Finding Number	Sponsor Site Findings	Finding Class:
1.0	**Data Integrity**	**CRITICAL**
1.1	*All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified* ***UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9).*** *29 Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance with - (a) the protocol relating to that trial, as may be amended from time to time in accordance with regulations 22 to 25;* ***UK Statutory Instrument 2004/1031 (as amended) 29 (a)*** *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).** **There are two issues with the Lucentis trial, in relation to ensuring that the data is robust, these relate to IMP administration and the 'masking' of the trial in relation to the pain score assessments (which are the primary objectives).**	
1.1.1	It is currently not possible to determine which patient received which IMP. The protocol requires that half the subjects receive eye drops alone and the other half receive eye drops plus lignocaine. The medical notes contain an entry on the date of the IMP administration; however each entry, for all subjects reviewed by the inspector, states that they received both drops and lignocaine, regardless of what was stated on the randomisation (for example for patients 129 and 25, the source notes states that the subjects received drops plus lignocaine, whereas the randomisation stated they were to receive drops only). Therefore it is currently impossible to verify whether all patients received both IMPs, or were dosed as per protocol. This in turn impacts on the integrity of the trial data, and the interpretation of the results. The drug accountability logs were not available during the inspection and appeared to have been misplaced. They were found 30 minutes before the closing meeting. Review of the accountability logs revealed that they did match the randomisation list. The contemporaneous source documents state that all subjects received drops plus lignocaine. Although the accountability logs appear correct, a number of patients (on some days up to 10) were dosed on the same day. Therefore the documentation	

	demonstrates that a number of batches of IMP were dispensed to the treating physician for that day, but it is not possible to determine with certainty which subjects received which IMPs. Although the intention was to dose according to the randomisation, the notes at that time record that each subject received both IMPs. *(post inspection note: the treating physician has confirmed that for all 131 patients in the trial the medical notes state that the subjects all received eye drops plus lignocaine)*	
	Corrective Action: Withdrawal of paper submitted to the journal Eye.	***Actionee:*** Mr Vasant Raman (study CI) ***Due Date:*** Completed
	Preventive Action: The error has been highlight to the physician concerned. It is hoped that the stigma of having a paper withdrawn will act as a learning catalyst to the physician. The incident is now highlighted in our mandatory research governance training to other researchers and I have added a new slide on PI oversight to the training (slide attached). In retrospect the error in the medical records was not detected by the study monitoring as we simply did not monitoring enough of the medical records to detect the error. We will update our Risk Assessment SOP (which informs our monitoring plan for a study) and also endeavour in future to obtain better access to medical records, however, this finding does highlight the issue that we often have great difficulty in accessing medical records as they are often out in other hospital clinics and therefore not available for checking source data.	***Actionee:*** Mr Vasant Raman (study CI) & Chris Rollinson ***Due Date:*** Completed ***Due Date:*** Risk Assessment SOP updated - complete
1.1.2	The Lucentis protocol also required that the pain assessment scores were handled by a 'masked assessor' who was not aware which treatment arm the subjects were randomised to. This was also not verifiable due to the following issues: • The masked assessments were primarily carried out by SA and JR, who were also delegated responsibilities in relation to drug accountability and pharmacy. The drug accountability logs unmasked the trial. • There were entries into the medical notes on the IMP administration page by JR, where the IMP was listed. • There were no written instructions/procedures to ensure that the masked assessors were not either present in theatre, or remained masked throughout the trial. For the first seven subjects in the trial, it was not recorded who performed the masked assessments, therefore it was not possible to verify if this was carried out by a masked assessor.	

1.1.3	For the Lucentis trial, page 1 of the CRF was required to be completed by the physician administering the IMP and confirming eligibility. For a number of patients this was completed either by a different physician, or by the study coordinator. For example subjects 19. 20, 22, 23-27: For all these subjects page 3 of the CRF – which must be completed by a masked physician – was completed by the same physician that completed page 1 (i.e. stating that they administered the IMP) – therefore if the CRF is to be believed then the assessing physician was also unmasked for these patients.
These findings invalidate the data produced by the trial. As part of the response the Sponsor is required to address the issue of publication of these results (it is understood that a paper has been submitted for publication).	
Corrective Action: Withdrawal of paper submitted to the journal Eye.	***Actionee:*** Mr Vasant Raman (study CI) ***Due Date:*** Completed
Preventive Action: 1) We have restructured our research nursing teams so that they do not work in isolation from other teams and they are overseen by an experienced senior research nurse, we are therefore now better able to better support less experienced research nurses. This has already been effective as we have had a recent near miss with a potential un-blinding (again in the Ophthalmology Dept.) which was picked up by the Senior Research Nurse who then took the necessary preventative action. 2) The recent repeat of a potential un-blinding has highlighted the need for further training in the Ophthalmology Dept. in research methodology, we propose to run training at the next Departmental meeting that will highlight the importance of blinding and accurate data recording. 3) The errors highlighted in the Inspection report are brought to the attention of all PHNT researchers when completing their mandatory Research Governance training every 2 years. 4) We plan to write to all our current researchers and report to the Trust's Quality Assurance Committee once we have approval of the CAPA. In the spirit of research being more transparent, we are also planning to publish the approved CAPA on our website (with approval from the MHRA, we plan to anonymise individual names). 5) We are in the process of employing a new member of staff to help support the monitoring of Trust studies, however, this is delayed until the new year when we know how the HRA central approval process will work (we	***Actionee:*** Chris Rollinson ***Due Date:*** The training materials have been updated; however we have a rolling programme of research training so dissemination of this update will necessarily take time. Lancet paper on blinding sent to Ophthalmology researchers – Completed. More ongoing training to be arranged New members of staff to start Feb 2015 completed. Dissemination of inspection findings on approval of the

have staff who would be able to transfer from governance checking to monitoring); 6) We have a strategy that where possible PHNT sponsored CTIMPs are run through a registered CTU. This however, is not always possible as we have recently discovered. CTUs have capacity issues regarding the number of studies they can manage and small pilot studies cannot be done through a CTU without greatly inflating the cost of the study which makes them unlikely to receiving funding. We are now considering how we can support these smaller CTIMP studies. We are currently considering a new small pilot CTIMP which the local CTU could not support as the funding wouldn't cover CTU costs. We are reviewing the study carefully to help highlight our processes that may need updating to ensure the study is done safely and correctly. 7) Update our Risk assessment SOP to help identify research risk more effectively (this feeds into our monitoring plans for studies)	CAPA by the MHRA. Report available to all on the R&D website - completed New members of staff to start Feb 2015 completed. Completed

Finding Number	Sponsor Site Findings	Finding Class:
2.0	**Organisation's Oversight of Clinical Trials of IMPs**	**MAJOR**
2.1	*12) A person who is a sponsor of a clinical trial in accordance with this regulation may delegate any or all of his functions under these Regulations to any person but any such arrangement shall not affect the responsibility of the sponsor.* ***UK Statutory Instrument 2004/1031 (as amended), Regulation 3 (12).*** *28 (1) No person shall - (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. (2) Subject to paragraph (5), the sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.* ***UK Statutory Instrument 2004/1031 (as amended) 28 (1) and (2)*** *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 process for sponsor oversight of trials once they have commenced is lacking in certain areas, and there is evidence**	

	that legislative requirements have not been met.
2.1.1	There were a number of examples of lack of oversight in relation to pharmacovigilance obligations: • For the OFT trial there were no Annual Safety Reports produced. There was no sponsor process in place to ensure that these are written and submitted. In the tripartite agreement for this study the CI was responsible for writing the DSUR, but the Sponsor was responsible for submitting to the MHRA/REC. This was never done, nor was it queried by the Sponsor. • For the Lenalidomide study, there was no annual safety report (ASR) generated for 2011 – 2012. ASR submission for this study was the responsibility of the study coordinating centre according to the 'allocation of governance responsibilities' document dated 14th October 2008. For the Lenalidomide study, there was no evidence of ASR submission to the MHRA for 2010 – 2011 or 2011 – 2012.
Corrective Action: Nil, filenotes produced. We have acknowledged that the sponsor was responsible for submitting the DSUR, not the MAH. All SAEs were reported within agreed timelines (24 hours) to the MAH. This was documented in the study specific SOPs and the requirement was written into each protocol. We have fax receipts for each time a fax was sent to the MAH and I can confirm that they were made aware of every SAE that was reported to 'the coordinating centre'.	***Actionee:*** Margie Berrow & Chris Rollinson
Preventive Action: The study sponsor has reinstated the original paper tracking system for tracking of study reports (see attached). We have also set-up an electronic system utilising the EDGE database that will alert R&D when reports are due for all current and future studies. Currently this is the responsibility of the Research Governance Manager with assistance from the R&D Information Officer. We now use a Task Allocation Matrix when sponsoring new studies to clearly define roles and responsibilities (template attached). We are currently developing an SOP to ensure this becomes embedded into our day to day practice.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed paper system and EDGE based system Completed
2.1.2	There were a number of examples of lack of oversight in relation to Ethics Committee obligations: • For the OFT trial there were no Annual Progress Reports produced, this was not tracked by the Sponsor • For the Lenalidomide study, there were no Annual Progress Reports generated for November 2009 – November 2010 or November 2010 – November 2011. (Note: this omission had been identified and documented in a note to file but not until 1st June 2014).

	• For the Lenalidomide study, the annual progress report for the period November 2012 – November 2013 had not been submitted to the REC until 1st June 2014. For the Lenalidomide study the ASR for 2012 – 2013 had not been submitted to the REC until 16th May 2014	
Corrective Action: Nil, filenotes produced.		***Actionee:*** Margie Berrow
Preventive Action: As stated for 2.1.1 the R&D Dept when acting on behalf of the Trust as study sponsor has set up a tracking system using the EDGE database to alert R&D when reports are due.		***Actionee:*** Chris Rollinson ***Due Date:*** As for section 2.1.1
2.1.3	There is currently no sponsor tracking of the requirements to notify MHRA of the end of trial and to provide the clinical trial summary report within one year post the end of trial notification. For the OFT trial the trial formally ended on 20 August 2013; however the end of trial was not notified until 6 months later. The summary report has not been submitted. (note: the inspectors were shown emails from the sponsor to demonstrate chasing up information in relation to end of trial however these all related to recruitment end date, actual study close date and the number of participants at the Plymouth site – however no mention was made of the legislative requirement to inform the MHRA/REC of the end of trial and produce the report). The current list of CI responsibilities that forms part of the Sponsor approval does not include production and submission of the clinical trial summary report.	
Corrective Action: The Summary Report will be submitted within the one year from the formal end of the study i.e. the date that the End of Trial Notification was submitted.		***Actionee:*** Margie Berrow
Preventive Action: As stated in section 2.1.1 we have set up a tracking system for reports. List of CI responsibilities will be updated to include production and submission of the clinical trial summary report.		***Actionee:*** Chris Rollinson ***Due Date:*** Completed

Finding Number	Sponsor Site Findings	Finding Class:
3.0	**Protocol compliance, Research Ethics Committee, staff delegation and responsibilities, TMF, record keeping/essential documents, CRF data/source data, quality systems, contracts and agreements and monitoring**	**OTHER**
3.1	**Protocol Compliance**	
3.1.1	Randomisation for the PASTIES study is based on stratification according to the type of pain (abdominal or musculoskeletal) and time of patient admission to the Emergency Department (morning or afternoon). Of the 24 CRFs selected for review for this study, 3 patients had been stratified incorrectly as afternoon admissions when they were admitted in the morning according to the patient recruitment forms in the source data. This appeared to occur as the baseline VAS assessments for these patients were conducted in the afternoon (regardless of the time of admission) and this had been used for randomisation. However, section 12.5 of the protocol for this study indicated that the time of admission and not the time of baseline assessment should be used for randomisation. Due to the stratified nature of the randomisation for this study, it was not possible to assess the impact of this finding during the inspection (i.e. did the patients receive the incorrect IMP). In addition to the response to this finding, please provide an assessment of IMP allocation in relation to the randomisation list, expanding the sample of patient CRFs to review for similar issues.	
Corrective Action: Recruitment (and therefore the requirement to randomise participants) finished on 31 January 2014 and confirmation sent to REC and MHRA at this time; the study was in follow up at the time of the inspection and therefore corrective action in the retraining of site staff was not possible. A review of all participants' data and study documentation has been instigated in response to this finding. The objective of the review was to determine the impact of this finding. The following can be confirmed: There are a number of cases in which the selection of 'am' or 'pm' stratification variable at the point of randomisation has been made incorrectly by investigator site staff. There are discrepancies in the way that the am/pm stratification variable is described within and between study documents (e.g. 'time of admission' in funding application; 'time of admission' and 'time of recruitment' in		***Actionee:*** Chris Hayward ***Due Date:*** Completed

protocol; 'time of baseline VAS score' in randomisation CRF) The correct description in terms of achieving the balance intended is 'time of baseline VAS score', since this marks precisely the point at which participants enter the 12-hour trial period. Despite the erroneous selections of 'am' or 'pm' detected, the data show that the allocated treatment arms are adequately balanced in relation to this stratification variable. In light of the final point above, we confirm that the incorrect selection of 'am' or 'pm' at the point of randomisation has had no significant impact on the trial integrity. From the perspective of the individual, allocation to treatment may have been 'incorrect' in the sense that the allocation sequence may have been thrown out by such an error but all participants received the same IMP (i.e. morphine – only the method of delivery was randomised), for which they were eligible and had consented. The review described has been discussed by the PASTIES Trial Management Team.	
Preventive Action: In some cases the errors detected in our review were caused solely by user error (i.e. nurses had simply selected the wrong variable, even when time of admission and time of baseline VAS score were in the same category (am or pm). This error might have been prevented in some of the cases had the website been designed to 'choose' the 'am' or 'pm' variable rather than the nurses at site. i.e. had the nurses been prompted to enter the time of baseline VAS. CTU SOPs describing CRF design and database design will be updated so as to advise developers to consider minimising the entry of superfluous data.	***Actionee:*** Chris Hayward ***Due Date:*** Completed
3.1.2	The protocol for OFT required a trial steering committee, however this was not done.
Corrective Action: Nil, as study closed so can't correct now.	***Actionee:*** Simon Rule
Preventive Action: TSC set-up is a condition of PHNT sponsorship for all CTIMP and Device studies now, as per the R&D Trust policy. However, the study was set up prior to the implementation of this policy, but in the future we will need to ensure that a TSC is in place and that the sponsor is copied in to reports (we now have an R&D representative sit as an observer on all TSCs for CTIMP and Device studies sponsored by the Trust). All PenCTU studies require a TSC a standard so should not happen for future PenCTU or Trust managed studies.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed

3.2	**Research Ethics Committee**
3.2.1	For the PASTIES study an amendment was submitted to the REC on 24th May 2012 which included changes to the study protocol and PIS/ICF. However, this was submitted for information only and as no approval was requested, the REC did not formally approve these revised documents. Included in this amendment was ICF version 2 which was subsequently used to consent a large number of patients at the Plymouth site for this study. It is expected that all information provide to subjects is formally approved by the REC.

Corrective Action:
We respectfully contend this finding as follows:

A substantial amendment to the trial was submitted to REC in March 2012. The amendment concerned addition of an investigator site (Exeter) and comprised an updated Part C of the REC application form. The covering letter (signed by the Sponsor) sent to REC noted that; "On receipt of the Committee's favourable opinion, the trial protocol and related documents will undergo *non-substantial* amendment to reflect the addition of the second site, and will be forwarded to the Committee in due course for information."

The substantial amendment was approved by REC on 04 April 2012 and the supporting documents (including protocol and PIS) were amended in May 2012 so as to reflect the substantial amendment. Despite there being no requirement to notify the REC or obtain an ethical opinion in the case of a non-substantial amendment (NRES SOP v5.1), all amended documents were provided to the REC on 17 May 2012. The covering letter in this case, signed by sponsor, stated: "The protocol and other documents have been amended primarily in order to make them more generic, reflecting the addition of a second Investigator site (as approved by your Committee on 4th April 2012). The Sponsor has considered the amendments made and adjudged them to be non-substantial, given that they do not significantly impact on the safety or physical or mental integrity of the clinical trial participants, or on the scientific value of the trial. As such, the purpose of this submission is to provide the Committee with the revised documents for information only".

Whilst we expect all participant-facing information to undergo REC review and approval, we do not consider it necessary for minor changes to the information to undergo the same review if the changes are considered to be non-substantial by Sponsor (who has responsibility for adjudging substantiality according to EC guidance 2010/C 82/01 and/or NRES SOP v5.1).

In this case, we feel that our documentation is sufficiently transparent and complete, and that we have observed

Actionee:
Chris Hayward

Due Date: n/a

the correct guidance in processing the amendment in question. Attached is the PIS version 2.0 sent to REC including tracked changes and comments added by the PenCTU Trial Manager as further explanation to the REC. Also attached is the REC cover letter sent with the document.	
Preventive Action: n/a	***Actionee:*** Chris Hayward ***Due Date: n/a***

3.2.2	Version 4 of the GP letter for the Lenalidomide study was not listed on the cover letter to the REC or R&D (although it was included in the submissions). As a result, neither the REC or R&D listed this document in their approval letter (note: this omission had been documented in a note to file but not until 15th May 2014). In addition, this GP letter does not formally have REC approval; however it is not clear whether this version was used in the trial.
Corrective Action: The omission of the GP letter from the list of submitted documents was a simple oversight. Neither REC or R&D listed the GP letter in their approval letters, despite it appearing both in the body of the submission letter and appended to the protocol. This lack of attention to detail was not limited solely to the trial coordinator. REC has now issued an amended letter (dated 1.07.2014) incorporating approval of GP Letter Version 4. This has been circulated to participating sites. R&D has issued an addendum letter in respect of protocol amendment 3 approval. This has been forwarded to the Plymouth site as the approval includes confirmation of continued local management approval. This version of the GP letter would have been used by the sites that recruited the final ten patients to the study.	***Actionee:*** Margie Berrow ***Due Date:*** Completed
Preventive Action: R&D does check REC approvals and for the presence of a GP letter (see attached examples of the checklist used at the time and the recently updated checklist). It would appear that in this case there was an oversight when checking the study documentation. The issue has been highlighted to our administrators.	***Actionee:*** Chris Rollinson ***Due Date:*** Complete

3.2.3	In the Lenalidomide study there was an incorrect reference to version 5 of the 'continuing consent' form in the REC and R&D approval letters (dated 26th July 2011 and 27th September 2011 respectively) which should have stated version 4. It was noted that this had been identified and documented in a note to file but not until 15th May 2014.

Corrective Action: REC has now issued an amended letter (dated 10.07.2014) documenting the approval of Continuing ICF version 4. This has been circulated to participating sites. R&D has issued an addendum letter in respect of protocol amendment 4 approval. This has been forwarded to the Plymouth site as the approval includes confirmation of continued local management approval.	***Actionee:*** Margie Berrow ***Due Date:*** Complete
Preventive Action: R&D do check our own and REC documentation. It would appear that again in this case there was an oversight when checking the study documentation. The issue has been highlighted to our administrators.	***Actionee:*** Chris Rollinson ***Due Date:*** Complete

3.2.4	Christies site R&D approval for the Lenalidomide study was granted on 13th November 2009 on the understanding 'that you abide by the Investigator agreement' but no such investigator agreement was available for the version of the protocol in place at the time this R&D approval was granted (version 2).

Corrective Action: The R&D Manager at the Christie has confirmed that the Investigator Agreement referred to in the approval letter is a local document. The agreement is between the Principal Investigator and the Trust (The Christie NHS Foundation Trust). A copy of the Trust's Investigator Agreement template is available if required. A retrospective Investigator Agreement Page for protocol version 2 has been signed by the PI at Barts and the PI at the Christie.	***Actionee:*** Margie Berrow ***Due Date:*** Completed

3.3	**Staff Delegation and Responsibilities**
3.3.1	For the Lucentis trial, JR was not delegated to administer the pain score on the delegation log, although she performed this task.

Corrective Action: Nil, study is now closed	***Actionee:*** Judy Robinson
Preventive Action: Ensure Trust and study procedures are followed in future i.e. try to ensure that similar situations are picked up when monitoring future studies. We will also update our G5 Delegation of duties SOP to ensure the wording and instructions are clear regarding the assignment of staff responsibilities.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed

3.4	**Trial Master File**
3.4.1	Documentation in the TMF for the OFT trial was inadequate in relation to major decisions taken throughout the study. It was not possible to reconstruct the decision to temporarily halt the trial and finally to end the trial. The TMF contained documentation demonstrating that the sites were informed of the halt and close to recruitment. However there was no documentation to demonstrate that these decisions had been communicated to the Sponsor.

Corrective Action: Nil, study has closed. However, we acknowledge that the documentation in the TMF for the OFT trial was inadequate in relation to major decisions taken throughout the study. We can confirm that there is documentation that demonstrates that the temporary halt and closure was communicated to the sponsor. Specifically the temporary halt (amendment 4) was submitted in the form of a letter for sponsor approval on 26 January 2012. The amendment was submitted to MREC at the same time. However, REC SOP changed and now requires sponsor agreement to this amendment, so Dr Vickers wrote to REC on 13 Feb 2012 to re-submit the amendment. This documentation is located in the 'amendments' section of TMF 13, furthermore is clearly documented on the 'audit trail of submissions to sponsor', which is held in the same file. With regard to study closure, the end of study notification was sent to Dr Vickers by Maria Robinson by email on 26 Feb 2014 and further email correspondence confirming the end date is dated 27 Feb 2014. This email correspondence is now located in the TMF.	***Actionee:*** Margie Berrow

Preventive Action: The Lymphoma Trials Unit had not been fully amalgamated into PenCTU at the time of these events. PenCTU have processes in place that ensure study reports and decisions are dealt with appropriately.		***Actionee:*** Chris Rollinson ***Due Date:*** Completed
3.4.2	There were missing Investigator agreements (used to indicate that the PI agrees to comply with the requirements of the study protocol) for the Lenalidomide study: • Agreements for Version 1 and 2 of the protocol from the PI at the Bart's and Christie's site. (these versions had been implemented while there were patients in the study at these sites). There was no Investigator agreement from the PI at the Christies site for protocol versions 5 and 6.	
Corrective Action: There were no patients on study at the Christie prior to the implementation of version 2 of the protocol. However, a retrospective Investigator Agreement Page for Protocol version 1 has been created and signed by the Principal Investigator at Bart's. A retrospective Investigator Agreement Page for protocol version 2 has been signed by the PI at the Christie and by the PI at Bart's. The Christie did not wish to recruit any patients to the extension phase of the study. Therefore, they have not been considered as an "active" centre for some time. Investigator Agreement pages for protocol version 5 and 6 were not necessary. A file note has been added to the file to explain this in more detail.		***Actionee:*** Margie Berrow
Preventive Action: Future studies are not likely to have protocol investigator agreement pages as agreeing compliance with the protocol is now part of the standard mNCA. The mNCA states under section 3 OBLIGATIONS OF THE PARTIES: 3.1.1. The current version of the Protocol. Substantial amendments to the Protocol shall form part of this Agreement following confirmation in writing by the Parties. We would confirm by e-mail with the study PI's and coordinators that any amendments made had been received by the sites and duly implemented.		***Actionee:*** Margie Berrow ***Due Date:*** Completed

3.4.3	There were missing IB receipts in the TMF for the Lenalidomide study, for example: • There were no receipts available for the Christies site There were no receipts from the Bart's site for versions 11 or 12 or 16 of the IB
Corrective Action: As stated in a file note dated 7th May 2014, there were no document receipts issued for Editions 11 or 12 of the investigator brochure. However, in response to the finding, a receipt for both editions has been created retrospectively and sent to sites for signature. Receipts for Editions 11 & 12, 13 and 14 of the investigator brochure have been signed by the PI at the Christie. Edition 16 of the IB was not sent to The Christie. The PI at Bart's has signed and returned the receipt for editions 11, 12 & 16	***Actionee:*** Margie Berrow ***Due Date:*** Complete
Preventive Action: Document receipts will be required for Investigator Brochures sent to sites for future studies; this will be highlighted in a new Trust / PenCTU SOP on Investigator Brochures.	***Actionee:*** Margie Berrow ***Due Date:*** Completed

3.5	**Record Keeping/Essential Documents**
3.5.1	The OFT trial underwent an interim analysis. The report produced was a single page report, which was not dated or signed. It was not clear who produced this report, whether it was reviewed and/or approved and when it was issued.
Corrective Action: Nil, study is now closed	***Actionee:*** Simon Rule
Preventive Action: The lymphoma trials unit had not been fully amalgamated into PenCTU at the time of these events. PenCTU have processes in place to ensure study oversight by formalised committees, (TSC & where appropriate DMC). It is standard practice to convene these committees at the start of the study with a 'Terms of Reference' document.	***Actionee:*** Margie Berrow ***Due Date:***

In advance of committee meetings formal reports are circulated. Meetings minutes are circulated so that significant decisions and recommendations are documented. It is a requirement that UKCRC-registered CTUs have a SOP relating to statistics, which would normally include a section on interim analysis, so this should help in future. However, interim analysis is study specific and the details should be written into a Statistical Analysis Plan (SAP). A CTU SOP is only able to say that the need for interim analysis should be considered and documented as part of the SAP. All CTU reports (from any CTU) would of course be versioned and dated.	Completed

3.6	**CRF Data/Source Data**
3.6.1	For the PASTIES study the recruitment form for patient 113 had not been annotated with the stratification details or treatment allocation for this patient (as required by the form). In addition, there was no evidence that a data query had been raised relating to this omission (as required according to the annotated patient recruitment form in the data management files for this study).

Corrective Action: We have checked the case in question and can confirm that the randomisation and stratification of participant 113 was executed correctly in accordance with study procedure, and data integrity is not impacted. The section of the form in question serves only as an aide to the person at the investigator site performing the web-based randomisation. As such, absent entries made in this section of the form do not require data query generation, and this was agreed between the data management staff but the annotated CRF was not updated accordingly. The annotated CRF in the data management file is therefore obsolete.	***Actionee:*** Chris Hayward ***Due Date:*** completed
Preventive Action: PenCTU SOP to be updated to ensure changes to data management/validation processes are documented adequately in the DM working file.	***Actionee:*** Chris Hayward ***Due Date:*** Completed

3.6.2	For the Lucentis trial, page 1 of the CRF was required to be completed by the physician administering the IMP and confirming eligibility. For a number of patients this was completed by the study coordinator. For example subjects 19, 20, 22, 23-27. Therefore for the CRFs completed by the study coordinator there was no record of a medic review and confirmation of eligibility as required.

Corrective Action: Nil, study is now closed. We only have verbal confirmation that the physician assessed the eligibility.	***Actionee:*** Chris Rollinson
Preventive Action: Produce an SOP to make clear the role of the physician in the documentation of eligibility of trial participants. The issue is already being highlighted in mandatory Research Governance training.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed

3.7	**Quality Systems**
3.7.1	SOPG2 R&D and Ethics Application states that the Director of R&D approves CTIMPs trials (as they are high risk), however the Director is also a CI for a number of trials. The Inspectors were informed that when this is the case the R&D Director would not be involved in this decision. However, in the interest of transparency this should be part of a formal process and documented.

Corrective Action: Update SOPG2 to ensure the process is transparent.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed
3.7.2	SOP G9 Research Related Adverse Event Report refers to an appendix 7 for an example DSUR. Appendix 7 does not exist and there is no example DSUR attached to the SOP.
Corrective Action: Update SOP G9 to ensure appendices are correct.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed

3.7.3	SOP G13 Study Closure states that 'it is considered good practice to submit a summary of the final report to the MHRA' This is incorrect as the MHRA request a final report following notification of the end of trial.
Corrective Action: Update SOP G13 to ensure that a final report following notification of the end of trial is produced and submitted in the appropriate timeline.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed
3.7.4	SOP RD1 Study risk assessment is inadequate. It does not contain any guidance on how the assessment is made, who performs this and how it is reviewed and approved. There is no requirement to communicate and distribute the risk assessment. It does not require mitigation of any risks identified. There is no process to ensure the assessment is updated (for example following a protocol amendment) and there is no process to ensure that the risk assessment is complied with
Corrective Action: SOP RD1 to be completely re-written and we note the inspector's comments in producing the next version of the SOP.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed

3.8	**Contracts and Agreements**
3.8.1	The contract between GSK and the Trust for the OFT study states that if the protocol and agreement contradict each other then, the terms in the agreement shall prevail. This is not acceptable as there is a legal requirement to follow the protocol.
Corrective Action: Nil, study has closed	***Actionee:*** Chris Rollinson
Preventive Action: Where ever possible we will try to use the NIHR Industry model contract in future, however, some commercial companies may insist on their own in-house contracts. If the mCTA is not used we will check that agreements are in line with the legal position and that they make a similar statement to the mCTA for pharmaceutical research. I have update the *aide memoir* which is attached to our Dept. SOP R&D 9_Contract review we use to help in checking contracts so this will not be missed in future. If the mCTA is not used we will check that agreements are in line with the legal position and they make a similar statement to the mCTA for pharmaceutical research. I have update the aide memoir we use to help in checking	***Actionee:*** Chris Rollinson ***Due Date:*** Completed

contracts so this will not be missed in future. The mCTA for pharmaceutical research states: 3. CLINICAL TRIAL GOVERNANCE. 3.6 Should there be any inconsistency between the Protocol and the other terms of this Agreement, or any other document incorporated therein, including the Sponsor's Standard Operating Procedures, the terms of the Protocol shall prevail to the extent of such inconsistency except insofar as the inconsistency relates to clauses 5, 6, 8 and/or 9 of this Agreement.	

3.8.2	For the Lenalidomide study a substantial amendment to the study was implemented to amend the IMP distribution process to direct distribution to other investigator sites from Celgene rather than distribution from Plymouth pharmacy. The contract between Plymouth and Celgene had been amended to update the costing for the study, however this revised contract still reflects the fact that Plymouth maintain responsibility for distribution of IMP to other sites in the study.
Corrective Action: Celgene will prepare an amendment to the contract to update Clause 4 and Exhibit B to reflect the changes to the IMP distribution process detailed in amendment 5 (protocol Version 6, dated 19 October 2011).	***Actionee:*** Margie Berrow ***Due Date:*** Completed-
Preventive Action: This was again before Plymouth Lymphoma Trials Unit was integrated into PenCTU who now have more robust procedures for contract review.	***Actionee:*** Chris Rollinson ***Due Date:*** Completed

3.9	**Monitoring**
3.9.1	For the Lenalidomide study, a monitoring visit had taken place (conducted by the trial co-ordinating centre) at the Christies site on 12th Jan 2011 but there was no monitoring visit report available. In addition, the monitoring visit log had been annotated to indicate 'report not done yet'. It was noted that this had been identified and documented in a note to file but this was not until 5th June 2014.
Corrective Action: Nil, the person responsible for producing the report has subsequently retired from the Trust. However, it should be noted that: there are handwritten monitoring reports and checklists relating to the visit in the master file, but a formal report was not completed and distributed to the site. This was again before Plymouth Lymphoma trials were fully taken over by PenCTU. We have more formal processes for conducting and reporting monitoring visits.	***Actionee:*** Chris Rollinson

3.9.2	For the OFT trial a monitoring visit had been recorded as taking place at the Plymouth site on 25 April 2012, however there was no corresponding report on file.

Corrective Action: A note to file has been added to explain the missing report; there is a half-page (typed and signed) monitoring report in the patient's CRF, together with partially completed handwritten monitoring reports/checklists relating to this visit. This was again before Plymouth Lymphoma trials were fully taken over by PenCTU. They now have more formal processes for conducting and reporting monitoring visits.	***Actionee:*** Margie Berrow ***Due Date:*** Completed

Signature of person with responsibility for completion of the responses
Research Governance Manager

Dr. Chris Rollinson
Research Governance Manager
PHNT

29th Jan 2015