process for handling reports of unplanned hospitalisation.</p>
<b>Root Cause Analysis</b>
<b>Further Assessment</b>
█

Section  
43

Corrective Action(s)	
Deliverable(s)	Due Date(s)
Preventative Action(s)	
Deliverable(s)	Due Date(s)

The following findings were identified in relation to the REASSURE study:

Finding	MI.1 d)
<p>The following findings were identified in relation to the Brief Pain Inventory (Short Form) (BPI-SF) that was completed by patients enrolled in the study:</p> <p>i. The REASSURE Data Handling Manual [REDACTED] section 5.1 stated <i>"It is expected that each BPI-SF can be assigned to the corresponding visit by its assessment date. However, in some cases this match by dates is not possible because some patients do not complete the BPI-SF on the injection date or visit date respectively, but a couple of days earlier or later. In order to assign these BPI-SF to the corresponding visits the field "Visit Assignment" is used in INTrial."</i></p> <p>It was noted that the BPI-SF did not include a prompt for visit assignment; this could be a useful addition to the form to avoid initiating multiple queries to the site. According to the CRF, this questionnaire could be completed at baseline, treatment and 6 Months FU visits. It was noted that the MAH had implemented a periodic check of BPI-SFs without a visit assignment and the report generated on 22-Jul-2019 identified 63 BPI-SFs from UK patients without a visit assignment which had to be sent to the Local Project Manager (LPM) for resolution.</p> <p>ii. The Data Handling Manual section 5.1 stated <i>"In a third step [REDACTED] Data Manager] provides Bayer Global with two listings on a regular basis:</i></p> <ul style="list-style-type: none"> <li>- <i>A listing of all visits with question "Did the patient complete the 'BPI-SF' questionnaire?" answered "yes" but no corresponding BPI-SF received by [REDACTED]</i></li> <li>- <i>A listing of all BPI-SF received by [REDACTED] which cannot be assigned to a visit</i></li> </ul> <p><i>Bayer Global distributes the listings to the Bayer Local Project Managers who will check these listings together with the sites. They complete the listings by indicating the correct visit or correct BPI-SF respectively on them and return them to [REDACTED] who will incorporate the information into INTrial."</i></p>	

Section  
43

Examples of this process were requested during the inspection (requests H2 and U1) and there was no evidence that the listings were completed and sent back to [REDACTED] therefore it was not clear if the missing BPI-SFs or missing visit assignments had been actioned by the LPM.

**Root Cause Analysis**

**Further Assessment**

**Corrective Action(s)**

**Deliverable(s)**

**Due Date(s)**

**Preventative Action(s)**

**Deliverable(s)**

**Due Date(s)**

#### **C.4.4 Comments**

In relation to the REASSURE study investigational site in Leeds the following points were noted:

1. There was a lack of oversight by the PI at this site which had resulted in issues such as late reporting of SAEs, incorrect cancer staging, failure to document eligibility assessments and failure to follow the approved study protocol. Whilst it's acknowledged that this study had not been granted the ENCePP seal, it is noted that the ENCePP Code of Conduct For Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies (EMA/929209/2011, 15-Mar-2018) states the following: *"The investigator(s) shall be responsible for the conduct of the study within the remits of their project, including the data collection and analysis, the interpretation of the study results as well as the preparation of study reports and publication of the study outcome."*
2. It was stated that an electronic application called 'ICE' had the functionality to pull in laboratory data from other hospitals outside of St James's for patients enrolled in the study. However, this resource had not been routinely reviewed in the context of recording laboratory test results for patients during their treatment phase.



## **SECTION D: CONCLUSIONS AND RECOMMENDATIONS**

### **D.1 Conclusions**

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. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. No additional responses are required at this time. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

### **D.2 Recommendations**

Given the seriousness of the inspection findings, the Inspection Action Group for GCP and Pharmacovigilance (IAG) has recommended that the next MHRA pharmacovigilance inspection is performed within the next 12 months, to review the impact of the actions taken in response to the inspection findings. Please note that this inspection may be conducted unannounced or at short notice.

## APPENDIX I REFERENCE TEXTS

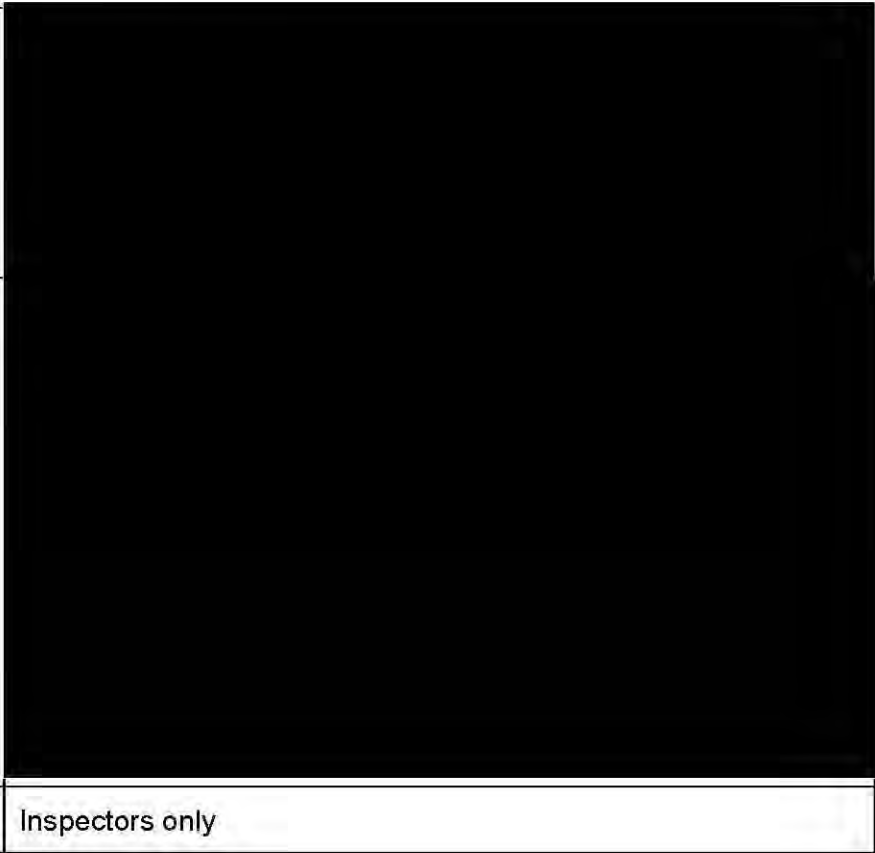

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- EMEA/CHMP/313666/2005: "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".
- EMEA/CHMP/PhVWP/235910/2005: "Guideline on conduct of pharmacovigilance for medicines used by the paediatric population".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

<b>MHRA INSPECTION NUMBER</b>	Insp GPvP 10/16303918-0002	<b>DAY</b>	1
<b>PHARMACOVIGILANCE INSPECTION OF</b>	Bayer	<b>DATE</b>	03 September 2019
<b>LOCATION</b>	400 South Oak Way, Green Park, Reading, Berkshire, RG2 6AD United Kingdom	<b>START TIME</b>	09:30 arrival for a 10:00 start
<b>Bayer representatives attending interviews:</b> [REDACTED]			
<b>Purpose of Interview</b>	<b>Session Lead</b>	<b>Staff to be interviewed</b>	
<b>Opening Meeting</b> Review of scope of inspection and inspection plan  <b>Company Presentation</b> Overview of the company, the pharmacovigilance system and the quality system, including significant changes since the 2018 MHRA GPvP inspection <i>(approx. 20 minutes)</i>	[REDACTED]	[REDACTED]	
Receipt and review of documentation	-	Inspectors only	
<b>LUNCH</b>	-	-	

Section 40


Section 40

<p><i>Ad hoc interview regarding EURAS LCS DM / Data Flow</i></p>		
<p><b>MAH responsibilities concerning non-interventional post-authorisation safety studies:</b></p> <p>To include (but not necessarily limited to):</p> <ul style="list-style-type: none"> <li>- Protocol development and maintenance</li> <li>- Ethics approval</li> <li>- Study classification and registration</li> <li>- MAH oversight of protocol adherence, CROs, data quality and integrity, etc.</li> <li>- Record management</li> <li>- Communication of study results</li> <li>- Role of the QPPV</li> </ul>		
<p>Document Review</p>	<p>-</p>	<p>Inspectors only</p>

<b>MHRA INSPECTION NUMBER</b>	Insp GPvP 10/16303918-0002	<b>DAY</b>	2
<b>PHARMACOVIGILANCE INSPECTION OF</b>	Bayer	<b>DATE</b>	04 September 2019
<b>LOCATION</b>	400 South Oak Way, Green Park, Reading, Berkshire, RG2 6AD United Kingdom	<b>START TIME</b>	09:00
<b>Purpose of Interview</b>	<b>Session Lead</b>	<b>Staff to be interviewed</b>	
<p><b>Data management for non-interventional post- authorisation safety studies:</b></p> <p>████████████████████</p> <p>████████████████████</p> <p>To include (but not necessarily limited to):</p> <ul style="list-style-type: none"> <li>- Procedures for the capture, management and retention of study data, including CRF design</li> <li>- Database quality control processes</li> <li>- Data integrations/transfers &amp; reconciliations</li> <li>- Queries</li> <li>- Database lock</li> <li>- Archiving</li> </ul>	<p>██████████</p>		
<b>LUNCH</b>	-	-	
<b>Part 2 – Study 16470 continued after lunch</b>		Please see above	




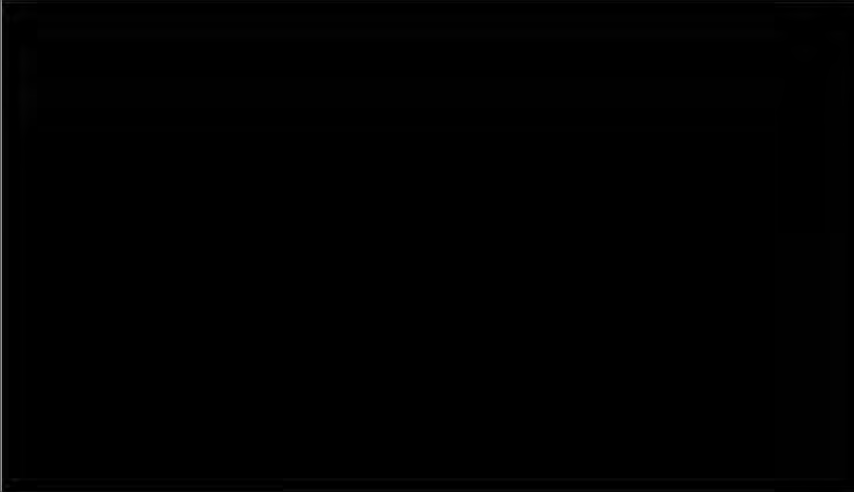
Section 40

Section  
40

<p><b>Site management and monitoring for non-interventional post-authorisation safety studies:</b></p> <p>██████████</p> <p>██████████</p> <p>Overview of site management, from feasibility to close out of investigator sites. To include (but not necessarily limited to):</p> <ul style="list-style-type: none"> <li>- Site selection and feasibility</li> <li>- Site initiation</li> <li>- Training of site personnel</li> <li>- Risk-based monitoring processes</li> <li>- Query resolution</li> <li>- Site close out</li> </ul>	<p>██████████</p>	
<p>Document Review</p>	<p>-</p>	<p>Inspectors only</p>




Section  
40

Document review	-	Inspectors only
<b>Pharmacovigilance for non-interventional post-authorisation safety studies:</b>   Procedures for capture, assessment and reporting of AEs / SAEs. To include (but not necessarily limited to): <ul style="list-style-type: none"> <li>- Collection and recording of AEs / SAEs</li> <li>- Case processing and assessment</li> <li>- Expedited reporting of ICSRs</li> </ul>	  	
<b>LUNCH</b>	-	-
Document review	-	Inspectors only



MHRA INSPECTION NUMBER	Insp GPvP 10/16303918-0002	DAY	4
PHARMACOVIGILANCE INSPECTION OF	Bayer	DATE	06 September 2019
LOCATION	400 South Oak Way, Green Park, Reading, Berkshire, RG2 6AD United Kingdom	START TIME	09:00
Purpose of Interview		Session Lead	Staff to be interviewed
ZEG EVDB demo on screen (WebEx call)			
Pharmacovigilance for non-interventional post-authorisation safety studies:  ██████████			
Document review	-	Inspectors only	
LUNCH	-	-	

Section 40

Document review	-	Inspectors only
Inspectors meeting	-	Inspectors only
Closing meeting	-	All welcome
N.B. Documents will be requested during the inspection. This inspection plan may need to be amended during the inspection. Inspectors: 		

Section  
43

<b>MHRA INSPECTION NUMBER</b>	Insp GPvP 10/16303918-0002	<b>DAY</b>	1
<b>PHARMACOVIGILANCE INSPECTION OF</b>	Bayer [REDACTED] site inspection)	<b>DATE</b>	25 October 2019
<b>LOCATION</b>	152 Staplehurst Road, Sittingbourne, Kent ME10 1QZ	<b>START TIME</b>	09:00 arrival for a 09:15 start

Study reference number 16470: European Active Surveillance Study of LCS-12

Item	Time	Staff to be interviewed
<b>Opening Meeting</b> Review of scope of inspection and inspection plan	09:15 – 09:45	All welcome
<b>Document and data review</b> (to include lunch at 12:30)	09:45 – 16:30	Inspectors only
<b>Closing meeting</b>	16:30 – 17:00 (approx.)	All welcome

N.B.

Documents may be requested during the inspection. This inspection plan may need to be amended during the inspection.

Inspectors: [REDACTED]

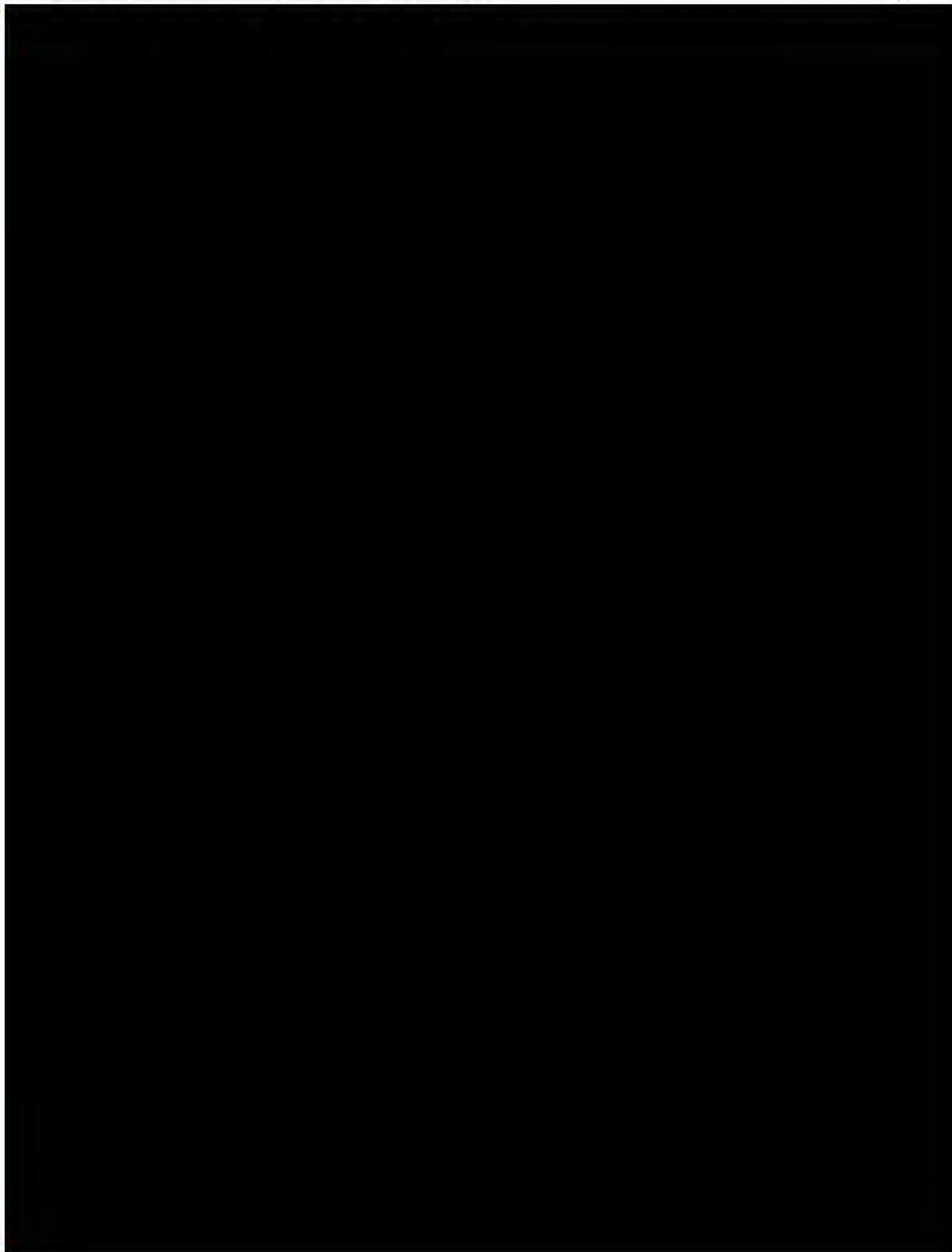
Section  
40

<b>MHRA INSPECTION NUMBER</b>	Insp GPvP 10/16303918-0002	<b>DAY</b>	1
<b>PHARMACOVIGILANCE INSPECTION OF</b>	MAH: Bayer Principal Investigator [REDACTED]	<b>DATE</b>	11 November 2019
<b>LOCATION</b>	The Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Beckett Street, Leeds, LS9 7TF	<b>START TIME</b>	09:00 arrival for a 09:30 start
[REDACTED]: REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC population for longterm Evaluation			
<b>Purpose of Interview</b>	<b>Time</b>	<b>Staff to be interviewed</b>	
<b>Opening Meeting</b> Review of scope of inspection and inspection plan	09:30 – 10:00	All welcome	
<b>Interview with site personnel</b>	10:00 – 11:30	[REDACTED]	
<b>Interview with Bayer Local Project Manager</b>	11:30 – 12:30	[REDACTED]	
<b>Document and data review (to include lunch at 12:30)</b> Please make available all relevant records, e.g. Investigator Site File, patient notes (all parts). EDC access, site specific procedures (if applicable)	12:30 – 17:00	Inspectors only	

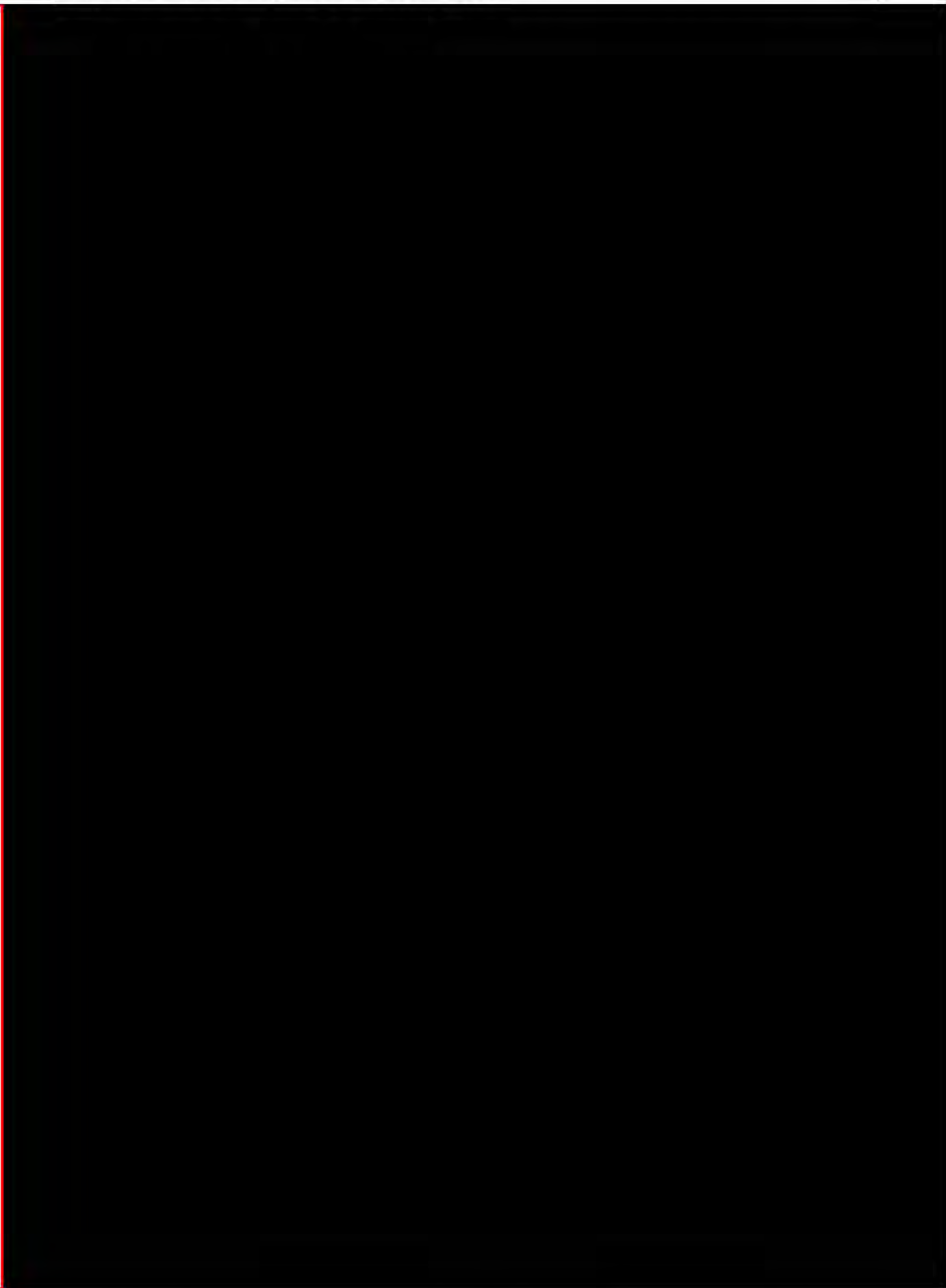
Section  
40

<b>MHRA INSPECTION NUMBER</b>	Insp GPvP 10/16303918-0002	<b>DAY</b>	2
<b>PHARMACOVIGILANCE INSPECTION OF</b>	MAH: Bayer Principal Investigator [REDACTED]	<b>DATE</b>	12 November 2019
<b>LOCATION</b>	The Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Beckett Street, Leeds, LS9 7TF	<b>START TIME</b>	09:00
<b>Purpose of Interview</b>	<b>Time</b>	<b>Staff to be interviewed</b>	
Document and data review (to include lunch at 12:00)	09:00 – 12:00	Inspectors only	
Interview with Principal Investigator	12:00 – 13:00	[REDACTED]	
Document and data review (to include lunch at 13:00)	13:00 – 14:30	Inspectors only	
Closing meeting	14:30 – 15:00 (approx.)	All welcome	
<p>N.B.          Documents will be requested during the inspection. This inspection plan may need to be amended during the inspection.          Inspectors: [REDACTED]</p>			

Section  
43



Section 40



Section  
43

