Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

Astra Zeneca

INSPECTION REPORT

INSPECTION No:
INSP GCP 17901/18897589-0001

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Inspection Summary

Inspection & Organisation Information	
Inspection Number	INSP GCP 17901/18897589-0001
Type and Purpose of Inspection	Statutory GCP Systems Inspection
Organisation Inspected	AstraZeneca
Organisation Address	Aaron Klug Building, Granta Park, Cambridge, CB21 6GH
Organisation Type	Commercial Sponsor
Dates of Inspection	4th June 2019 (Office Based Inspection – All Inspectors) 11th – 14th June 2019 (On-site Inspection – All Inspectors) Half day during 9th – 11th July 2019 (Office Based Inspection, [redacted]) Half day on 27th June 2019 (Office Based Inspection [redacted]
Lead Inspector	[redacted] Inspector
Accompanying Inspector(s)	[redacted] Inspector [redacted] and [redacted] Inspector [redacted] Inspector [redacted] Inspector
Date of Closing Meeting	14th June 2019
Inspection Report Date	24th April 2020 Correction to finding 2.4.2 made on 1st May 2020 and reissued.

Clinical Trials TMF Reviewed (Other trials were identified for review, however, time constraints prohibited TMF review of these)	
Protocol Reference and Title	[redacted] A Phase III Randomized, Open-Label, Multi-Center, Global Study of [redacted]
EUDRACT Number	[redacted]
REC Ref Number	[redacted]
IMP Details	[redacted]

Protocol Reference and Title	[redacted] Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study [redacted]
EUDRACT Number	[redacted]
REC Reference Number	[redacted]

IMP Details	[redacted]

Protocol Reference and Title	[redacted] Study to Evaluate the Effect of [redacted] on the [redacted]
EUDRACT Number	[redacted]
REC Reference Number	[redacted]
IMP Details	[redacted]

Protocol Reference and Title	[redacted] Randomised Exploratory Open-Label Study Aiming [redacted]
EUDRACT Number	[redacted]
REC Reference Number	[redacted]
IMP Details	[redacted]

Investigator Site(s) Inspected	
Name of Investigator	[redacted]
Organisation Inspected	Clinical Research Facility, Centre for Health Science
Organisation Address	Old Perth Road, Inverness, Scotland, IV2 3JH
Organisation Type	NHS Hospital
Dates of Inspection	10th – 11th October 2019
Lead Inspector	[redacted] Inspector
Accompanying Inspector(s)	None
Date of closing meeting	11th October 2019
Protocol Reference	[redacted] Study to Evaluate the Effect of [redacted]
EUDRACT Number	[redacted]

Investigator Site(s) Inspected	
Name of Investigator	[redacted]
Organisation Inspected	Queen Mary University of London
Organisation Address	Old Anatomy Building, Charterhouse Square, London, EC1M 6BQ

Organisation Type	NHS Hospital
Dates of Inspection	7th – 8th October 19 and 24th October 2019 (return visit)
Lead Inspector	[redacted] Inspector
Accompanying Inspector(s)	[redacted] Inspector
Date of closing meeting	24th October 2019
Protocol Reference	[redacted] A Phase III Randomized, Open-Label, Multi-Center, Global Study of [redacted]
EUDRACT Number	[redacted]

Background Information

Astra Zeneca (AZ) has 2 locations in the UK, Cambridge where 2500 staff are based and Luton, where approximately 40 staff responsible for site management and monitoring (SM&M) of trials are based. Staff involved in clinical trial management are also field based in the UK.

AZ was comprised of [redacted] This recent reorganisation and the process of mapping the legacy processes (which are to be retained) to the new organisation was ongoing at the time of the inspection. The [redacted] organisation that was acquired by AZ was now fully integrated and the reference to this name will be dropped. AZ continues to manage trials both internally and via CROs.

[redacted]

AZ has had 4 previous MHRA GCP systems inspections, the last inspection was started in December 2014 and reported in July 2015 (INSP GCP 17901/833864-0001).

The previous inspection had a critical and major finding for essential documents (TMF) and a major finding for archiving, therefore, at this inspection, it was a priority to assess whether effective remedial actions had been taken in these areas. Additionally, there was a major finding for pharmacovigilance and as many organisations had also recently had critical findings in this area, this was selected as a system to examine this time. Monitoring was not examined as a system at the last inspection, so this was also selected this time for review.

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 **1 Critical finding** identified during this inspection relating to Pharmacovigilance. ***The critical finding details below are those that were reported by letter on 19JUL19 following the inspection. Responses to the critical finding were provided by AstraZeneca on 27SEP19. Follow up to closure of the critical finding has already commenced separately and NO further information should be provided relating to this critical finding in a response to this inspection report.***	
1.1	**Pharmacovigilance** *If the sponsor proposes to make a substantial amendment to a clinical trial authorisation which consists of, or includes, an amendment to - (a) the terms of the request for authorisation of the clinical trial; or (b) the particulars or documents that accompanied that request, he shall send a valid notice of amendment to the licensing authority, whether or not he is also required to send a notice in accordance with paragraph (4).* ***UK Statutory Instrument 2004/1031 (as amended), 24 (3).*** *If the sponsor proposes to make a substantial amendment to a clinical trial authorisation which consists of, or includes, an amendment to - (a) the terms of the application for an ethics committee opinion in relation to the clinical trial; or (b) the particulars or documents that accompanied that application, he shall send a valid notice of amendment to the relevant ethics committee, whether or not he is also required to send a notice in accordance with paragraph (3).* ***UK Statutory Instrument 2004/1031 (as amended), 24 (4).*** *Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance with (b) the terms of - (i) the request for authorisation to conduct that trial, and any particulars or documents accompanying that request or that application.* ***UK Statutory Instrument 2004/1031 (as amended), 29.*** *Notification of suspected unexpected serious adverse reactions.* ***UK Statutory Instrument 2004/1031 (as amended), 33*** *As soon as practicable after the end of the reporting year, a sponsor shall, in relation to each investigational medicinal product tested in clinical trials in the United Kingdom for which he is the sponsor furnish the licensing authority and the relevant ethics committees with - (a) a list of all the suspected serious adverse reactions which have occurred during that year in relation to - (i) those trials, whether at trial sites in the United Kingdom or elsewhere, or (ii) any other trials relating to that product which are conducted outside the United Kingdom and for which he is the sponsor, including those reactions relating to any investigational medicinal product used as a placebo or as a reference in those trials; and (b) a report on the safety of the subjects of those trials.* ***UK Statutory Instrument 2004/1031 (as amended), 35.*** *No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *The necessary procedures to secure the quality of every aspect of the trial shall be complied with.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).***

	All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9).*** *The Investigator's Brochure (IB) in effect at the start of the reporting period should serve as the reference safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug.* ***EMA/CHMP/ICH/309348/2008 ICH guideline E2F on development safety update report, 2.6*** *If the IMP has a marketing authorisation in several Member States concerned with different SmPCs, the sponsor should select the most appropriate SmPC, with reference to subject safety, as RSI.* ***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"), June 2011, 54.*** *The RSI may change during the conduct of a clinical trial. This is typically a substantial amendment* ***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"), June 2011, 55.*** *The IB as last amended and approved by the national competent authority or equivalent document (e.g. SmPC for marketed products) serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.* ***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), March 2010, 58*** *The expectedness of an adverse reaction is determined by the sponsor in the reference safety information ("RSI").* ***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"), June 2011CT3, Paragraph 51*** *Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.* ***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"), June 2011CT3, Paragraph 50*** *The RSI may change during the conduct of a clinical trial……For the purpose of SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR applies.* ***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) Paragraph 55,*** *The RSI in effect at the start of the reporting period serves as the RSI for the reporting period.* ***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) Paragraph 129*** The inspection identified that case processing was not in compliance with UK legislation and guidance documents CT-3 and CT-1 and CTFG Q&A RSI, that there was a failure to implement CAPA for previous major inspection findings and there were new findings in clinical trial pharmacovigilance. These issues can have a significant impact on the reporting of safety information to regulatory authorities and taken together these constitute a critical finding grading.
1.1.1	**Reference Safety Information (RSI)**
	The format, implementation and use of the Reference Safety Information (RSI) for expectedness assessments for serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) was not in accordance with CT-3 Guidance and Clinical Trial Facilitation Group (CTFG) Q&A Reference Safety Information (RSI) (November 2017). Therefore, there was significant potential for under-reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) due to use of unapproved terms being classed

	as "expected" events. It was acknowledged that since May 2019 a planned deviation to the CTFG RSI guidance was in place to ensure the Investigator Brochure (IB) and RSI only contain Preferred Terms (PTs) and not medical concepts. However, there was a lack of a Corrective and Preventative Action (CAPA) to ensure that any unapproved terms had been deactivated in the safety database (named [redacted]) and what impact there had been on expedited SUSAR reporting or the content of Develop Safety Update Reports (DSURs).
1.1.1.1	<u>There were more adverse reaction terms considered expected in the safety database used for SAR case assessment than contained in the RSI that had been approved by the MHRA in the Clinical Trial Authorisation (CTA).</u> There were additional preferred terms (PTs) programmed as expected in the safety database [redacted] than approved in the RSI due to use of medical concepts and synonymous terms. It was explained in a document request provided to the inspectors that for Astra Zeneca (AZ) Investigational Medicinal Products (IMPs) which held a marketing authorisation, the core data sheet section 4.8 undesirable effects was used as the RSI which contained medical concepts and synonymous terms and *"When medical concepts are transferred to* [redacted] *the PTs relevant to that concept (and agreed by the Global Safety Physician) are input to* [redacted] *as IB listedess".* Therefore, additional terms were considered expected than approved in the CTA for a trial as there was an additional assessment which could be made by the Global safety Physician for PTs to be included as expected. As a result, the following IMPs contained significantly more expected PTs than what was approved in the RSI: • [redacted] PTs were programmed as expected in [redacted] (e.g. [redacted]"), yet in IB Edition [redacted] approved by the MHRA on 10JAN17, the RSI contained only [redacted] expected PTs: [redacted] An example of an incorrectly assessed case was [redacted] of [redacted] which was drug related and considered expected despite not being listed in IB edition [redacted] or the [redacted] trial (the inspector was informed via a document request that [redacted]" was included as a medical concept of [redacted]"). • [redacted] PTs had been programmed as expected in [redacted] of which [redacted] were removed (deactivated) on 19MAR19 and [redacted] removed on 03MAY19. Of the remaining [redacted] PTs programmed as expected at the time of the inspection, one of these terms, [redacted]" was not approved for the [redacted] trial. CTA approval dated 04AUG17 contained a remark that [redacted] could not be considered expected, yet this had already been programmed as expected on 19MAY17 with an activation date of 02MAY17. Other examples of terms that had been considered expected which were not stated in the approved RSI at the time included (not an exhaustive list) [redacted] (all added 18JAN19 and removed 19MAR19).
1.1.1.2	<u>Incorrect use of SmPC for identification of expectedness Preferred Terms</u> There was no requirement in the quality system to ensure only section 4.8 of the SmPC was used for expectedness assessments of comparator products (not AZ products). It was explained during interview that the Global Safety Physician reviews the entire SmPC including warnings and contraindications to determine events which should be considered expected and autolabelled in [redacted] Therefore, more terms

	than approved in the CTA application SmPC section 4.8 could be programmed as expected in the safety database.
1.1.1.3	Implementation of Regulatory Authority Requests for RSI in the Clinical Trial Authorisation Remarks and comments provided on MHRA Clinical Trial Authorisations (CTAs) approvals regarding the format of RSI that were requested to be addressed in the next substantial amendment had not been addressed. This was not performed at subsequent amendments and there was no formalised process to ensure feedback and requirements in relation to the RSI were addressed at the next RSI or IB update (until a Grounds for Non-Acceptance was issued). The impact of the lack of a process was illustrated by review of the MHRA CTU comments for the [redacted] rial. The [redacted] IB submitted for the [redacted] trial received remarks from the MHRA on 04AUG17 regarding the RSI format within IB edition [redacted] dated 13JAN17. The remarks were not addressed in IB edition [redacted] dated 24JAN19 which received a Grounds for Non-Acceptance by the MHRA on 28MAR19. The comments were then incorporated into IB edition [redacted] dated 13MAY19 which was awaiting MHRA approval at the time of the inspection. There was evidence of the remarks not being adhered to for this trial as per finding 1.1.1.1. The remarks below, for example, show that relevant information kept outside of the RSI was being questioned on both occasions by the MHRA. Example of remarks stated in CTA approval letter dated 04AUG17 regarding IB edition [redacted] *Remark concerning the Reference Safety Information (RSI) section: table 1, currently included in the covering letter, must be added to the RSI section at the next IB update; serious adverse reactions occurred once cannot be considered expected unless a written rationale is provided and approved by the Competent Authority [redacted] cannot be considered expected). The Sponsor is reminded that should a serious event occur for any term which has only ever previously been seen as non-serious this should be considered unexpected and therefore a SUSAR. The Sponsor is also reminded that use of medical concept and grouping of Preferred Terms is strongly discouraged.* GNA issued for IB edition [redacted] issued 28MAR19: *Remarks: Clinical Grounds for Non-Acceptance The present substantial amendment with regard to updates in the Investigator's Brochure is refused. A new substantial amendment should be submitted to address the following: 1. Tabulated list of adverse reaction does align with the SmPC but if the sponsor has chosen to use IB as RSI for this clinical trial then the RSI section in the IB must be compliant with the CTFG RSI guidance i.e. by adding only serious ADR in [redacted] and to include life-threatening and fatal data. 2. [redacted] This approach is not acceptable. 3. The synonymous terms must be removed from the footnotes and to be included within the expected table.*
1.1.2	**Failure to Implement effective CAPA for previous major MHRA inspection finding for Pharmacovigilance or for New Guidance** The inspection findings in relation to the major finding for pharmacovigilance from the last MHRA GCP inspection had not been addressed with a robust CAPA in a timely

	manner and there was evidence that implemented actions had been ineffective. Additionally, there was a delay in implementing new regulatory guidance.
1.1.2.1	The following issues were identified that demonstrated a delay in implementation of CAPA to comply with the previous inspection response actions accepted by the MHRA or delay in complying with new/existing guidance: (A) The Safety database had been updated only recently on 17NOV18 to include the following system functionality addressing the findings from the previous inspection, indicating that the submitted CAPA had not been implemented in a timely manner • Requirement to use the RSI in effect at the time of onset of an event for initial cases (Finding 2.2.2 from the previous inspection) • Requirement for follow up cases to be reviewed against the RSI in effect at time of onset (Finding 2.2.4 from the last inspection) (B) Findings 2.2.5 and 2.2.6 from the previous inspection regarding approval of comparator IMP RSIs and review of updates/changes to comparator RSIs to determine if a substantial amendment would be required prior to implementation (as required by CT-1) was not actioned until 22NOV18 when a cross functional process for management of comparator RSIs was instigated and procedures were updated. These actions were expected to be completed by September 2015 (finding 2.2.6) and Q1 2016 (finding 2.2.5). A resultant process for management of comparator RSIs including ensuring the necessary regulatory approvals were obtained was not actually implemented until 24APR019 ([redacted] effective 24 April 2019). There had not been a retrospective review performed to determine if any SUSARs had been previously been underreported. There was also a lack of information in the procedure to ensure that the approved comparator RSI approved at the time of event onset is used to determine expectedness of the SAR. (C) Until 31MAY19, AZ did not expedite comparator SUSARs within 7/15 days (as relevant). The process was revised following review of the MHRA blog published on 09APR19 and the current CAPA actions were pending: • [redacted] will be updated by 30JUL19 • Data Entry Process instructions will be updated by 30JUN19 • [redacted] data entry site were training on 30MAY19. AZ had not performed a retrospective review to expedite any relevant cases and the justification for this was provided as follows "For the process change on 31MAY19, it was concluded that the benefit-risk profile of the comparators would be minimally affected by these individual case safety reports (event terms that are expected SAR for the AZ IMP), and therefore it was decided that they would be unblinded and submitted at end-of-study unblinding according to the previous process, and that no retrospective updates would be done." (D) Until 17NOV18, life threatening reactions were considered expected provided the event term was listed in the RSI. There was no confirmation of whether the severity of "life threatening" was also listed in the RSI and approved by the

	MHRA prior to considering these event terms expected. Following review of the CTFG Q&A RSI (November 2017), business rules in the [redacted] database were updated on 17NOV18 to ensure that the severity of life threatening is taken into consideration when determining if an event is expected. Note: This was always a requirement from CT-3 since 2006, see current section 7.2.2 (50), but had not been implemented by AZ until 17NOV18. AZ had not performed a retrospective review to determine whether any SUSARs had not been reported as a result of this previous system configuration. This issue had the potential to impact expedited reporting of SUSARs to MHRA, Ethics Committees and notification to investigators. (E) The IB management process had been updated to ensure that the RSI would be implemented once all approvals were received relating to auto expectedness functionality in [redacted], but it did not come into effect until 19JAN17 ([redacted] effective 19JAN17). It was acknowledged that version [redacted] of the SOP required approval of substantial amendment, but the whole process on how this was tracked and amended in the database was delayed from the expected CAPA implementation date of the end of 2015. **There was no retrospective impact assessment performed of the above issues on under-reporting of SUSARs or on DSURs content. Therefore, prior to these changes in November 2018 use of the RSI was not in accordance with CT-1 and CT-3 despite a number of these issues being highlighted during the inspection in early 2015.**
1.1.2.2	The following issues were identified that indicated that the CAPA that had been implemented was ineffective: (A) There was evidence of implementation of updated RSIs without MHRA approval which was a repeat of a finding from the previous inspection (Finding 2.2.1). For example, the IB edition [redacted] and [redacted] for [redacted] which included a change to the RSI were implemented prior to MHRA approval; IB edition [redacted] had received a "grounds for non-acceptance (GNA)" from MHRA on 28MAR17 and at the time of the inspection IB edition [redacted] had not received MHRA approval either. However, 2 new terms of [redacted] and [redacted]" were programmed as expected PTs in safety database effective from 05FEB19. These had been removed on 11JUN19 (just prior to the inspection). This had been identified as a response to a pre inspection request from the inspectors on 04JUN19 for information about RSI implementation and approvals for the selected IMPs that would be examined in the inspection. It was acknowledged that AZ stated that during this period no cases were received which would have been affected and would have required expedited reporting. This finding demonstrated that the current processes for ensuring an RSI would not be implemented prior to CTA approval was ineffective. (B) There was delayed notification of SAEs to the sponsor and delayed expedited reporting as per Finding 2.2.7 at the previous inspection. There was evidence that an unacceptable level of delay in notifications was still occurring. This indicated that the scheduled CAPA accepted by the MHRA had not been effective. Examples were seen of cases being passed to [redacted] and/or expedited to MHRA and REC late due to various reasons. More specifically, many were due to issues identified with the [redacted] safety reporting module functionality, for example, the email alert not being set-

	up correctly, the SAE mailbox was not set-up to receive [redacted] alerts and a [redacted] programming error resulting in initial SAEs (issue logged in the [redacted] trial deviation log provided to the inspectors) or SAE follow-up information not being sent to [redacted] (serious breach [redacted] reported prior to the inspection). • [redacted] Case [redacted] (late reporting to [redacted] MHRA, REC) Company receipt date was incorrectly recorded as 11APR16 in [redacted] this should have been 21APR16, event onset was 20APR16. The case was not passed to [redacted] until 05MAY16 (14 days after AZ receipt) and the case was not expedited to MHRA and REC until 25MAY16 due to a [redacted] processing error, which was 34 days after AZ receipt and 20 days after [redacted] receipt. • [redacted] (late reporting to [redacted]), [redacted] (late reporting to [redacted] [redacted] (late reporting to [redacted] MHRA, REC) There was a delay in cases being submitted to [redacted] because the email alert to [redacted] was not set up correctly in [redacted] at that time (the set-up was corrected on 28AUG17). • [redacted] [redacted] (reported 10 days late to [redacted]) There was an initial request for more detailed compliance information (Reason for Delay and CAPA) to Clinical Development Manager on 22AUG17 and has subsequently followed-up with further requests on 25AUG17 and on 26AUG17. No response has been received from the study team. • [redacted] (late reporting to [redacted] MHRA, REC) This was a processing error, in terms of set up of the required mailbox. In the UK all SAE alerts are sent to SAE mailbox and this mailbox is monitored twice daily. The AZ representative responsible for monitoring this mailbox would enter the "AZ Aware date" in [redacted] However, for the [redacted] trial, this email ID was not set-up to receive the alerts. Hence, even though monitor received SAE alert he/she did not complete "AZ Aware date" in [redacted] because they assumed that this would be completed by the AZ representative who was monitoring the SAE mailbox. On 23FEB16, by review of a regular SAE reconciliation report it was identified that this SAE was reported in [redacted] but not available in the safety database. [redacted] identified the reason as, "monitor did not select 'Yes' option in [redacted] which triggers the alert to [redacted] n the AZ Aware form". The response to this finding should include a comprehensive review of the entire process for SAE submission and receipt by AZ and [redacted] and a full impact assessment undertaken to determine the extent of late reporting since 01JAN16 (or the date implementation of [redacted] SAE reporting module if later).
1.1.3	**Failure to implement a conservative approach for missing investigator causality** A conservative approach was not applied where the investigator's causality assessment is missing on an SAE report submitted from the investigator site. Instead, the assigned company causality would drive reporting requirements as stated in section 4.4.3.4 of [redacted] version [redacted] (17MAY16). This resulted in delayed reporting of SUSARs and had the

	potential for under reporting of SUSARs. Examples of late reporting of SUSARs were noted as a result of this issue: • UNREPORTED SUSAR: Case [redacted] was received on 26JUL18. The investigator causality was missing, and company causality was "not related". This was an unexpected event. Causality was chased by AZ and the investigator stated that causality was "unknown". The case was not expedited with the most conservative approach. • LATE REPORTED SUSAR: Case [redacted] was received on 05MAR19. The investigator causality was missing, and company causality was "not related". The event was considered not reportable and the event was fatal and unexpected. The investigator causality was provided in a follow up report on 12MAR19 as "related" and the case was expedited on 14MAR19, however, the due date for this SUSAR should have been 12MAR19 based on when AZ were first made aware of the event. • LATE REPORTED SUSAR: Case [redacted] was received on 25JAN18. The investigator causality was missing, and company causality was "not related". Event was unexpected. The database event was updated to version [redacted] with new event PT [redacted] with the investigator causality as missing and the company causality as "not related". The case was not expedited until after 20DEC18, when the reporter causality of "related" was received (case version [redacted]), however, the due date for this SUSAR should have been 09FEB18 based on when AZ were first made aware of the event. The issues above would also impact: • The periodic line listings of SUSARs provided to investigators for the trial because the functional specification for these reports would be based on the [redacted] data field expectedness assessment made at the time of case processing (as per [redacted] version [redacted] approved 24JAN19) • The DSUR cumulative listing of SARs during a reporting period if a conservative approach was not taken. This would be because the functional specification for the DSUR would not include these cases in the listing ([redacted] version [redacted] approved 01 Sep 2017).
1.1.4	**Inconsistency o[redacted] and [redacted] Databases** A listing of all SAEs entered into the [redacted] clinical database for the [redacted] trial was requested so that this could be compared with the SAE listing provided from the [redacted] safety database. Review of the [redacted] listing identified SAEs which were recorded in [redacted] but not in the safety database. It was noted that these events are relatively recent. A response to this finding should provide details on the timing of [redacted] and [redacted] reconciliation activities and whether these had been undertaken at the required frequency. If not, the response should include an initial investigation into whether all SAEs have been recorded in the safety database and the impact of any delayed reports. The review should be performed for this and all UK trials live since 01JAN16 (or when [redacted] SAE reporting commenced if after this date) to ensure the SAE information in [redacted] has been reconciled with the data in [redacted] • Patient [redacted] SAE of '[redacted]". The event became serious

	on 17SEP18. • Patient [redacted] SAE of [redacted] rate". The event became serious on 25APR19. • Patient [redacted] SAE of [redacted] The event became serious on 28MAY19.

2.0 Major Findings There were **4 Major findings** identified during this inspection relating to Archiving, Quality Assurance, Essential Documents (Trial Master File) and Monitoring.	
2.1	**Archiving** *The sponsor shall keep a trial master file for a clinical trial. The sponsor and the chief investigator shall ensure that the documents contained, or which have been contained, in the trial master file are retained for at least 5 years after the conclusion of the trial and that during that period are—(a) readily available to the licensing authority on request; and (b) complete and legible. The sponsor shall appoint named individuals within his organisation to be responsible for archiving the documents which are, or have been, contained in the trial master file and, subject to paragraph (2) [The sponsor shall ensure that the trial master file is readily available at all reasonable times for inspection by the licensing authority or any person appointed by the sponsor to audit the arrangements for the trial], access to those documents shall be restricted to those appointed individuals. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.* ***UK Statutory Instrument 2004/1031 (as amended), Regulation 31A (1), (2), (7) and (9)*** ***Finding 2.1.2 below was very similar to the inspection finding 2.3.1 from the last MHRA GCP inspection and considering Finding 2.1.1 below, appropriate CAPA as per the last inspection response has not been implemented.***
2.1.1	The named archivists (2 persons) had responsibility only for the [redacted] system containing essential documents. Other electronic systems were being used as set out in Finding 2.3.1, but there was no oversight of these to ensure all documents/data in these systems would be archived at the same time, therefore ensuring the complete TMF would be archived and that the necessary subsequent oversight of maintenance and retrieval from the archive would be in place. Therefore, this arrangement did not meet the requirements of the legislation
2.1.2	There had been no detailed assessment of the systems used for essential documents that were not [redacted] in terms of how the system would be locked at archive, the format of data/files retained & maintenance of readability and how access would be controlled in accordance with the legislation under control of the named archivist (see 2.1.1). Whilst it was stated in '[redacted] MAY 2019 (not a quality system document) that archiving was undertaken according to the systems own procedures, there was not an overall procedure in the quality system for overseeing the TMF archiving as it was fragmented and not all systems appear to be addressed. It was stated that the AZ Global Retention and Disposal (GRAD) schedule would be followed, but it was not clear whether essential documents/data are retained as part of the [redacted]
2.2	**Quality Assurance** *No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial*

	shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *The necessary procedures to secure the quality of every aspect of the trial shall be complied with.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).*** *Non-compliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance. If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016 5.20.1***
2.2.1	There was a lack of root cause analysis and impact assessment applied to determine an effective Corrective and Preventative Actions (CAPA) in response to previous GCP inspection findings. As a result, it was clear that previous major findings for pharmacovigilance, essential documents (TMF) and archiving and the critical finding for essential documents (TMF) at the last MHRA GCP Inspection (INSP GCP 17901/833864-0001 issued 02JUL15) had not been adequately or completely addressed during this inspection and this issue also contributed to the critical finding for PV. ***As part of the response to this finding, AstraZeneca are required to review the previous inspection findings and ensure they have all been implemented.*** ***Where changes to an agreed CAPA or delays are encountered, the organisation should have procedures in place to contact the lead inspector to notify them of the issue – AZ should confirm that such procedures are in place.***
2.2.2	There was a lack of QA oversight and tracking to ensure that findings from the last inspection had been implemented within the required due dates. For example (not an exhaustive list): • Previous inspection Finding 2.3.1: Archiving issues were not resolved (see finding 2.1 above), however, no due dates were provided in the response to this finding of 11AUG15. • Previous inspection Findings 2.2.2 and 2.2.4: [redacted] safety database was not updated until 17NOV18 to ensure the RSI in place at the time of onset was used for expectedness assessments • Previous inspection Findings 2.2.5 and 2.2.6: A cross functional process for management of comparator RSIs was not implemented until 22NOV18 as per finding 1.1.2.1. It was explained that this was a result of a lack of a formal procedure for tracking of inspection findings from the last MHRA GCP inspection to ensure planned implementation dates were recorded and followed up. It was acknowledged that a process was now in place (Process [redacted]).
2.2.3	In October 2018, AZ identified that 213 SUSAR cases had not been submitted to the EMA due to deficiencies in the [redacted] (AZ safety database) product lists supporting reporting to EMA, particularly [redacted] cases were processed correctly and were successfully submitted to other receivers. The root cause analysis identified that "Key

	Ingredient" lists for IMPs had not been correctly maintained and reviewed and the process for maintaining and monitoring such information was not adequately documented in the AZ QMS. Following identification of this issue, affected SUSAR cases were reported to EMA and production of a monthly report was instigated, whereby all IMPs were listed and checked in [redacted] However, despite this issue being logged as a critical quality incident on 25OCT18, the QMS at the time of the inspection had not been updated to document the revised process. Also, the critical quality incident report provided from [redacted] (reference [redacted] did not document the update to AZ procedures as a deliverable. Note, the overall target CAPA completion date was recoded as June 2019 on the [redacted] report, 8 months after the issue was identified and was still open at the time of inspection; this was not timely given the impact failure to comply with the revised process could have on SUSAR reporting. This finding also provides another example of an issue that has impacted on SUSAR submissions – see finding 1.1.2.2 B). ***As part of the response to this finding, AZ are asked to confirm all deliverables associated with this incident and their completion / target completion date.***
2.3	**Essential Documents (Trial Master File)** *No person shall – (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *The necessary procedures to secure the quality of every aspect of the trial shall be complied with.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).*** *The sponsor shall keep a trial master file for a clinical trial* ***UK Statutory Instrument 2004/1031 (as amended), Regulation 31A (1)*** *The master file shall at all times contain the essential documents relating to that clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Regulation 31A (3)*** *The essential documents relating to a clinical trial are those which — (a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and (b) show whether the trial is, or has been, conducted in accordance with the applicable requirements of Directive 2001/83/EC, the Directive, the GCP Directive and Commission Directive 2003/94/EC.* ***UK Statutory Instrument 2004/1031 (as amended), Regulation 31A (4)*** *Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents. The storage system (irrespective of the media used) should provide for document identification, search and retrieval. Depending on the activities being carried out, individual trials may require additional*

	documents not specifically mentioned in the essential document list. The sponsor and/or investigator/institution should include these as part of the trial master file. ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016 8.1*** ***There was improvement with respect to the Trial Master File (TMF) critical finding due to the implementation of the new eTMF system since the last inspection. For this reason, a critical finding was not given despite issues identified as follows. These concerned ensuring the system was properly defined and that it was used correctly such that a complete TMF would be readily available for inspection. Therefore, some aspects of the major finding at the last inspection were still an issue (for example missing documents). In addition, new issues were identified concerning the oversight of TMFs managed by CROs. Following receipt and review of the responses, AZ may be required to provided quarterly reports to the MHRA to demonstrate the implementation of the CAPA for this finding.***
2.3.1	Not all TMF systems that were being used to hold essential documents had been defined in a formal quality system procedure, such as [redacted] For example, the use of the [redacted] for storing essential documents was identified in an email from the trial monitor initials [redacted] for the [redacted] trial on 26FEB18 concerning the HRA approval email which stated, "I'll pdf and save to the [redacted]". The only systems identified were the eTMF [redacted], [redacted] (decommissioned). Some of the systems would contain documents during the live phase (e.g. [redacted]), but the systems had not been included as part of the TMF definition, which was inappropriate as the TMF could be inspected during the live phase (see issue below with empty IMP section in the [redacted] trial). Some of the other systems were only referenced in the Master TMF Index at the artefact level so it was difficult to quickly obtain an overview of the TMF, the systems it contained and which categories of essential documents were held in which system. [redacted] MAY 2019 was provided that did identify more, but not all, systems, however, it did not appear to be part of the formal quality system. See also the recommendation concerning the quality system documentation concerning the TMF.
2.3.2	There were issues identified relating to the quality of the eTMF, particularly for the [redacted] trial eTMF as follows. Missing Documents • MHRA acknowledgement letters dated 24NOV16, 26SEP17, 17JAN19 and 05FEB19 for [redacted] trial not present in the eTMF. • MHRA submission letter 21SEP17 of the batch analysis data as per the condition and updated CMC for [redacted] trial not in the eTMF • There were no documents in the IP section at site level [redacted] trial eTMF, e.g., no drug shipment and no other system defined, e.g. [redacted] for this. The TMF plan (V3 08MAY19) stated that these would only be filed after database lock, which

would not be acceptable.

- There were no documents in the [redacted] site level file for the [redacted] site to demonstrate site training in GCP, eCRF or [redacted]
- For the initial REC submission for the [redacted] trial, the Letter from REC for information and the AZ response to request for info letter 26APR17 were not in the eTMF.
- The expected acknowledgment letters from the REC for the [redacted] trial submissions were not present. This was particularly evident for SUSAR submissions, as the submission form would be signed by the REC administrator and returned to the sponsor to confirm receipt. There were only 4 unsigned (initial plus 3 follow ups) out of the 8 SUSAR submissions in the eTMF as listed below. These had been retained elsewhere and not filed in the TMF.
    - EC form notification 30JUL18 - not signed by REC - case [redacted] initial – sponsor receipt date 24JUL18
    - REC form notification 14AUG18 - not signed by REC - case [redacted] – sponsor receipt date 10AUG18
    - REC form notification 17AUG18 - not signed by REC - case [redacted] – sponsor receipt date 10AUG18
    - REC form notification 10SEP18 - not signed by REC - case [redacted] – sponsor receipt date 06SEP18

[redacted]

[redacted] June 2019 did not adequately cover the filing of correspondence for reporting safety information to the REC (i.e. only cover letters to REC, not the acknowledgements/correspondence received from REC) and this accounted for the incomplete documentation.

- The [redacted] trial eTMF did not contain (or signpost) certain essential documents for the trial, for example, information from [redacted] around unit testing of the [redacted] or the executed UAT scripts for the [redacted]

Misfiled Documents

- Subsequent Communications about the MHRA approval with conditions for [redacted] of the investigator brochure for the [redacted] trial were not filed at country level.
- Email 10MAY17 to [redacted] trial investigator sites sending REC/MHRA approvals (REC package) and HRA initial assessment letters (promised HRA approval to follow), i.e., site level correspondence and not correspondence with the REC was

filed in REC section and not in the site level correspondence.

- Email 05MAR18 in the [redacted] eTMF REC section was site level correspondence informing sites to implement amendment [redacted]

Duplicated Documents

- MHRA submission cover letter 22NOV16 for [redacted] located in the eTMF twice once described as initial, once as an amendment.
- The Integrated Quality and Risk Management Plan [redacted] was duplicated in the [redacted] eTMF.
- HRA approval 15MAY17 for [redacted] trial was duplicated in the eTMF.
- [redacted] trial Email to REC 01NOV17 regarding change of contact person was duplicated with dates 01NOV17 and 06NOV17.

- Additionally, for the [redacted] trial, there were examples of duplicated records in the REC folder in [redacted] the CV for person initials [redacted] 05NOV13, Thank you card 05SEP15 and the patient information sheet and consent forms [redacted] and [redacted]

Misnamed Documents

- An MHRA approval dated 18FEB19 with conditions about the Investigator Brochure [redacted] relating to the [redacted] was in the eTMF as description "rejection of IB [redacted] , when it was not a non-acceptance letter.
- HRA assessment/categorisation email of amendment [redacted] 06JUN17 for the [redacted] trial was incorrectly labelled as HRA approval in eTMF, whereas it should be correspondence.
- HRA approval amendment 23FEB18 for the [redacted] trial (the document in the eTMF was actually an email forwarding the approval from the Chief Investigator, therefore, the document in the system has a later document date of 26FEB18, which was not the date of HRA approval as the label suggested)

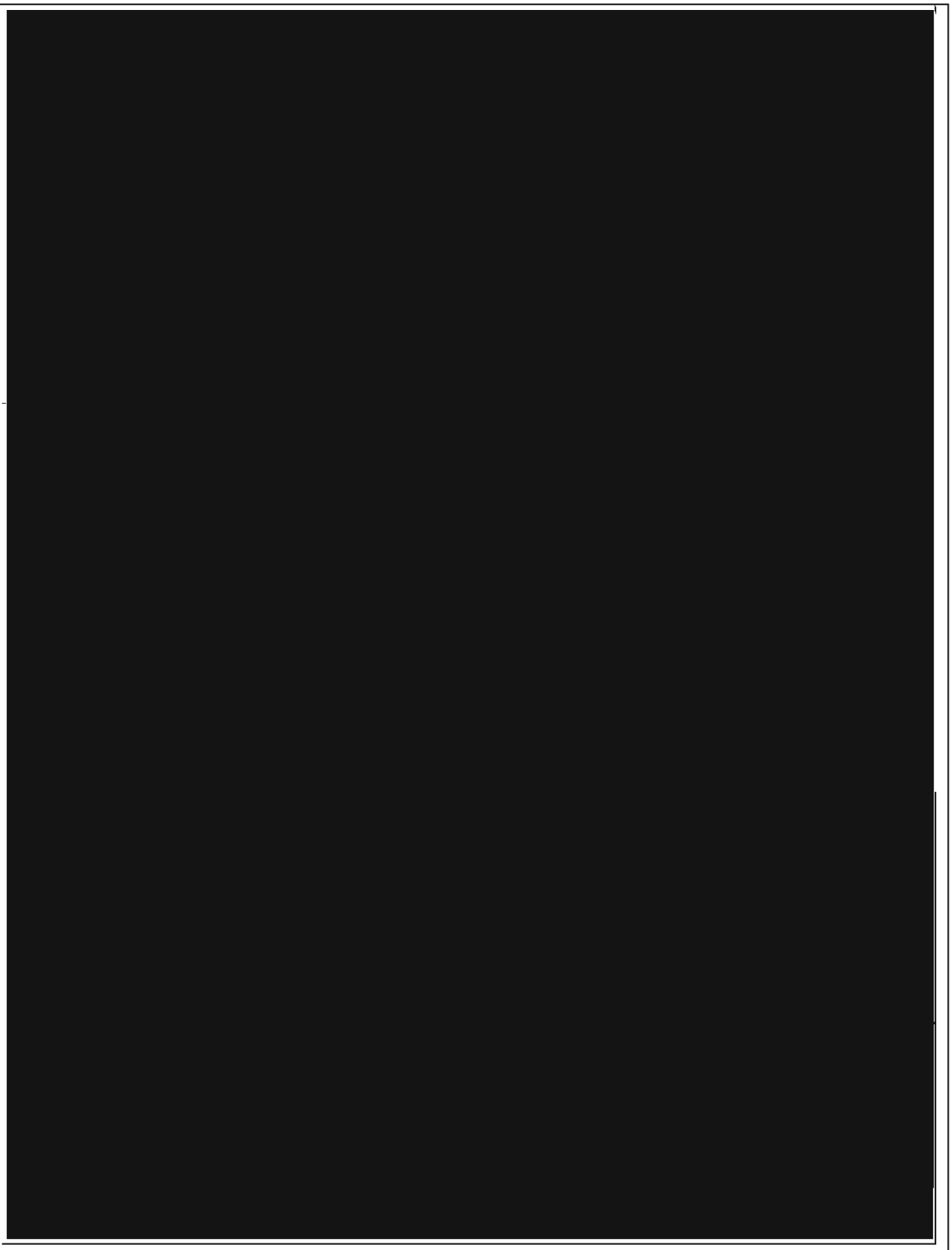
- Additionally, for the [redacted] the labelling of documents didn't always assist with review and provide enough information on the content of a document, for example, all of the UK monitoring visit reports were labelled [redacted]

Certification of Documents

- In the [redacted] trial eTMF there was an example of an uncertified wet ink copy (IMP release form signed 28JUN17 for [redacted] site at [redacted]). [redacted] was made effective 05APR18 and it was noted that the guidance stated that "any legacy documents scanned and uploaded to [redacted] eTMF and either approved or in progress, before the copy certification process is enabled in [redacted] will not be certified in the [redacted] eTMF". It was not possible to determine whether this was a legacy document or not. The original paper version was not provided, but the guidance stated that paper documents should be retained per [redacted] 08MAY19 also stated they should be retained. The paper version of the document was requested, but a scanned version was provided post inspection and there was no evidence that it wasn't the electronic version tidied up, especially when it was called "rotation" and had no creation date. Therefore, it could not be confirmed that the paper version was available during the inspection rather than just an uncertified copy.

	• There was no certification process in place at launch of eTMF and no formal process was in place to undertake QC for certification, i.e. to check that if certification was required, that it had been completed. [redacted] 01MAR17 did not address certification checks. Document Scan Quality • For the [redacted] trial, there was an example of a scanned image that was upside down: [redacted] Management of emails • In the [redacted] trial eTMF, there were emails, for example, the covering letter to the REC for amendments dated 22MAY17 and 22JAN18, the covering letter for Annual Progress Report dated 16MAY19, email 21NOV17 to PI to confirm no IB update needed, and an email 15MAY17 to all investigators sending the HRA approval letter) where the prescribed process in the quality system had not been followed for the attachments to the email. In these cases, it was not attached, was not in the source document as it was a PDF and the document metadata information said no attachments. [redacted] 01MAR17 did not address checking of email attachments.
2.3.3	The [redacted] trial was contracted to CRO, so the arrangements for the TMF would be more complex. The [redacted] trial TMF consisted of the AZ [redacted] eTMF as well as the CRO eTMF. The main trial eTMF was maintained by the CRO [redacted] in their [redacted] system. It was explained during interview that all documents would be stored in the [redacted] eTMF for the trial with a few oversight documents in the AZ eTMF. This was consistent with the [redacted] JUNE 2018 that stated that the "Study Manager, or delegate should ensure that the AZ eTMF is completed with the Sponsor owned documentation that is not shared with CROs." However, the following issues were identified upon review of the eTMF for the trial: • The AZ eTMF was lacking in documents and did not contain essential documents such as the trial protocol, IB, CRF, monitoring plan, data management plan etc. Whilst these documents existed in the [redacted] eTMF, review of the audit trail for the [redacted] eTMF demonstrated that the system was only accessed by AZ staff performing QC activities in relation to the eTMF. It was not accessed by the AZ functional project team members at all. Instead AZ functional team members accessed an ancillary system, [redacted], to access essential documents required for the trial, which was not identified as a TMF system in the [redacted] May 2019. Document request [redacted] stated the following regarding [redacted] *area contains various types of documents that provide an overview of the study to the project team members. As an example, the folder in which essential study documents such as latest version of CSP, IB, ICF & CRF, is called 'Study Documents'. Team members can easily access [redacted] folder and work collaboratively on materials such as presentations and reports. With reference to core final study documents, the team do not make any changes, as such documents are 'read only' versions".* A list of users with access to [redacted] was provided and 100 AZ [redacted] staff had access at the time of the inspection which demonstrated it was used as an eTMF

	instead of AZ staff accessing [redacted] eTMF and the AZ [redacted] eTMF. • The inspector was not provided with direct access to [redacted] despite it containing essential trial documents in order to review what oversight AZ had of the trial.
2.3.4	It was evident that for preferred suppliers (e.g. for [redacted] there was some oversight of the TMF at programme level via the [redacted] strategic CRO partnership and that there are AZ employees who access the [redacted] eTMF for QC proposes (for example in the [redacted] trial). However, the [redacted] trial TMF contracted to [redacted] required substantial remediation to be suitable for an MHRA GCP inspection in March 2018 of [redacted] and therefore it appears that oversight of the quality of the TMF had not taken place. AZ had no documentation to demonstrate that a review of AZ [redacted] sponsored trials had taken place where the TMF was externally managed. Therefore, it appeared that these trials were not reviewed prior to this March 2018 inspection, which was after the previous MHRA inspection of AZ or indeed after this March 2018 inspection to determine the TMF quality and if remediation was needed in the same way for other trials. ***As part of a response to this finding, AZ are required to conduct a review of all sponsored UK trials that have been opened since 01 January 2010 that have contracted out TMF management. The trials should be assessed on a risk-based approach, for example, consideration to factors such as those that are currently live and those that are being undertaken or have supported a marketing authorisation (approved/in progress/to be submitted) etc. A plan, with the process and timelines should be produced followed by a report of the implementation of the review and both submitted to MHRA when available. The reviewed trials should include the name of vendor/CRO, extent of TMF quality oversight (mechanism by which it was undertaken or state if not been done) and whether the trial would be currently in an inspectable state. This would provide assurance to the MHRA that AZ does not have sponsored trials where the TMF would not be in an inspectable condition as was the case for the [redacted] trial managed by [redacted] and if there were issues, there would be a formal plan to rectify the situation.***
2.3.5	There was evidence of some data integrity issues in the eTMF where the document date was after the document approval date, particularly for the [redacted] trial and some instances for the [redacted] trial, which requires explanation (Note: the [redacted] trial does not appear to have such issues). There was also some evidence that the document approval date was sometimes a significantly long time after the date of the document, however, it was acknowledged that this may be due to data migration issues or documents that were older, but were acquired recently (for example, certificates). Finally, there was some evidence of an increase in documents being approved in the eTMF following the notification that the trial would be inspected, particularly for the [redacted] trial, indicating that the TMF was not up to date. For the [redacted] trial on 10JUN19 there were 44025 documents, but on 21MAY19 (date informed of trial) there were 40829 documents, therefore 7.3% of total documents were uploaded in this period and the rate had reduced since the inspection finished. For the [redacted] trial on 10JUN19 there were 47315 documents, but on 20MAY19 there were 44214 documents, therefore 6.6% were added in this period. For the [redacted] trial, there were 300 documents on10JUN19, which had increased from 185 on trial notification, a 38% increase.



	[redacted]
2.3.6	There was evidence that the Quality Control (QC) of the eTMF was not being fully performed: • The periodic QC for the [redacted] trial was not undertaken for Safety and Clinical Samples [redacted] Documentation until May 2019 and may have initially been omitted as a requirement. It was noted that other functional QC was being

	undertaken approximately quarterly as per the TMF plan [redacted] 08MAY19. • For the periodic QC of the [redacted] trial eTMF, the QC of the country level and the UK site level files had occurred twice a year since 2018 but not quarterly, for example, Country level was undertaken December 2017 and December 2018 and site level was undertaken in January 2018 and November 2018 and more recently in February and May 2019.
2.3.7	In the [redacted] trial eTMF, even when documents were sorted by document date in the library view, the documents did not appear in date order due to an inconsistent date convention being used. i.e. DD/MM/YYYY was required, but D/M/YYYY was being used.
2.3.8	The Annual Progress Report (APR) submissions to the REC were not filed in the [redacted] eTMF at the time of the inspection but were provided upon request for the [redacted] rial. Note the only APR provided was 11JUN19 and no APRs were provided prior to this despite FSFV (UK) occurring on 23NOV17. As part of the response to this finding confirmation would be required if earlier APRs were not submitted at all or if they were and not filed.
2.4	**Monitoring** *No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *The necessary procedures to secure the quality of every aspect of the trial shall be complied with.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).*** *The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication. Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up.* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016; 5.18.6 (a) (e)*** *Monitors Responsibilities: Verify that source documents and other trial records are accurate, complete, kept up-to-date and maintained. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution. Verifying that written informed consent was obtained before each subject's participation in the trial. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs. Determining whether the investigator is maintaining the essential documents* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016; 5.18.4 (k), (h), (e), (m), (p)***
2.4.1	There were a significant number of monitoring reports that were completed past the required 30 days period stipulated in SOP [redacted] Version [redacted] 31OCT18. For example, of those reports completed in 2017, 2018 and 2019:

	• 20 reports took over 200 days (examples: [redacted] visit 27JUN17, report 3APR18; [redacted] visit 26FEB16, report 19JAN17) • 50 reports took between 100 and 200 days (examples [redacted] 24OCT17, report 20APR18, [redacted], visit 9NOV17 report 18APR18) • 300 reports between 30-100 days (examples [redacted] visit 20FEB18, report 23MAY18, D0816C00002 [redacted] 21FEB17, report 30MAY17 There was, however, some indication of an improvement through time. [redacted]
2.4.2	The monitoring of the sites inspected did not appear to be sufficiently robust due to a number of issues identified at the investigator site inspections, but this was in particular an issue for the [redacted] site in the [redacted] trial. It was noted in the [redacted] trial that the arrangements with [redacted] that outlines the monitoring oversight requires that weekly meeting minutes should be provided to AZ for oversight and an example of these was seen dated 23MAY19, but there were no monitoring visit report metrics, just an open issues listing was provided and furthermore, there were no co-monitoring visits or [redacted] review performed by AZ for the [redacted] trial. Whilst risk-based monitoring was taking place, which can sometimes explain data discrepancies between the CRF and source data, there appeared to be some fundamental issues in how the trial was being conducted that should have been mitigated by effective monitoring via interview, process, source data and document review at the site by monitors. The sponsor should ensure these issues are examined from a system basis in addition to addressing the detail reported in the investigator site findings. Issues identified with monitoring included the following: • Unreported AEs and concomitant medications (Finding 8.1.2 and 8.1.3), quality of source data completion and attributability (Findings 8.1.4 to 8.1.6) and an ineligible patient not detected (Finding 9.7.1). • Failure to effectively identify, document and ensure review of all the source data

	was possible (Finding 8.1.1). • Failure to address the issues identified in Pharmacy at [redacted] site (Finding 8.2) and review of pharmacy process to ensure they are effective as seen at [redacted] where there was no documented review of all site pharmacy trial specific procedures (e.g. dispensing, code breaking, IMP receipt etc) by the trial monitor at trial start to ensure that compliance with the trial protocol (the CRA only reviewed the prescription). • Not ensuring the informed consent process was robust (Finding 8.3) • General Quality of documentation at the sites as outlined in various findings at the investigator sites, for example, in Findings 6.1, 6.3.1, 6.6.1, 9.1.1, 9.2.1 and 9.5). • Not identifying source data in the CRF contrary to protocol (Finding 5.1.1) • The use of paper instead of [redacted] issue was not detected by the monitor in a timely manner. The issue was seen in patient visits from end of 2017/start of 2018 but was not noted in monitoring visit documentation until November 2018. There was also no audit trail evidence available (when requested as document request [redacted]) that the CRA had access the [redacted] portal to monitor the compliance of completion of the [redacted] assessments and where the problem would have been found (Finding 5.1.4) • Failure to ensure documentation in place to demonstrate medical oversight by the Principal Investigator (e.g. Findings 6.4.1, 6.4.2, 9.3.2, 9.3.3, 9.3.4) • Not performing checks on [redacted] access by the PI (Finding 6.9.1) • Insufficient control of implementation of protocol amendments (Finding 6.8.1)

3.0 Other Findings

There were **6 Other findings** identified during this inspection relating to Contracts and Agreements, Data Integrity Process Controls, Quality Systems, Computer Systems Validation, Medical Oversight and Data Integrity.

3.1	**<u>Contracts and Agreements</u>**
3.1.1	The scope of work agreement with [redacted] for endpoint adjudication for the [redacted] trial was dated 23FEB17 signed 06MAR17 and a start-up agreement was in place 08AUG16 signed 12AUG16 (however, this didn't cover actual activity of adjudication). The first patient was recruited 08FEB17, therefore the contract was not executed in a timely manner as it was not executed prior to the trial commencing. Although it was acknowledged, that the services would be required later than this, the risk was that an event could occur that required adjudication and the contract could have been delayed and not in place at the appropriate time.
3.1.2	The agreements for the [redacted] (that receives data from devices for post hoc analysis, electronic symptom survey information for patient entry, and direct patients for additional biomarker sampling) with the software company [redacted] consisted of a Professional Services Agreement (dated 31OCT16) and a

	series of Scope of Work agreements. Whilst the Professional Services Agreement did contain the requirement to work to "relevant laws" the agreements did not cover other important issues such as maintaining and archiving the relevant sections of the Trial Master File. Therefore it lacked detail on essential documents and how they would be managed and retained, such as emails, meeting minutes, trial specific validation documentation, issues log/resolutions in Helpdesk/IT Ticket system and also the details concerning the retention and sponsor access to non-trial specific documentation; for example, software/system life cycle validation and maintenance documents, SOPs, training records, etc. Finally, the agreement did not address the investigator's control and ownership of their data. The requirements for contractual arrangements with eSystem vendors are contained in the following: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp
3.2	**Data Integrity Process Controls**
3.2.1	For the [redacted] trial, the [redacted] and the data from the devices set out in the protocol Appendix [redacted] (such as FEV_1 and PEF, nitrous oxide, inhaled medication) collected by the patients and transmitted to (or entered into) the '[redacted] was not available to the investigator. A portal was available for the investigator to review, but this did not contain the source data, only the compliance data (i.e. whether the patient had actually entered any data). The source data for the trial should be under the control of the investigator. There was no robust rationale for why the data was not accessible to the investigator as this was an open-label trial and therefore not necessary to blind the investigator (note: MHRA CTU medical assessor agreed with this position) .
3.2.2	The flow of source data for the [redacted] trial was non-compliant with GCP requirements. Source data was captured via the [redacted] and acquired by the Sponsors data platform [redacted] before being transmitted to the clinical database held by [redacted] This meant that the investigators source data was under the sole control of the sponsor, which would not be acceptable. It was noted that this trial had not yet enrolled any patients at the time of the inspection and no data has been in sole control of the sponsor, so this was a potential breach at this point and was therefore not a major finding.
3.3	**Quality Systems**
3.3.1	There was no process within the quality system to ensure that changes to electronic systems in relation to substantial amendments would not be deployed and implemented prior to Regulatory approval.
3.3.2	In the [redacted] section 4.2 it was stated that "Change Request, Impact Assessment & Approval All changes must be reviewed and approved by appropriately authorised personnel prior to implementation. Changes with potential impact to regulated areas must be identified and authorised to proceed by an appropriate individual; regulated areas, as a minimum, comprise GxP, Sox, Legal Hold, Export

	Compliance and Data Privacy." Although the standard states this, there was no formal process to ensure that this would occur.
3.3.3	There was no formal process for the identification, escalation and reporting of an Urgent Safety Measure (USM) when taken by an investigator at a site to relieve an immediate hazard to the trial subject. There was also a lack of information in the quality system on the oversight and completion of any actions required as a result of the USM (e.g. risk mitigation measures). Document Request [redacted] demonstrated that procedures required tracking of notifications/communications and not necessarily that the required actions had been implemented.
3.3.4	There was no formal process to ensure that the Reference Safety Information (RSI) effective date would be tracked at a trial level rather than IMP level. The RSI was implemented at a product level, yet when questioned during interview, it could not be explained how it was ensured that all trials with the IMP had received approval for that RSI version prior to implementation. MHRA clinical trial authorisation would be given for an individual trial and therefore there should be a process to ensure that if approval was received for a particular trial with the IMP then that the RSI would not be applied to other trials without a trial specific MHRA approval.
3.3.5	There was delayed implementation and lack of clarity within the quality system on how the RSI would be applied from the moment of occurrence as specified in RSI SOP [redacted]" Version [redacted], effective 14JUN18. The SOP did not specify what the moment of occurrence was or how this related to case processing of an SAE in the safety database. The [redacted] safety database was upgraded on 17NOV18 to ensure the onset date was used to determine expectedness for auto-labelling (a delay of nearly 5 months after the SOP had come into effect). An email was sent to Case Handling personnel to notify that the onset date will be used to determine expectedness following the upgrade to the safety database. The email also stated if the onset date is missing then the database rules default to the case receipt date as this is a mandatory field. However, this level of additional instruction was not in a formalised procedure and it was not known how new starters who joined after 14JAN19 (date of the email) would also be informed of this process.
3.3.6	There was a lack of robust procedure to ensure data used for dose escalation (or other important safety decisions) would be subject to QC to confirm accuracy unless justified otherwise in a trial protocol approved by the MHRA (the QC undertaken should be documented to demonstrate what was checked and when). The [redacted] Version [redacted] effective 20DEC18 stated *"The data will be compiled (this may include un-validated data) and will consist of the available data including data collected during the DLT evaluation period".* The use of potentially inaccurate data would not be acceptable unless transparent to and approved by the MHRA. ***It was acknowledged that AZ had confirmed that they were aware of the MHRA blog on Dose Escalation and were holding meetings to ensure process improvement (as per request [redacted] As part of the response to this finding, in addition to the CAPA, a review across ongoing trials should be undertaken to ensure that safety decisions would be based on robust data.***
3.3.7	It was described during interview that there was a lack of in-process check to ensure the trial data collated within the DSUR was accurate (e.g. all trials were contained).

3.4	**Computer Systems Validation**
3.4.1	For the '[redacted] the [redacted] document ([redacted] 18JAN19) referred to a major issue in relation to no patients showing up in the overview (identified as [redacted] It was stated in the document that this issue would be resolved before the end of User Acceptance Testing (UAT). The UAT documentation (UAT report 25MAR10 and Validation report 03APR19) did not refer to the issue and whether it had been resolved or not. It was noted that evidence was provided that the issue had been closed out, however this was not formally documented in the CSV reports.
3.4.2	There was a lack of oversight of the validation of the [redacted] trial [redacted] by AZ as the sponsor. This resulted in the release of a system which was not compliant with the approved protocol. Validation, data management and monitoring activities had been delegated to [redacted] and [redacted] and whilst AZ were aware of an issue upon UAT, there was a lack of follow up from AZ to ensure the issue had been resolved. On 21MAR19, [redacted] became aware that the [redacted] questionnaire had been incorrectly programmed in the [redacted] system regarding change questions (the protocol required "change questions" in relation to the patient's [redacted] symptoms to be performed weekly up to week 16. In order to determine if symptoms had worsened or improved since the previous week). Due to an incorrect use of ">" instead of "<" in [redacted] product design specifications (version [redacted] dated 07MAY17), these questions incorrectly appeared after week 16 rather than before as required by the trial protocol. These specifications were approved by all parties including the sponsor. Through sponsor UAT, an issue was identified regarding these questions, yet there was a lack of follow up to ensure the issue had been resolved prior to sign off of UAT by all parties on 05JUL17 and release of the system on 07JUL17. There was inadequate oversight of data management and monitoring activities delegated to [redacted] to ensure that this issue had been identified sooner (First Patient was randomised on 26 September 2017). [redacted] ***was a secondary efficacy endpoint on the trial and this issue had been identified and was being investigated prior to the inspection; therefore, this finding has not been graded higher than "Other". As part of the response to this finding, an update on the investigation (including any impact to patient safety and data integrity) as well CAPA should be provided. AZ are reminded that whilst activities can be delegated to third parties, AZ maintains overall responsibility as sponsor for compliance with the trial protocol and that any vendors must also adhere to this requirement.***
3.5	**Medical Oversight**
3.5.1	The process described in [redacted] 28AUG2018 and [redacted]

	[redacted] 15AUG18 for out of hours testing was examined by the inspectors. The out of hours medical call testing did not include an end to end test, as evidenced in the examples reviewed for testing on 01MAY18, 17OCT18 and 08MAR19. It went only as far as the medical information support service, so not actually testing being able to speak to a Medical Monitor (qualified doctor) with knowledge of the trial. This was a result of deficiencies in the documented procedures.
3.6	**Data Integrity**
3.6.1	In the [redacted] trial, patient [redacted] was mis-stratified in the [redacted] as the patient was confirmed as a non-smoker in screening worksheets and [redacted] but the medical notes indicated that the patient gave up smoking > 40 years ago. Therefore, this information was entered incorrectly into [redacted] as a "never smoker" rather than an "ever smoker". However, there was no process to ensure that the patient would be placed in the correct strata for analysis and CSR production purposes. AZ confirmed that the primary analysis, subgroup analyses and covariates would be based on the values entered into [redacted] at randomization, even if it was subsequently discovered that these values were incorrect although the erroneous stratifications would be addressed in the report. It seems inappropriate not to correct the data to the accurate known value to avoid any spurious analysis results.

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

Observations
Data Integrity Control Processes • For unblinding incident [redacted] incorrect programming of the [redacted] system allowed the sponsor/CRO to view one stratification parameter, which, when combined with other information could potentially unblind. It was noted access to the system was immediately revoked, however it was noted audit trials were not reviewed to confirm if anyone had actually accessed these reports. **Patient Eligibility** • For the [redacted] and [redacted] trials, they required patient age to calculate the GFR, however, [redacted] laboratory did not have the full date of birth. As a result, initially the GFR was calculated incorrectly, until age was added to the requisition form. It was noted that 3 patients in the [redacted] trial were not randomised in error due to falsely failing exclusion criteria 3 as below, but no patient were affected in the [redacted] trial. This has been made an observation and not a finding as it wasn't the case that ineligible patients were recruited, which would be a potential consequence of such errors. [redacted] (initial value: 85 updated to 64) [redacted] (initial value: 23 updated to 26) [redacted] (initial value: 23 updated to 25) **Essential Documents**

- For the additional SUSAR request for [redacted] trial (REC submissions), there was no evidence to demonstrate the actual case submission/receipt by MHRA of the 9 cases. It consisted of some code to show receipt date; therefore, its provenance was not confirmed.

Data Integrity

- The data supplied from the CTMS for the monitoring visit reports had almost 20% of records (415/2311) with missing or spurious data.

Serious Breach Reporting

- During the inspection, serious breach reference [redacted] was discussed to further understand the issue and the root cause. It was agreed by the inspector that the issue and CAPA would continue to be followed up as part of the serious breach reporting process and not the inspection.

Project Management

- The [redacted] trial CTA tracker was misleading as it contained two rows for IB edition [redacted] Row 298 stated IB version [redacted] approval date as 28MAR19 and row 300 stated IB [redacted] Query/ Rejection 28MAR19. IB edition [redacted] was rejected and never approved by the MHRA and IB edition [redacted] was submitted to the agency on 20MAY19 to address the GNA. The tracker was therefore misleading and implies that IB edition [redacted] was approved.

Medical Writing

- [redacted] Protocol Version [redacted] summary of changes referred to an interim analysis, however the synopsis of the protocol stated no interim analysis was planned for the trial and section 8.13 was not reflective of the changes which referred to exploratory analysis instead of interim.

Recommendations

Monitoring

- A review of Monitoring workload revealed a monitor who was responsible for 9 trials and 21 sites, and another monitor who was responsible for 8 trials and 17 sites. It would be recommended to review whether this would be an appropriate workload in order to comply with monitoring plans/SOPs.

- The Clinical Research Associate/Monitor handover process was not part of an SOP, but it was referred to in the monitors handbook, which was referred to in SOPs. It was recommended that this was formalised in the Quality System, along with the associated form.

- The review of the monitoring visit reports was done on a risk-based approach depending on experience of the monitor, or if there are site issues. It was recommended to document this rationale.

- During interview the monitor stated that she would review audit trials for the eCRF to see who made entries and timelines. It was recommended that this was formally part of the monitoring plan or quality system.

Essential Documents

- As there was no documented detailed assessment of the [redacted] and [redacted] eTMF functionality or interoperability with AZ systems and how a TMF plan would be developed, it was recommended that a detailed review was undertaken of these preferred suppliers.

- SOP [redacted] 28APR18 did not contain any requirements regarding contractual arrangements with vendors so that there would be assurance that contract contained appropriate language regarding the provision of essential documents/data to AZ or where the vendor retains them, that access to them would be provided to AZ for the retention period (for example, non-trial specific core software validation documents are usually retained by the vendor, but are essential to demonstrate the validated state of the software). Whilst the TMF plan was mandatory and covers aspects of this, it was recommended that the SOP, for example, could contain more detail on this and require the TMF Plan to contain information on the documents and data that the vendor retains after trial completion and maintenance of access to these.

- There were many guidance documents and instructions concerning the maintenance of the TMF provided in response to request [redacted] some were simple presentation slides, and many were not part of the quality system. It was recommended that a review of all the procedures/guidance/training documents was undertaken and streamlined into a smaller set of documents that are part of the formal quality system.

Pharmacovigilance

- In document request [redacted] it was stated, "As per our system set up and the process – we do not request Reason for Delay and Corrective and Preventive Action for cases that were sent late from the studies to AZ and not resulted in any late regulatory submission." AZ may want to consider investigating / trending these periodically.

- [redacted] version [redacted] effective 14JUN18 stated that an IB could only be updated once annually. Whilst it was recommended for the RSI update to align with the DSUR reporting period, if required, the RSI can be updated more than once, subject to approval of a substantial amendment.

- Where IB production was outsourced to a vendor, there was a lack of review of the vendor's QC process to ensure that they were of an appropriate standard or equivalent standard to AZ procedures. It was recommended that this was addressed.

Finding Number	Investigator Site Findings – [redacted] Clinical Research Facility, Centre for Health Science, Old Perth Road, Inverness, Scotland, IV2 3JH

4.0 Critical Findings

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

5.0 Major Findings

There was **1 Major finding** identified during this inspection relating to Data Integrity Control Processes.

Note that the major finding for monitoring reported at the investigator site has been included in the sponsor findings above.

5.1	**Data Integrity Control Processes** *No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *The necessary procedures to secure the quality of every aspect of the trial shall be complied with.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).*** *All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9).*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).*** *The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016, 6.4.9*** *The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data. The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016, 8.1***
5.1.1	Whilst there was no source data being placed in the eCRF at this site, the monitoring plan allowed ethnicity, nicotine use, Vital Signs (BP, Pulse, Height, weight) and pregnancy test to be directly entered as source into the eCRF (Monitoring Plan [redacted] 29MAY18 section 6) , but details of the source data entry into the CRF was not stated in the trial protocol as required by ICH GCP.
5.1.2	Not all data would be provided back to the investigator site, for example, the [redacted] data and audit trail and the user account/access log eCRF. It was also noted that changed [redacted] data was not provided to the site following a data change request (evidence of change was seen in the [redacted] audit trail). For example, for patient [redacted] a request was

	made to change the enrolment date from 11MAY18 to 10MAY18 logged by helpdesk 06JUN18, but there was no documentation of its resolution at the site. A similar situation occurred for a change in stratification parameter for patient [redacted] who was entered into the system as no [redacted] present at enrolment, but later confirmed [redacted] therefore a change request raised.
5.1.3	A primary endpoint for [redacted] or a [redacted] that was submitted for adjudication was recorded by sponsor as requiring a deletion to protect information that could identify the patient (reference [redacted] . There was no evidence of this in the source data at site (e.g. correspondence and amendments and resubmission) as the CRA had made the changes to the submitted documents, rather than the investigator site staff who submitted them, which would allow reconstruction of the process at the trial site.
5.1.4	The site had problems with connectivity of the [redacted] device and instead made extensive use of the sponsor provided paper PRO instead. The sponsor stated that these data would not be entered, resulting in the data being omitted from the trial data analysis. The sponsor's decision implied that there was therefore no-back up of the [redacted] system as paper alternatives would not be accepted. In this case the [redacted] was a secondary, not an exploratory objective of the trial, therefore the lack of back-up would potentially impact on the trial objectives. It was noted, however, that this occurred on 28 assessments globally in the trial, of which 16 were at this site (handwritten record provided by AZ representatives at the site), therefore the impact in this case would be likely to be small given the total number of assessments in the whole trial, but the sponsor should assess and confirm this in the response. ***A response from AZ should include details of how [redacted] system failures would be mitigated for trials where the primary objective concerned the collections and analysis of this type of data.***
5.1.5	The [redacted] audit trail provided for the site as a document request was incomplete. It did not provide details of actions in the system during the trial, only data changes, for example from helpdesk tickets. It was not possible to verify whether who from the site staff had undertaken which activities in the system and whether the PI or other delegated staff had accessed the system.

6.0 Other Findings

There **9 Other findings** identified during this inspection relating to Record Keeping/Essential Documents, Case Report Form/Source Data, Training, Medical Oversight by the Principal Investigator, Protocol Compliance, Staff Delegation and Responsibilities, Clinical Sample Processing, Project Management and Medical Oversight by the Sponsor.

6.1	**Record Keeping/Essential Documents**
6.1.1	The Investigator Site File (ISF) did not have the complete records for the MHRA approval process as it was generally restricted to the approval letters only. All the covering letters should also be filed.
6.1.2	All of the relevant study emails were not present in the ISF at the time of study closure as these were printed on 08OCT19. The sponsor had provided emails on CD, which

	indicated that the site was not maintaining the ISFs contemporaneously by adding emails themselves when received. The monitor therefore had not ensured that a complete ISF was present at the time of close out visit (17-19SEP19).
6.1.3	There was no documentation to demonstrate the chain of custody of the PK samples being added and removed from the -20°C freezer.
6.1.4	The ISF did not contain the first SUSAR listing for 20DEC16 to 19JUN17 distributed to the site on 04AUG2017.
6.2	**Case Report Form/Source Data**
6.2.1	There were no laboratory results for patient [redacted] from samples taken at visit [redacted] on 03OCT17.
6.3	**Training**
6.3.1	There was no documentation of read/awareness training for protocol amendment [redacted] 26OCT17 for the site personnel.
6.4	**Medical Oversight by Principal Investigator**
6.4.1	There was evidence that the Principal Investigator was not documenting timely review of the safety information provided by the sponsor (only one was timely).

DATE OF DISTRIBUTION BY PSLL&SUSAR DISTRIBUTION TEAM	Date of Evidence of Review by Principal Investigator
04-Aug-2017	**None**
29-Jan-2018	27MAY19 (**Untimely)**
17-Jul-2018	27MAY19 (**Untimely)**
24-Jan-2019	01FEB19
30-Jul-2019	24JUL19 (**erroneous?)**

6.4.2	There was no formal documentation by medically qualified person at the site of the AE seriousness, severity and causality prior to it being recorded in the CRF as entry was undertaken by the data manager and only verbal confirmation of this assessment by a medically qualified person was undertaken. An example of this was the AE for [redacted] for patient [redacted] where no such documentation was seen.
6.5	**Protocol Compliance**
6.5.1	There was no source data agreement in place at the site and the protocol section 9.2.2 stated this would be in the contract, but this was not the case.

6.5.2	A SAE (case ID[redacted] patient[redacted]) was not reported in a timely manner (24 hours as per the protocol section 6.4), as the site were aware of the case on 03FEB19 but did not report to the sponsor until 22FEB19.
6.6	**Staff Delegation and Responsibilities**
6.6.1	Authorisation of staff member[redacted] for conducting trial duties by the PI was not at the time of delegating the duties, as they started 19JUN17, but the PI did not sign until 27MAY19.
6.7	**Clinical Sample Processing**
6.7.1	There was no assessment by the sponsor prior to the trial to determine the requirement for documentation of tracking of processing of PK samples, for example, the analyte could be unstable and therefore it would be required to confirm the validated sample processing had been followed. It was noted that the Laboratory manual[redacted] 30APR18 required the centrifuging of the samples within 30 minutes, 10 minutes in the centrifuge at 1800g and storing at -20°C within 30 minutes. There were no records to confirm this process had been followed. It was noted that AZ have since MAY 2019 a log to document these requirements[redacted] ***A response to this should address the issue of the lack of the risk assessment (and process for it) and any integrity implications for the sample analysis.***
6.8	**Project Management**
6.8.1	The process for protocol implementation by the sponsor and investigator site requires some additional control. In this trial, the email to implement protocol amendment[redacted] (26OCT17) was sent to the site on 01MAR18 from the monitor. This stated that "all the approvals were in place and the amendment can be implemented at your site". This, however, was not robust as illustrated by the following observations. • This was sent prior to local R&D approval on 14MAR18 (but it was noted the email said they had waited 35 days after submission.) • As this point the protocol had not been signed by the PI, as this was not until 22JUN18. • Patient[redacted] was recruited on 10MAY18, whilst after the date the sponsor told to implement the amendment, it was before the PI had signed the protocol. • The previous (and incorrect) version of the eligibility checklist was used for patient[redacted] (for protocol[redacted]04JAN17), not the one related to protocol amendment[redacted] However, it was noted that the changes were minor and fortunately in this case did not appear to impact on the eligibility of the patient.
6.9	**Medical Oversight by the Sponsor**
6.9.1	There was no formal sponsor process to check that a person at site with the

	investigator role had successfully logged into [redacted] to confirm emergency unblinding was functional for the trial prior to or at the time IMP arrives on site. In this case, the Investigators had received the log-on envelopes 20JUN17 and 27JUN17 prior to [redacted]T activation on 29JUN17 IMP arrival (confirmed at site on 04JUL17); however, the inspector was informed that the investigators never actually logged onto the system to confirm the supplied credentials were functioning and the correct role and permissions assigned. It was noted that a letter from the monitor 30NOV17 stated that they had not activated the [redacted] account, however, this check was not in a timely manner. Note: it was not possible to check the investigators' access as the audit trail was incomplete (see Finding 5.1.5).

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

Observations

Essential Documents

- It was noted that there was a disagreement between the site staff and the sponsor concerning a file note (23SEP19) that the PI, RN and R&D had signed which stated the sponsor's CRA had made additions to the delegation log activities (21-23 relating to adjudication, [redacted] and IMP prescribing) to a staff member without the knowledge of the PI, but the CRA would not document that they had done so upon request of the site. The expectation would be that the delegation log should only be amended with knowledge of PI, particularly where changes are made after initial sign off and these changes should be made in a GCP compliant manner (initials, date, reason for change and if required PI approval). In this case, the amendments had not met that expectation.

Recommendations

Archiving

- It was noted that documentation from the sponsor had been provided on CD (emails, blank CRF). The use of electronic archiving rather than paper is a challenge for investigators and sponsors involved in clinical trials and is currently a hot topic for the clinical trial community. It was recommended that the sponsor and the Health Board keep themselves informed of developments and guidance in this area relating to how long-term access to the documents will be maintained taking account of media and software redundancy (i.e. requirements and process for electronic archiving), given the need for these to be readable for potentially a long period of time.

Source Documents/Case Report Form

- It was recommended that the site design the eligibility checklist to reflect the 2-step process for confirmation that the patient is eligible for the trial (i.e. the need to wait for laboratory results).

Investigational Medicinal Product/Pharmacy

- The pharmacy did not sign off protocol amendment [redacted] until 18APR18, which was much later than the date the sponsor informed the site to implement the amendment. It was

recommended, as due diligence, that pharmacy works with R&D and the investigator to ensure that all necessary changes to trial documents/eSystems are made/approvals in place etc. when implementing an amendment on the instruction of the sponsor.

- It was suggested that pharmacy considers testing the recall of IMPs as set out in SOP [redacted] August 2018.
- It was recommended that pharmacy also includes the day on the version control of SOPs.
- It was recommended, as a due diligence activity by the pharmacy, that a check that the emergency unblinded system for blinded trials is functional prior to dispensing the first IMP; for example, envelopes received (no [redacted] or that a person at the site has successfully logged into the [redacted] and confirmed they can access emergency unblinding functionality.

Finding Number	Investigator Site Findings - [redacted] Queen Mary University of London Old Anatomy Building, Charterhouse Square, London, EC1M 6BQ

7.0 Critical Findings

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

8.0 Major Findings

There were **4 Major findings** identified during this inspection relating to Case Report Form/Source Data, IMP Management/ Pharmacy, Informed Consent and Urgent Safety Measures.

Note that the major finding for monitoring identified at the investigator site has been reported in the sponsor findings above.

8.1	**Case Report Form/Source Data** *No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *The necessary procedures to secure the quality of every aspect of the trial shall be complied with.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).*** *The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (11).*** *All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9).*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).*** *The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should*

	be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016, 4.9.0*** *The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016, 4.9.1, 4.9.2***
8.1.1	There was no source data agreement and source data were recorded in multiple locations which were paper and electronic such as: • Hospital charts and records (paper) • Research files and source worksheets (paper) • Clinic letters (paper and electronic) • [redacted] electronic which also included clinical entries and laboratory results) • [redacted] (which contained clinic letters) • [redacted] (electronic [redacted] prescribing system which also contained clinical information such as vital signs taken by the [redacted] nurses) • Paper printouts from electronic systems (not certified) in research files. For example, monitors did not have access to [redacted] or [redacted] and so laboratory results and prescribing records were printed from the system for CRAs. Numerous issues were identified with the source documentation presented on the inspection: • Patient [redacted] notes were not in chronological order and there was a lack of assessment to verify if the notes set was complete in order to review entire patient record. There were 5 volumes of notes provided and a gap in the notes between 2016 – 2017 (at the time of trial entry) was identified during the interview. The site staff were able to provide [redacted] access on the return inspection to view any [redacted] entries during this period. • There were examples of photocopies of records and drug charts in patient [redacted]s volume of paper hospital notes which were not certified. • There was no formal process for certifying copies of records. Examples were noted for patient [redacted] and [redacted] where printouts were stamped with the word "copy" yet there was no process formalised for using this stamp or what it entailed (e.g. it was a true and complete copy of the original). For example, patient [redacted] notes dated 19JUN18. • A number of issues were identified by the inspectors regarding ~~CRS~~. The inspector access was not displaying all records within the system during the first part of the inspection due to access issues. This was resolved for the return inspection. • Radiology scans were entered in [redacted] and examples (e.g. scans taken 25APR17 and 06JUN17) were noted for patient [redacted] where the report had been amended significantly after the scan was taken (For example, scan date 25APR17, an amended report was produced on 08JUN17 and scan date 06JUN17 had an amended report produced on 20JUN17). The previous/ original report record could not be viewed to review what had changed.

	This limited the inspector review so the inspectors were required to return for a subsequent inspection one day visit to continue review of records once access to notes was granted electronically and all records could be reviewed.

8.1.2	Review of the source data identified numerous unreported AEs which had not been recorded in the eCRF or AE log for the patients.
	
	• For example, for Patient [redacted] (not an exhaustive list and for the following, the causality assessment, start and stop dates and in most cases, severity was missing):
	
	  • AE of [redacted] as recorded in clinic letter dated 02DEC16 was not recorded in the eCRF or source AE log.
	
	  • AE of [redacted]" and '[redacted] reported in the clinic letter for the visit 23DEC16 were not recorded in the source AE log or the eCRF.
	
	  • AE of [redacted] grade 1 prior to [redacted] documented in clinic letter dated 22JUN17 (clinic visit date 06JUN17) was not recorded in eCRF or source AE log.
	
	• On review of Patient [redacted] inpatient admission records, a number of AEs were reported that were not on the AE Log or in the eCRF.
	
	  • AEs of [redacted] reported on 08APR16, [redacted] reported on 29MAR16 (which was subsequently documented that "likely that this is related to the side effects of [redacted]
	
	  • Fatigue reported on 29MAR15 [redacted] (including a physiotherapist's entry of [redacted]") reported on 29MAR16 [redacted] reported on 07APR16.

8.1.3	There were examples of missing entries in the eCRF and concomitant medications log (created by site to record medications) for patient [redacted] • Patient experienced [redacted] (as per clinic letter dated 02DEC16) and was started on [redacted] once daily, this was not recorded in the eCRF or concomitant medications log (paper log). • Discharge summary dated 12JUL17 stated that the patient was prescribed and administered [redacted] once daily (which was to be reduced and eventually weaned to go back to [redacted] treatment instead). The use of [redacted] from 30JUN17-12JUL17 was not recorded in the eCRF or concomitant medications log. (Note there were protocol restrictions on the use of these concomitant medications in the protocol - see finding 9.7.1 below).
8.1.4	There were issues identified where source data entries were not attributable to a member of the staff and ensure that a suitably authorised person had made the entry. For example (not an exhaustive list):

	• Patient [redacted] entry for weight of "82kg" and [redacted] vital signs worksheet was not attributable. • Patient [redacted] had changes to the AE log after the Investigator had signed to confirm review. It was also noted that an entry made by a doctor had been amended by a clinical trial assistant (CTA). Patient [redacted] with [redacted] had an outcome of "5" when signed by sub-investigator [redacted] but it was changed to "3" by CTA initials [redacted] on 07SEP16.
8.1.5	Causality decisions had been entered into eCRF without having supporting source data available at time of entry as the source documentation for causality was after entry into eCRF by the CTA. This was seen for patients [redacted] and [redacted] for example for patient [redacted], they had an SAE of [redacted]" with onset 06SEP16, and the causality was reported into the eCRF for both IMPs on 07SEP16, yet the CRA raised query on 20SEP16 to request that the source information was recorded. The eCRF implied the SAE was related to both [redacted] and [redacted] However, the source AE log, it was stated to be related to [redacted] only with no causal relationship for [redacted] stated. Instead for [redacted] where the AE log stated, "if NO- list all other suspect causes, see key", the investigator did not use a key and instead wrote '[redacted], implying the SAE was related to [redacted] only. Therefore, the eCRF causality assessment was not in accordance with the source record for this SAE.
8.1.6	The AE Log/Worksheet (which was source data), required causality to be recorded for an AE. However, it did not require separate causality assessments to be completed for each of the IMPs ([redacted] and [redacted]) as the eCRF did, for example, for patient [redacted] the events of [redacted] 09AUG16 and [redacted] 16AUG16. It also did not capture whether the AE was [redacted] as required by the eCRF. In addition, the following issues were also identified with the AE log/Worksheet: • For patient [redacted] there were multiple amendments to the entries which had not been signed or dated. • Columns referred to a key for completion (e.g. action taken and outcome). However, for patient [redacted] numbers were entered into these columns, yet the key was a list of bullet points and not numbers. • Entries were also not dated; therefore, it was not possible to verify when the information was entered.
8.1.7	There was no documented review by a member of the clinical trial team to acknowledge that patient [redacted] was admitted to another hospital for [redacted] on 27JUN17 – 28JUN17 and whether this was an SAE. It was stated by site staff during the inspection that this may have been [redacted] but it was not documented as such in the source. (Note: Notification of this hospitalisation (at another hospital) was not in the EPR or in trial file, it was located in the patient's hospital paper notes). ***In the response, there should be confirmation whether this was an SAE and should have reported as such.***

8.2	**IMP Management/ Pharmacy** *No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *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).*** *Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (2).*** *All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9).*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).*** *The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016, 4.9.0, 4.6.3, 4.6.4***
8.2.1	Training slides were created by pharmacy for the trial in lieu of a dispensing procedure for pharmacy staff to use for training. However, the following issues were identified with these: • No version control (number, date, page numbers on the slides) • No reference to the protocol number or IMP handling guide used to create them • IMP handling guide was updated to version [redacted] yet there was no documentation of the assessment of the changes and whether this warranted any changes to procedures or training materials. • Slides did not mention retention of [redacted] for no longer than [redacted] as per the protocol requirements. There was reference to [redacted] and it was explained by pharmacy that only one expiry time could be used for the label and so all IMP was stored in the fridge after preparation It was acknowledged that since AUG18 the pharmacy started creating dispensing procedures for trials, however one was not available for this trial and there was no documented rationale for this.
8.2.2	The training log required name and signature, but not initials. However, in the trial documentation initials were used and this raised questions during interview when

	trying to ascertain whose initials were documented as these were at times different to signatures. For example, interviewees could not say with certainty which releasing pharmacist signed the [redacted] worksheet for patient [redacted] [redacted]
8.2.3	There was no documentation available to demonstrate when prepared IMP ~~infusion bags~~ were placed into the fridge in pharmacy and when they were collected by clinic in order to verify that the IMP had been kept at 2-8 °C. An example was noted for patient [redacted] where the IMP was prepared in pharmacy on 18JUL16 and administered to the patient on 19JUL16. There was no documentation available to confirm how this IMP had been stored prior to administration.
8.2.4	The [redacted] Regimen worksheets were programmed and checked by the same individual. There was no independent review to ensure the requirements of the protocol were met and the steps were correct. For example, the [redacted] worksheet was reviewed and approved by [redacted] on 14DEC15 (version [redacted]) and 04MAR016 (version [redacted] , it was stated that a check occurred, but it was not documented according to pharmacy.
8.2.5	There were no[redacted] confirmations for registering shipments in [redacted] filed in the site file or sent to site staff.
8.3	**Informed Consent** *No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended), 28*** *Principles based on Articles 2 to 5 of the GCP Directive:* *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).*** *For the purposes of this Schedule, a person gives informed consent to take part, or that a subject is to take part, in a clinical trial only if his decision - (a) is given freely after that person is informed of the nature, significance, implications and risks of the trial; and (b) either - (i) is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent, or (ii) if the person is unable to sign or to mark a document so as to indicate his consent, is given orally in the presence of at least one witness and recorded in writing.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 1, (3)*** *The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).*** *The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.* ***Integrated Addendum to ICH Topic E6 (R1) Note for guidance on good clinical practice, E6 (R2), 15 December 2016, 4.8.2***

8.3.1	A number of letters were sent to site informing them of important new safety risks identified with the IMP and a requirement to for PIs to verbally consent patients straight away upon notification of the new information (e.g. letter 28JAN17 regarding risk of [redacted], letter to REC referenced a letter 30SEP15 regarding the risk of [redacted] and letter 04MAY17 regarding risk of [redacted]). There was a lack of control of the verbal dissemination of important safety information to 2 trial patients and ensuring that it was fully documented and that the patients were re-consented in a timely manner in two examples seen by the inspector. ***Note: It was not determined if this was the case for the other trial patients. This should be determined as part of the response to the finding.*** • For patient [redacted] there was no documentation to suggest they were informed of [redacted] and reconsented verbally or in writing to patient information sheet/consent form [redacted] (which did contain the safety information). It was acknowledged that the patient died on 27AUG17 and was in hospital at [redacted] however they missed re-consenting at the retreatment visit in July 2017. The patient only signed version [redacted] of the consent form and did not sign versior [redacted] or version [redacted]. (A file note to document delayed implementation was created on 02OCT19, prior to the inspection. There was a lack of actions taken or impact documented in the file note) • Whilst patient [redacted] had verbally re-consented following notification of the risk of [redacted] the patient had not signed version [redacted] of the Patient Information Sheet/Consent Form which contained this update. • Patient [redacted] was contacted on 16JAN17 to be informed of the updated risk of [redacted]. Calls made on 21NOV17 and 12DEC17 regarding the risk of [redacted], but with no answer. Additionally, the patient was only verbally updated regarding new amendment relating to Patient Information Sheet/Consent form [redacted] 22MAR19 on 06JUN19 (Person with initials [redacted] clarified on 07SEP19 that this was in reference to the [redacted] Study update).
8.3.2	Postal consent was obtained for patient [redacted] for Patient Information Sheet/Consent Form [redacted] 22MAR19, however this process had not been approved by the REC.
8.3.3	There was an example where the consent process was not sufficiently documented. For Patient [redacted] nitial consent, the Principal Investigator had documented "consented today" (on 24FEB16) and the worksheet detailed the version used. There was a lack of source data available to demonstrate when the patient referral was received and although another entry indicated the patient information sheet was provided the day before, <u>there was no contemporaneous record</u>. There was no evidence that the ICF was signed prior to study procedures and that the Patient received a copy.
8.4	**<u>Urgent Safety Measure</u>** *(1) The sponsor and investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. (2)If measures are taken pursuant to paragraph (1), the sponsor shall immediately, and in any event no later than 3 days from the*

	date the measures are taken, give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures. ***UK Statutory Instrument 2004/1031 (as amended), 30***
8.4.1	A number of Dear Investigator Letters (DILs) were sent to site informing of important new safety risks identified with the IMP and a requirement for PIs to verbally consent patients straight away upon notification of the new information (e.g. letter 28JAN17 regarding risk of [redacted] (DIL letter dated 02DEC16), letter to REC referenced a DIL dated 30SEP15 regarding risk of [redacted] and DIL dated 04 MAY17 regarding risk of [redacted]. For example, Letter dated 02DEC16 ([redacted]) stated: • "Prior to the consent being approved by IRBs/IECs any new patient who is being enrolled and is signing the last version of the consent should be verbally informed about the new risk of [redacted] and a statement added to the patient notes stating that the patient was verbally informed of this risk and still agreed to consent to the study. Once approved by the IEC/IRB patients who are still receiving [redacted] will be asked to sign the updated consent that includes the [redacted] risk" • "Prior to the consent being approved by IRBs/IECs any patient who is still receiving treatment with [redacted] or patients who are in the 90 day follow up period post permanently discontinuing [redacted] should be verbally informed about the new risk of [redacted] and a statement added to the patient notes stating that the patient was verbally informed of this risk and if on drug agreed to continue receiving study drug. Once approved by the IEC/IRB patients who are still receiving study drug will be asked to sign the updated consent that includes the [redacted] risk." These letters were not reported as urgent safety measures. These letters required a change to the approved consent process by verbally informing patients until the informed consent documentation (information sheet and consent form) was approved and in some cases to monitor patients closely for symptoms of [redacted] and [redacted](letters dated 27JAN17 and 04MAY17 respectively). ***These were discussed with the MHRA and HRA who confirmed no USMs had been submitted for the trial and in the opinion of HRA should have been submitted as USMs. In order to determine if these were USMs for the MHRA as well, AstraZeneca are required to confirm if the wording in the letter matched the approved protocol at the time and where this was stated. If there was a discrepancy between the letter and the protocol, then these should be explained along with how the protocol ensured the required actions were still taken (e.g. discontinuation of the IMP or further follow up).***

9.0 Other Findings

There were **7 Other findings** identified during this inspection relating to Staff Delegation and Responsibilities, Training, Medical Oversight by the Principal Investigator, Pharmacovigilance, Record Keeping/Essential Documents, Data Integrity Process Controls and Patient Eligibility.

9.1	**Staff Delegation and Responsibilities**
9.1.1	There was late sign off of the delegation log by the PI for individuals, which were significantly after their start date. For example (not an exhaustive list): • [redacted] start date 15MAR17, PI signed 03SEP19 • [redacted] start date 24JAN17, PI signed 03SEP19 • [redacted] start date 03DEC15, PI signed on 03SEP19
9.1.2	There was an electronic entry of weight for patient [redacted] within [redacted] by an individual who was not on the delegation log (initials [redacted]
9.2	**Training**
9.2.1	The training log was completed for individuals to confirm that they had performed protocol training. However, the following issues were identified with training documentation in the investigator site file and pharmacy file: • The protocol version was not referenced in the training log for individuals trained after 14DEC15, therefore it was not possible to confirm the version of the protocol used to train for self-training. For example, training completed by Sub Investigators [redacted] and [redacted] on 15MAR17 and 24JAN17 respectively. • There was no documented training on protocol amendments [redacted] for any individuals in the clinic. • There was evidence of individuals using SIV training slides (protocol version [redacted]) to perform training after version [redacted] of the protocol had been approved. For example, Clinical Trials Assistant [redacted] signed the training log and referenced "SIV slides" on 20MAY19, after version [redacted] of the protocol had been approved and implemented at site. • There was evidence of individuals performing tasks in pharmacy prior to training on trial dispensing slides, for example [redacted] received IMP shipment [redacted] on 16DEC15 but didn't train until 29FEB16. • There was no documented evidence of protocol training (or training on specific pharmacy/ IMP guides) for screening pharmacists who worked on the trial.
9.3	**Medical Oversight by the Principal Investigator**
9.3.1	The GP letters were sent significantly late and there was a lack of source documentation to verify when emergency contact cards were provided to patients in order to ensure any issues could be reported immediately to the site (e.g. for patients [redacted] and [redacted] . For example, for Patient [redacted] the GP Letter [redacted] 17SEP15 was sent on 21SEP16, but [redacted] Day 1 was 11MAR16 and [redacted] Visit was on 27JUN16. It was acknowledged that this was an open label trial and as such an emergency

	code-break was not required.
9.3.2	There was a lack of documentation to support the [redacted] entered into the eCRF for patient [redacted] which from March 2017- June 2017 showed [redacted] on scans but was not documented as [redacted] until prior to [redacted] on 04JUL17. The investigator stated this was due to clinical symptoms not showing [redacted] however, there was no documentation in the source to demonstrate this rationale for the decisions taken. The eCRF also required Investigator confirmation of [redacted] and the entry in the eCRF was [redacted] during this time period.
9.3.3	The documentation supporting eligibility was not documented as reviewed until after Patient [redacted] had entered the trial on 11MAR16. For example: • Screening [redacted] was conducted on 26FEB16 and reported on 09MAR16. The investigator documented the review on 10MAY16 • Screening [redacted] was conducted on 26FEB16 and reported on 03MAR16. The investigator documented review on 10MAY16 • Sections of the Screening Worksheet were not completed by the investigator until 10MAY16, including the [redacted] History, Prior Surgery, Prior [redacted] Prior [redacted] Therapy, AEs and Concomitant Medications
9.3.4	None of the important safety notifications mentioned in the informed consent Finding 8.3 above were signed and acknowledged by the PI.
9.4	**Pharmacovigilance**
9.4.1	There was a late reported SAE of [redacted]" for patient [redacted] who was transferred to [redacted] hospital on 29MAR16. The SAE was reported in [redacted] on 05APR16; however, the patient's laboratory results from the in-patient stay were signed by sub investigator [redacted] on 29MAR16.
9.5	**Record Keeping/ Essential Docs**
9.5.1	It was explained during interview by the PI that patient status, safety information, trial updates and training were discussed at joint team meetings, however these meetings were not documented at the time of the trial.
9.5.2	Records of screening pharmacist review where held electronically in pharmacy and not signposted in the site file to indicate their existence and location.
9.6	**Data Integrity Process Controls**
9.6.1	The "AZ AWARE" date was entered into the eCRF by staff at AZ, which then sent the SAE notification to the pharmacovigilance department. For example, for patient [redacted] the "AZ AWARE" dates of 07SEP16 and 16SEP16 by AZ staff [redacted] and [redacted] respectively. However, this was a data field entry in the eCRF which the PI has not delegated to AZ staff. The sponsor would be strongly discouraged from having edit rights to the eCRF.
9.6.2	Smoking status and histology ([redacted] were the 2 stratification

	factors that were required to be entered into the [redacted] system by the site to randomise a patient. However, the [redacted] confirmations only displayed 1 of the values entered (histology). Therefore, the site did not have a complete copy of the data entered into the [redacted] system. This was seen for patient [redacted] randomised 16DEC16 and patient [redacted] randomised 21JUN16.
9.6.3	There was no inspector read-only access available to the [redacted] system as it was not built into the system functionality.
9.7	**Patient Eligibility**
9.7.1	An ineligible patient was identified based on the retreatment eligibility criteria, exclusion criteria [redacted] (current or prior use of [redacted] medication within 14 days before the first dose of [redacted] or [redacted] There was an exception for systemic [redacted] at physiological doses not to exceed [redacted] of [redacted] or its equivalent). Patient [redacted] received retreatment with IMP on 26JUL17. However, the patient had received [redacted] within 14 days of this date as demonstrated by the drug administration record whilst the patient was an inpatient. The Sub-Investigator had crossed out a dispensing record in the patient's paper notes on 18JUL17 and stated that patient stopped taking the [redacted] on 11JUL17, this was incorrect as shown by the in-patient records which matched the discharge summary (see Finding 8.1.3). It was confirmed with the research nurse during the inspection that a dose of [redacted] of dexamethasone was greater than [redacted] of [redacted] ***As part of a response to this finding a review of eligibility of the other patients at this site should be (planned to be) undertaken.***

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

Observations
Monitoring • The site initiation visit follow-up letter 08DEC15 provided instructions for the PI to perform an emergency code-break, however this was an open label trial.

Recommendations
Source Data /Case Report Form • It was recommended that a patient alert in [redacted] system [redacted] is added to notify other hospitals and departments within the trust that patient is on a trial and who to contact in emergency.

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]		✓		TMF review focused on clinical trials authorisation, protocol compliance, pharmacovigilance and quality assurance activities.
[redacted])		✓		AZ TMF country level and partial review of study level documents. [redacted] eTMF partial review of country level documents.
[redacted])		✓		Country and study level documents primarily relating to regulatory and ethics committee sections and documentation concerning pharmacovigilance and monitoring. Review of site level documentation for 1 site.
[redacted]		✓		Computer systems validation of the [redacted] only.

Inspected Organisation				
Activity	Assessed			Comment
	Yes	Partial	No	
Analytical Laboratory			✓	
Archiving	✓			As part of TMF system interviews
BE/ BA activities			✓	
Clinical Pathology Laboratory			✓	
Clinical Trial Reporting			✓	
Computerised Systems		✓		For one trial [redacted] as above.
Contracts & Agreements		✓		As part of TMF review only.
Data Management			✓	
eCRF / Diaries / IVRS		✓		As part of TMF review only.
IMP Management		✓		As part of TMF review only.
Medical Affairs		✓		As part of TMF review only.
Monitoring	✓			
Pharmacovigilance	✓			
Project management	✓			
Quality Assurance	✓			
Quality Systems			✓	
R&D Unit (Non-commercial only)			✓	
Regulatory Affairs		✓		As part of TMF review only.
Statistical Analysis			✓	
Technical Facility (i.e. x-ray)			✓	
Training			✓	
Trial Master File/Essential Documents	✓			
Other				

Investigator Site [redacted] Clinical Research Facility, Centre for Health Science, Old Perth Road, Inverness, Scotland, IV2 3JH				
Activity	**Assessed**			**Comment**
	Yes	**Partial**	**No**	
Principal Investigator	✓			
Research Nurse	✓			
Sub-Investigator	✓			
Laboratory			✓	
IMP Management/Pharmacy	✓			
Consents	✓			All patients.
CRFs, e-CRFs, Patient Diary, IVRS		✓		Patients [redacted] and [redacted]
Source Data		✓		Patients [redacted] and [redacted]
Site Master File	✓			
Technical Facility (i.e. x-ray)			✓	
Other				

Investigator Site [redacted] Queen Mary University of London Old Anatomy Building, Charterhouse Square, London, EC1M 6BQ				
Activity	**Assessed**			**Comment**
	Yes	**Partial**	**No**	
Principal Investigator	✓			
Research Nurse	✓			
Sub-Investigator			✓	
Laboratory			✓	
IMP Management/Pharmacy	✓			
Consents	✓			
CRFs, e-CRFs, Patient Diary, IVRS		✓		Patients [redacted] and [redacted] only
Source Data		✓		Patients [redacted] and [redacted] only
Site Master File	✓			
Technical Facility (i.e. x-ray)			✓	
Other			✓	